Review: Clinical Trial Outcomes

CLINICAL INVESTIGATION

# Targeted therapy for hepatocellular carcinoma: current status and future direction

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**Following the proof of evidence on the use of sorafenib in patients with advanced hepatocellular carcinoma (HCC), targeted therapy has become an important element in management of advanced HCC. Novel targeted therapies are designed to inhibit the aberrant signaling pathways or oncogenic mechanism at a molecular level with an aim to improve the clinical outcome. An increasing number of targeted agents have been tested in HCC in the clinical setting in the past few years. This review aims to summarize the current status of clinical development of targeted therapy in HCC focusing on novel agents targeting angiogenesis, signal transduction and epigenetic dysregulation of tumors. The future direction of drug development for HCC will also be explored.**

**Keywords:** biologic • cancer • liver • treatment

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Hepatocellular carcinoma (HCC) is the fifth most common cancer globally [1,2]. More than half of the patients who present with advanced disease are beyond curative surgery or loco-ablative therapy. Advanced stage HCC is commonly associated with aggressive disease course and poor prognosis. Median overall survival is generally less than 1 year [3,4]. Over the past two decades, drug development for HCC has been slow, and one of the major reasons is the large proportion of patients with comorbid cirrhosis, thus significantly limiting the tolerance to systemic therapy. Conventional cytotoxic chemotherapy has been developed for treatment of advanced HCC. The use of single-agent chemotherapy, such as doxorubicin, is associated with approximately 10% radiological and 30% serological response rates in alpha-fetoprotein [5,6]. However, chemotherapy has not been widely accepted by most clinicians as the standard treatment for HCC because of toxicity.

Sorafenib is currently the only approved targeted therapy for advanced HCC. The drug is a multitargeted tyrosine kinase inhibitor (TKI) that inhibits VEGF receptors (VEGFRs), PDGF receptors (PDGFRs) and Raf serine-theonine kinases. According to two similar designed Phase III clinical trials in Caucasian and Asian populations of HCC, sorafenib consistently demonstrated a modest but significant 2-month improvement in median overall survival compared with placebo [7,8]. Toxicities of sorafenib include skin rash, hand–foot reaction and diarrhea; however, the drug is generally better tolerated than cytotoxic chemotherapy. The exact mechanism of how sorafenib works in HCC remains unclear although it has been postulated that the agent acts mainly via inhibition of VEGFRs [9,10].

Following sorafenib, a number of novel agents have been investigated for patients with advanced HCC [11]. These novel agents include multitargeted TKIs that target the level of membranous receptors or intracellular molecules, and monoclonal antibodies (mAbs) that mediate their activities via inhibition of circulating factors or extracellular portion of membranous receptors (Figure 1). There have also been

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novel therapies targeting the oncogenic mechanism apart from signaling pathways. In this review, we summarize the current status of new drug development for HCC and focus on agents being investigated in Phase III studies or agents with promising activity in early clinical trials.

## Targeting angiogenesis

HCC is characterized by its hypervascularity and tendency to invade vasculature [12]. Angiogenesis is mediated by a complex network of growth factors acting on both tumor cells and endothelial cells. VEGF is the most studied mediator. It exerts its effects via binding to VEGFRs of which there are three subtypes: VEFGR1, 2 and 3 [13]. Apart from VEGF, the angiogenic process in HCC is also mediated by the interaction of a number of factors including PDGF, FGF and angiopoietin 1 and 2 and their respective receptors [14–16]. Both anti-angiogenic approaches, namely TKI and mAb, are currently tested in HCC. Table 1 summarizes a list of potential anti-angiogenic agents for treatment of HCC.

## Tyrosine kinase inhibitors

### Sunitinib

Sunitinib is an oral multitargeted TKI against VEGFR1, 2, PDGFRs, FMS-like tyrosine kinase 3 and c-kit. The agent has been approved for use in renal cell carcinoma and gastrointestinal stromal tumor. For HCC, early Phase II clinical trials reported disease control rate ranging from 38 to 52% and overall survival ranging from 8.0 to 9.8 months [17,18]. These encouraging Phase II data have led to a multicentered Phase III randomized clinical trial comparing sunitinib with sorafenib as the first-line treatment for advanced HCC. However, this study was terminated prematurely because of inferior overall survival (7.9 vs 10.2 months; p = 0.0010) in the sunitinib arm. Furthermore, sunitinib was associated with more toxicities and higher incidence of Grade 3 or 4 bleeding events (12%), thrombocytopenia (30%) and neutropenia (25%) [19]. These adverse events resulted in suboptimal dosing and thus worse outcomes in the sunitinib arm. The lack of benefit from this Phase III study has precluded further development of sunitinib in HCC. However, *post hoc* subgroup analysis indicated that patients carrying the hepatitis B virus derived less clinical benefit from sorafenib compared with patients with chronic hepatitis C virus infection. This finding has led to postulation that response to targeted therapy differs amongst HCC populations of different viral etiology. This hypothesis remains to be confirmed by future prospective clinical trials.

### Brivanib

Brivanib is a dual VEGFR and FGFR inhibitor [20]. Additional inhibition of FGFR could improve the treatment

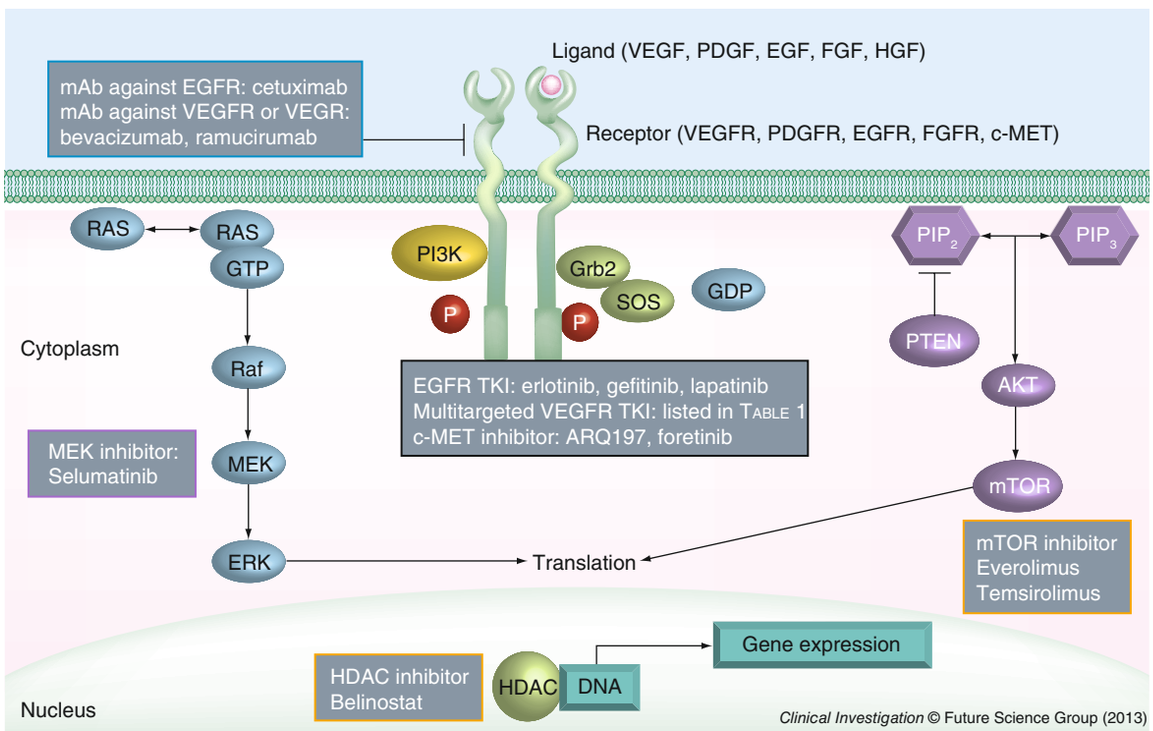


**Figure 1. Mechanism of targeted agents for hepatocellular carcinoma.**
HDAC: Histone deacetylases; mAb: Monoclonal antibodies; P: Phosphorylation; TKI: Tyrosine-kinase inhibitors.

**Table 1. Summary of antiangiogenic targeted agents under development for hepatocellular carcinoma.**

| Agent (manufacturer) | Target | Phase of development | Ref. |
|---|---|---|---|
| Monoclonal antibody | | | |
| Bevacizumab | VEGF | II | [26–30] |
| Ramacirumab | VEGFR2 | III | [104] |
| Tyrosine kinase inhibitor | | | |
| Sorafenib (Nexavar, Bayer and Onyx) | VEGFR2,3, PDGFRβ, RAF, Flt-3, c-kit | IV; approved | [7,8] |
| Sunitinib (Sutent, Pfizer) | VEGFR1,2, PDGFRs, Flt-3, c-kit | III | [19] |
| Brivanib (BMS-582664; Bristol-Myers Squibb) | VEGFR2,3, FGFR | III | [89,103,119] |
| TSU-68 (SU6668; Taiho) | VEGFR2, PDGFRβ, FGFR | I–II | [90,120] |
| Linifanib (ABT-869; Abbot) | VEGFR2, PDGFRβ, CSF-1R | II–III | [91,121] |
| Axitinib (AG013736; Pfizer) | VEGFR1,2,3, PDGFRβ, c-kit | II | [122–124] |
| Cediranib (AZD2171; AstraZeneca) | VEGFR1,2,3, PDGFRs, c-kit | II | [125] |
| Pazopanib (GW786034; GlaxoSmithKline) | VEGFR1,2,3, PDGFRs, c-kit | I | [92] |
| Vandetanib (Zactima; AstraZeneca) | VEGFR1, EGFR1, RET | II | [126] |
| Regorafanib (BAY73–4506; Bayer and Onyx) | VEGFR-2,3, PDGFRβ, Flt-3, c-kit, Tie2, Raf | II | [93] |

efficacy because FGFR is involved in mediating the resistance to this anti-VEGFR agent [21]. Brivanib has been evaluated as a first-line agent in advanced HCC by a Phase II study that reported median overall survival of 10 months and time-to-progression (TTP) of 2.7 months. Major toxicities included fatigue, hypertension and transaminitis; however, few patients experienced Grade 3 or higher adverse effects. In a Phase II study in patients with prior anti-angiogenic therapy for HCC, brivanib attained TTP of 2.7 months [22,23]. Two randomized Phase III clinical trials are ongoing. The first one (BRISK-FL study; [101]) is a head-to-head comparison of brivanib with sorafenib as first-line therapy for patients with advanced HCC. It was recently announced that the BRISK-FL trial failed to meet its primary end point of overall survival benefits [102]. Full-print publication is awaited. The second study (BRISK-PS study [103]) is a placebo-controlled study that evaluates the use of brivanib as second-line therapy for patients who have failed or cannot tolerate sorafenib. According to the abstract presented at the 47th Annual Meeting of the European Association for the Study of the Liver and Annual Conference of Interenational Liver Cancer Association in 2012, BRISK-PS failed to meet its primary end point of improving median overall survival (brivanib 9.4 months vs placebo 8.2 months; p = 0.3307) [24,25]. However, brivanib was associated with longer median TTP (4.2 vs 2.7 months; p = 0.0001) and higher disease control rate (71 vs 49%; p <0.0001).

## Monoclonal antibodies

### ■ Bevacizumab

Bevacizumab is a recombinant humanized mAb against VEGF ligand. The agent has been evaluated as a single agent and in combination with other drugs in Phase II studies [26–30]. Bevacizumab has mild-to-moderate single-agent activity in HCC [26], which is associated with radiologic response rates of 10–20%. However, bevacizumab is potentially associated with high incidence (up to 11%) of severe hemorrhagic complications in cirrhotic patients [26]. The overall clinical benefit of bevacizumab requires confirmation in a prospective randomized study.

### ■ Ramucirumab

Ramucirumab binds directly to VEGFR2. Zhu *et al.* reported disease control rate of 50% and progression-free survival (PFS) over 4 months in a single-arm Phase II study on ramucirumab [31]. A Phase III clinical trial (REACH study [104]) compares ramucirumab with placebo in HCC patients who failed prior anti-angiogenic therapy. This study is actively recruiting patients.

## Targeting EGFR

EGFR is amongst the best described therapeutic targets in cancer, and targeting EGFR has proved successful in lung and colorectal cancers [32,33]. Pre-clinical evidence indicated that EGFR-related signaling is involved in hepatocarcinogensis [34]. Clinical trials have been conducted on both mAbs and EGFR TKIs.

### ■ Cetuximab

Cetuximab is a mAb against EGFR, which has been tested as a single agent in two Phase II studies [35,36]. Both studies reported minimal activity with no tumor response short PFS. Cetuximab has also

been studied in combination therapy with capecitabine and oxaliplatin in a small-scale Phase II study [35,36]. Tumor response rate was 10% in 20 evaluable patients, but significant toxicities including diarrhea and hypomagnesemia prevented further investigation of the combination [37].

### EGFR TKIs

Single-agent EGFR TKIs, including erlotinib, gefitinib and lapatinib, were investigated and radiologic response rates ranged from 0 to 9% with median PFS ranging between 1.9 and 3.2 months [38–41]. Efficacy of single-agent anti-EGFR TKI is generally considered modest and not advisable for future development. On the other hand, combination of EGFR TKI and anti-angiogenic treatment may be more promising [38–41]. The combination of erlotinib and bevacizumab was reported to be associated with overall survival of 15 months in a Phase II study [28]. However, another Phase II study failed to reproduce this favorable survival duration with a similar combinational regimen of bevacizumab and erlotinib [29]. An ongoing placebo-control Phase III study compares the combination of erlotinib and sorafenib with sorafenib alone as the first-line treatment for patients with advanced HCC (SEARCH study [105]). The study has completed accrual.

## Targeting HGF/c-MET

c-MET is a membrane receptor that plays an important role in hepatocyte and tissue remodeling of liver after hepatic injury [42,43]. In cancer cells, activation of HGF/c-MET axis leads to cancer cell proliferation, invasion and metastases [44,45]. Silencing of c-MET expression is associated with antineoplastic effects in growth inhibition of HCC cell lines. c-MET receptor protein is overexpressed in 20–48% of human samples of HCC [46–49], and is found to be a prognostic marker [50–52]. It is intriguing to notice that cell lines without c-MET expression do not have response to c-MET inhibitor, which suggests that c-MET expression is a potential predictive biomarker [53]. Future development of c-MET inhibitors should be supplemented with evaluation of biomarkers.

### Tivantinib

Tivantinib (ARQ 197) is an oral TKI of c-MET. A Phase I study in 21 HCC patients who failed prior treatment reported ten stable diseases at 2 months, with five of these continuing to have stable disease at 4 months. Common toxicities included asthenia (43%), anemia (43%) and neutropenia (38%) [54]. A randomized Phase II study in patients who have failed one line of systemic therapy has recently been completed. In the study, subjects were randomized in 2:1 ratio to tivantinib or placebo. The initial treatment dose of 360 mg twice-daily was later reduced to 240 mg twice daily because of significant neutropenia [54]. Preliminary data from ASCO 2012 indicated statistically significant improvement in TTP (1.6 vs 1.4 months, respectively; HR = 0.64; p = 0.04) [55]. The investigators have also looked into the impact of c-MET protein over-expression as the predictive biomarker. Using the definition of immune-histochemical staining of c-MET $\geq$2 in more than 50% of tumor, the benefit in TTP of tivantinib was more apparent in the c-MET-overexpressed group compared with placebo (2.9 vs 1.5 months; HR = 0.43; p = 0.03). A Phase III clinical trial comparing tivantinib with sorafenib as first-line therapy is being planned.

### Cabozantinib

Cabozantinib (XL184) is an oral multitargeted TKI against c-MET and VEGFR2. The agent was investigated in a Phase II randomized discontinuation trial in HCC. All enrolled patients received cabozantinib 100 mg daily and were assessed for tumor response at week 12. Patients with partial or complete responses continued to receive cabozantinib while patients with stable disease were randomized to cabozantinib or placebo. Patients with progressive disease were discontinued from the study [56]. At week 12, there were two partial responses and 32 stable diseases, giving a disease control rate of 66%. Tumor shrinkage was seen in both patient groups who were treatment-naive or treated with sorafenib. A total of 22 (out of 44) enrolled patients were randomized. Cabozantinib was generally well tolerated with common Grade 3 or above toxicities such as diarrhea (20%), hand–foot skin reaction (15%) and thrombocytopenia (15%). Biomarker analysis is not available at present, but will likely be conducted in future.

## Targeting mTOR

The PI3K/Akt/mTOR axis is involved in multiple cellular processes including survival and proliferation [57]. This pathway is initiated when membrane receptors are activated by binding of growth factors, which in turn recruit and activate PI3K. The activation of PI3K leads to a cascade of activation of downstream effectors, including the serine-threonine kinases Akt and mTOR. Comprehensive genomic analyses have shown that components of the PI3K/Akt/mTOR pathway are dysregulated in 40–50% of HCC [58,59].

### Everolimus

Everolimus is an oral mTOR inhibitor that has been approved for treatment of late stage renal cell

carcinoma. A small Phase I/II study (n = 28) on patients with prior therapy demonstrated anti-tumor activity with disease-control rate of 44% and an overall survival of 8.4 months [60]. Everolimus was well tolerated and the most common side effects included fatigue and hyperglycemia [60]. These encouraging results have led to an ongoing Phase III EVOLVE study comparing everolimus with placebo in patients who have failed sorafenib treatment [106].

### Temsirolimus

Temsirolimus is another mTOR inhibitor, which is administered by intravenous infusion only. This drug is also approved for treatment of renal cell carcinoma. Our group is currently conducting a Phase I/II study on the role of single-agent temsirolimus as first- or second-line treatment for patients with inoperable HCC [107]. Accrual is completed and mature data are expected by 2013. Temsirolimus has also been tested as combination therapy with bevacizumab. This Phase II study reported that two of 25 patients (8%) attained partial response while 16 other patients remained progression-free at week 16 [61]. However, treatment outcome is not better than single-agent bevacizumab. A Phase I study on the combination of temsirolimus and sorafenib is ongoing [62]. Preliminary results suggested that the maximal tolerated dose of temsirolimus is 10 mg weekly and sorafenib at 200 mg twice-daily.

## Targeting epigenetic dysregulation

Epigenetic mechanism refers to any modification of expression of the genome without alteration in the nucleotide sequence. Nucleotide hypermethylation and histone acetylation are the two most important regulatory mechanism. Carcinogenesis may involve aberrant methylation of cytosine of cytosine–guanine dinucleotide islands clustered around promoter regions, and this could lead to downregulated expression of tumor suppressor genes. Methylation of the genome is regulated by a family of DNA methyltransferases (DNMTs) that cooperate with each other in maintaining the methylation pattern and inducing *de novo* methylation in cancer cells. On the other hand, the expression of tumor suppressor genes is influenced by coiling and uncoiling of DNA around histones, which is largely mediated by histone acetylation. Acetylation of histones results in less condensed chromatin that leads to inactivation of gene expression, while histone deacetylases (HDACs) remove the acetyl groups from histones and lead to condensed and transcriptionally silenced chromatin. The status of histone acetylation depends on balance of activity of histone acetyltransferases and HDACs. Both epigenetic mechanisms are known to be accumulated along hepatocarcinogenesis, when the dysplastic nodule progresses to HCC [63].

Epigenetic deregulation is a unique target because of its reversibility by DNMT inhibitor and/or HDAC inhibitor. Epigenetic therapeutics have emerged as an active class of anticancer agents in hematological malignancies. Azacitinine, a DNMT inhibitor, has been approved in the treatment of myelodysplastic syndrome [64]. Two HDAC inhibitors, namely vorinostat and romidepsin, have also been approved for the treatment of peripheral T-cell lymphoma [65,66].

### Belinostat

Preclinical studies showed that treatment with this inhibitor could induce apoptosis in HCC models [67–69]. Our group has recently published a National Cancer Institute Phase I/II study using belinostat, a HDAC inhibitor, in advanced HCC. The study demonstrated clinical responses and good safety profile in a heavily pretreated population of HCC [70,71]. From 42 patients, 38% of them had previously received more than one line of systemic therapy. More than 47% of them had partial response or stable disease. The PFS was 2.6 months. The drug was safe, with lower than 10% of Grade 3 or higher side effects. Further clinical trials are indicated to develop epigenetic therapy as a single agent or in combination with other drugs for HCC.

## Combinational treatment

Targeted therapy is typically associated with low response rate. In order to improve the response rate, there is a strong rationale for combinational therapy, either with transarterial chemo-embolization (TACE) or different systemic agents, for treatment of HCC. Also, since the overall survival of patients with advanced HCC is short, most patients may not have the opportunity to receive second-line treatment. Combinational treatment allows the patients to be treated with more than one agent at the same time, and this may delay disease progression.

## Combination of TACE & anti-angiogenic targeted therapy

HCC is a highly vascular tumor and for this reason TACE may induce tumor hypoxia. Post-treatment surge of angiogenic factors including VEGF may occur within hours after TACE. The sudden increase in angiogenesis may contribute to revascularization of tumors thus reducing the efficacy of TACE [72,73]. Microscopic tumor progression is relatively common during the interval between each treatment cycle of TACE [74]. Therefore, combining antiangiogenic drugs

with TACE is a rational approach to improve treatment outcomes [75].

Efficacy and safety of the combination of anti-angiogenic agents and TACE are being actively investigated (Table 2) [76–78]. Optimal schedule of the combination remains to be defined. A randomized Phase III study on patients who completed TACE showed similar survival between the sorafenib and placebo group [77]. In contrast, a single-arm Phase II study on sorafenib starting at 1 week after TACE using drug-eluding beads, reported disease control rate of 95% according to RECIST criteria and objective response rate of 58% according to European Association for the Study of the Liver criteria [78]. Our group is conducting a single-arm Phase II study on the use of axitinib, a novel multikinase inhibitor against VEGFR1, 2 and 3, PDGFRs and c-KIT, in combination with TACE in patients with inoperable HCC [108]. All eligible patients are given axitinib for 4 weeks prior to TACE. Axitinib is withheld for 24 h prior to TACE and restarted at 24 h after TACE if there is no Grade 3 toxicity.

### Combination of chemotherapy & anti-angiogenic agent

Sorafenib is also combined with cytotoxic chemotherapy such as capecitabine, tegafur, gemcitabine, docetaxel, oxaliplatin and doxorubicin [79–83]. Abou-Alfa *et al.* completed a randomized Phase II trial comparing the combination of sorafenib 400 mg twice-daily and doxorubicin 60 mg/m$^2$ every 3 weeks with doxorubicin alone in patients with inoperable HCC [81]. They reported an overall survival of 13.7 months in the combination arm compared with 6.5 months in the doxorubicin arm. The proportion of patients

**Table 2. List of current and ongoing clinical trials on combinational targeted therapy and transarterial chemoembolization.**

| Study/Phase | Design | Mode and time of targeted therapy | Status | Ref. |
|---|---|---|---|---|
| Sorafenib | | | | |
| S-TACE Phase I | Single-arm study (n = 14) | Continuous with TACE | Published | [76] |
| SOCRATES Phase II | Single-arm study | Interrupted (withheld 3 days before and started 1 day after TACE) | Ongoing | [110] |
| START Phase II | Single-arm study | Interrupted (withheld 3 days before and started 3 days after TACE) | Ongoing | [111] |
| Phase II | Single-arm study (n = 35) | Interrupted (started at 1 week after TACE) | Published | [78] |
| Phase II | Single-arm study | Continuous with TACE | Ongoing | [112] |
| Phase II | Single-arm study | One cycle of TACE followed sorafenib | Ongoing | [113] |
| Phase II | Randomized (sorafenib vs placebo) | Continuous with TACE | Ongoing | [114] |
| TACTICS Phase II | Randomized (open label) | Interrupted (withheld 2 days and started 3 days after TACE) | Ongoing | [115] |
| SPACE Phase III | Randomized (sorafenib vs placebo) | Continuous with TACE | Accrual completed | [116] |
| Phase III | Randomized (sorafenib vs placebo; n = 458) | Delayed (started 1–3 months after TACE) | Completed | [77] |
| ECOG 1208 Phase III | Randomized (sorafenib vs placebo) | Interrupted (withheld 24–48 h before and 7–14 days after TACE) | Ongoing | [117] |
| Brivanib | | | | |
| BRISK TA Phase III | Randomized (brivanib vs placebo) | Delayed (adjuvant) after TACE | Ongoing | [118] |
| Axitinib | | | | |
| Phase II | Single-arm study | Interrupted (withheld 24 h before and resumed 24 h after TACE) | Ongoing | [108] |

TACE: Transarterial chemo-embolization.
Modified with permission from [94].

with tumor shrinkage was also significantly higher in the combination arm (62 vs 29%) [81,84]. One of the most significant toxicities of the sorafenib–doxorubicin combination was left ventricular systolic dysfunction (all-grade 19 vs 2%). It remains unclear on the mechanism of increased cardiac toxicity. It may be related to a higher concentration of doxorubicin from the combination, or due to the synergistic toxicity conferred by VEGF inhibition of sorafenib. This regimen is currently being investigated in Phase III trial comparing it with single agent sorafenib [109].

## Future perspective

Despite the initial success with sorafenib, development of molecular targeted therapeutics for HCC remains a challenge, as the science is complex and the tumors are highly heterogeneous. There is no clear evidence on the presence of a driver oncogene. This limitation has partly accounted for recent failures in Phase III trials testing novel targeted agents in HCC. A number of projects based on different sequencing or microarray platforms are being conducted to decipher the molecular profiles and classification of HCC [85–88]. It is anticipated that the results could facilitate the development of personalized targeted therapy for patients with HCC. On the other hand, the accomplishment of personalized therapy will likely have to rely on the identification of tissue biomarker in HCC. For such, tumor biopsy is essential to the success of development of molecular targeted therapy for HCC.

## Financial & competing interests disclosure

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## Executive summary

### Background

- At present, sorafenib is the only targeted agent approved for treatment of advanced hepatocellular carcinoma (HCC).
- A number of novel targeted agents are under clinical development for treatment of HCC.

### Targeting angiogenesis

- Sunitinib is found to have inferior toxicity profile and efficacy compared with sorafenib in the first-line setting.
- In both Phase III clinical trials on the use of brivanib as first- or second-line treatment, brivanib failed to demonstrate superiority over sorafenib and placebo, respectively.
- Bevacizumab is not recommended for routine treatment of HCC because its efficacy and toxicity has not been evaluated by Phase III clinical trials.
- Ramucirumab is currently evaluated by a Phase III clinical trial comparing it with supportive care in patients who failed or became refractory to sorafenib.

### Targeting EGFR

- The activity of tyrosine kinase inhibitors (e.g., erlotinib and gefitinib) is minimal in HCC.
- Phase II clinical trials showed that cetuximab was associated with low radiologic response in HCC.

### Targeting c-MET

- A number of c-MET inhibitors (e.g., tivantinib and cabozantinib) have demonstrated potential efficacy in Phase II clinical trials. Further clinical development is warranted.
- c-MET over-expression is a potential predictive biomarker for c-MET inhibitors. The optimal methodology and definition of c-MET over-expression remains to be explored.

### Targeting mTOR

- Two agents including everolimus (Phase III vs sorafenib) and temsirolimus (Phase II) are undergoing testing in HCC.

### Targeting epigenetic dysregulation

- Hepatocarciongensis is characterized by epigenetic dysregulations, which is reversible with epigenetic therapeutics.
- Belinostat, a HDAC inhibitor, demonstrated potential activity and good safety profile for advanced HCC.

### Combinational treatment

- A Phase II randomized study showed that the combination of sorafenib and doxorubicin had significantly better response rate and overall survival compared with doxorubicin. A Phase III trial is currently underway.
- Combination of antiangiogenic targeted therapy and transarterial chemoembolization is another direction of combinational treatment for HCC. A number of clinical trials on different agents are currently ongoing.

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