

Molecular targeted therapy for hepatocellular carcinoma: Current and future

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Abstract

Hepatocellular carcinoma (HCC) is one of the most frequent tumors worldwide. The majority of HCC cases occur in patients with chronic liver disease. Despite regular surveillance to detect small HCC in these patients, HCC is often diagnosed at an advanced stage. Because HCC is highly resistant to conventional systemic therapies, the prognosis for advanced HCC patients remains poor. The introduction of sorafenib as the standard systemic therapy has unveiled a new direction for future research regarding HCC treatment. However, given the limited efficacy of the drug, a need exists to look beyond sorafenib. Many molecular targeted agents that inhibit different pathways involved in hepatocarcinogenesis are under various phases of clinical development, and novel targets are being assessed in HCC. This review aims to summarize the efforts to target molecular components of the signaling pathways that are responsible for the development and progression of HCC and to discuss perspectives on the future direction of research.

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Key words: Hepatocellular carcinoma; Targeted therapy; Molecular agents; Sorafenib

Core tip: Sorafenib is the first drug to prolong survival of patients with advanced hepatocellular carcinoma (HCC). This advance has shifted the paradigm of systemic treatment for HCC toward molecular targeted therapy. This review aims to summarize the efforts to target molecular components of the signaling pathways that are responsible for the development and progression of HCC and to discuss perspectives on the future direction of research.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a common solid cancer and the third most frequent cause of cancer-related mortality worldwide. The 5-year relative survival rate for patients with HCC is only 7%, and very few patients with symptomatic disease survive for > 1 year^[1]. One of the primary reasons for the poor prognosis of patients with HCC is the lack of effective treatment options, especially for those with advanced disease. Although surgery and percutaneous ablation can achieve long-term control in some patients with early HCC, fewer than 40% of patients are diagnosed at early stages; hence, only a minority of HCC patients are eligible for potentially curative therapies, such as resection, transplantation, or percutaneous ablation^[2]. Furthermore, systemic therapies (such as stan-

dard chemotherapeutic agents) do not provide significant efficacy in HCC based on randomized trials^[3].

In recent years, improved knowledge of the oncogenic processes and signaling pathways that regulate tumor cell proliferation, differentiation, angiogenesis, invasion and metastasis has led to the identification of several potential therapeutic targets, which has driven the development of molecularly targeted therapies. An ideal cancer target meets the following criteria: (1) the target is relatively specific for cancer cells (not expressed or expressed at very low levels in normal cells but overexpressed in cancer cells). Meanwhile, overexpression of the target is associated with malignant biological phenotypes and/or poor prognosis; (2) inhibition of the target is efficacious (the target plays an essential role in cancer initiation and progression, and inhibition of expression or activity of the target induces growth suppression and/or apoptosis in cancer cells); and (3) the target is “drugable” as an enzyme (*e.g.*, a kinase) or a cell surface molecule (*e.g.*, a membrane-bound receptor) that can be easily screened for small-molecule inhibitors or targeted by a specific antibody^[4].

The aim of this article is to review the efforts to target molecular components of the signaling pathways that are responsible for the development and progression of HCC and to summarize the evidence for the clinical activity of these agents in patients with HCC.

HCC DEVELOPMENT AND SIGNALING PATHWAYS

Hepatocarcinogenesis is a multistep process initiated by external stimuli that lead to genetic changes in hepatocytes or stem cells, resulting in proliferation, apoptosis, dysplasia and neoplasia. The majority of HCC cases are related to chronic viral infections. However, the mechanisms by which hepatitis B virus (HBV) or hepatitis C virus (HCV) induce malignant transformation seem to differ. HBV DNA integrates into the host genome, inducing chromosome instability and insertional mutations that may activate various oncogenes, such as cyclin A^[5-7]. Viral proteins, in particular X protein (HBx), act as transactivators to upregulate several oncogenes (such as c-myc and c-jun) and transcriptional factors [(such as nuclear factor- κ B)]^[8-10]. Additionally, HBx activates promoters of genes encoding IL-8, tumor necrosis factor (TNF), transforming growth factor (TGF)- β and epidermal growth factor receptor (EGFR)^[11]. HBx can also stimulate several signal transduction pathways, including the JAK/STAT, RAS/RAF/MAPK, and Wnt/ β -catenin pathways^[12-14].

The contributions of HCV to hepatocarcinogenesis are mediated by viral proteins, including core, NS3 and NS5A proteins. HCV core protein can promote apoptosis or cell proliferation through interaction with p53 or upregulation of Wnt-1 at the transcriptional level^[15,16]. NS4A and NS4B proteins mediate translational inhibition and degradation of various cellular proteins^[17]. Cirrhosis

is present in approximately 80%-90% of HCC patients and constitutes the largest single risk factor. In cirrhotic liver, changes in fat metabolism associated with the activation of adipocyte-like pathways are thought to be involved in neoplastic transformation^[18].

MAPK PATHWAY (RAS/RAF/MEK/ERK)

The Raf/MAPK/extracellular-signal-regulated kinase (ERK) pathway is an important pro-survival signaling pathway that is primarily involved in cell growth and survival and regulates cell differentiation. This pathway transduces extracellular signals from membrane-bound tyrosine kinase receptors, such as EGFR, insulin-like growth factor receptor (IGFR), vascular endothelial growth factor receptor (VEGFR), c-Met and platelet-derived growth factor receptor (PDGFR), to the nucleus. Growth factor binding results in receptor phosphorylation, which activates an adapter molecule complex known as GRB2/SHC/SOS. This sequence in turn activates the RAF/mitogen/extracellular protein kinase (MEK)/ERK pathway, which triggers a cascade of specific phosphorylation events^[19]. Within this pathway, the small GTPase RAS and the serine/threonine kinase Raf are the key signal regulators^[20]. Intermediate signaling is regulated by MEK1 and MEK2, which are responsible for phosphorylating and activating the final downstream signaling molecules extracellular-regulated protein kinases (ERK)1 and ERK2^[21]. ERK1/2 regulates cellular activity by acting on more than 100 substrates in the cytoplasm and nucleus. RAS also regulates the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway, the phospholipase C/protein kinase C pathway and the ral guanine nucleotide dissociation stimulator pathway^[22,23].

Up-regulated activation of the Raf/MAPK/ERK signaling pathway has been well documented in HCC and correlates with advanced stage^[24,25]. Mechanisms for the increased activity of the Raf/MAPK/ERK signaling pathway in HCC include down-regulation of Raf kinase inhibitor protein (a suppressor of the Raf/MAPK/ERK pathway) and induction by hepatitis viral proteins (such as the hepatitis B X protein and the hepatitis C core protein)^[26-28].

Targeting Raf kinase is one of the most promising targeted approaches for the treatment of HCC. Sorafenib has strong inhibitory activity against Raf-1 (C-Raf) kinase and B-Raf (wild-type B-Raf and mutant V600E B-Raf) and has been shown to inhibit other serine/threonine kinases, the pro-angiogenic receptor tyrosine kinases VEGFR, PDGFR and FGFR1, and tyrosine kinases such as c-kit, Flt-3 and RET, which are involved in tumor progression and overall prognosis (Figure 1)^[29].

Selumetinib (AZD6244) is an oral non-ATP-competitive small-molecule inhibitor of the mitogen-activated protein kinase MEK1/2. A recent study has shown that selumetinib plus rapamycin exerts antitumor and antiangiogenic effects in preclinical models of human HCC^[30]. In a phase I / II study of selumetinib in combination with

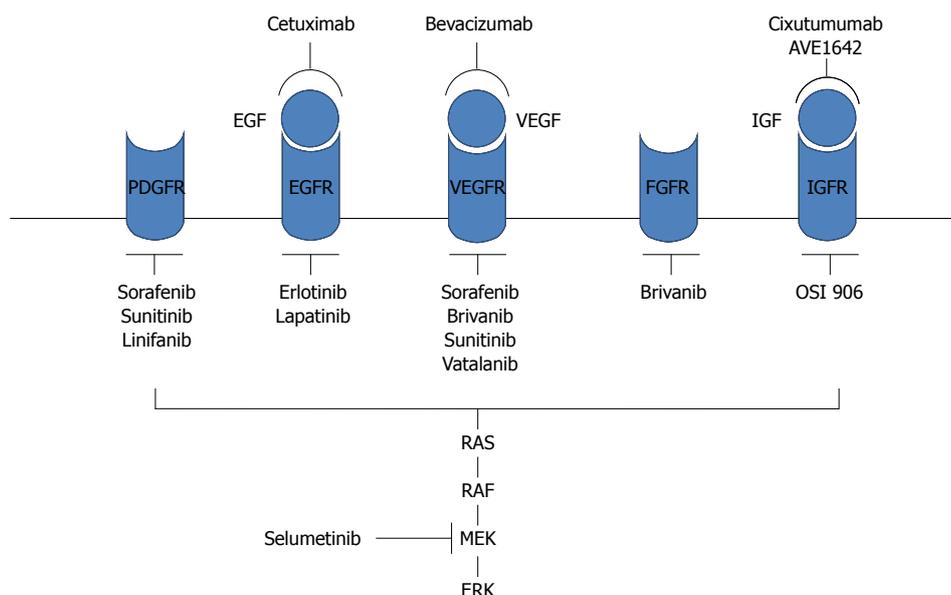


Figure 1 Ras/Raf/MEK/ERK signaling pathways and molecular targeted agents which is currently available or in development for hepatocellular carcinoma. EGF: Epidermal growth factor; EGFR: EGF receptor; ERK: Extracellular signal-regulated kinase; FGFR: Fibroblast growth factor receptor; IGF1R: Insulin-like growth factor receptor; PDGFR: Platelet-derived growth factor receptor; VEGF: Vascular endothelial growth factor; VEGFR: VEGF receptor; MEK: Mitogen/extracellular protein kinase.

sorafenib in advanced HCC, the objective responses were 3 partial response (PR), 6 stable disease (SD) and 2 progressive disease (PD) among 11 patients, and the common toxicities were diarrhea, rash, fatigue, and hypertension^[31].

Another phase I / II study has evaluated the combination of the MEK inhibitor RDEA119 and sorafenib in patients with advanced cancer (NCT00785226).

PI3K/AKT/MTOR PATHWAY

The PI3K/Akt/mTOR pathway also plays an important role in cell growth, survival regulation, metabolism and anti-apoptosis^[32]. The binding of growth factors (such as IGF and EGF) to their receptors activates PI3K^[19]. PI3K subsequently produces the lipid second messenger PIP3b (phospho-inositol triphosphate), which in turn activates the serine/threonine kinase AKT. Activated AKT also phosphorylates several cytoplasmic proteins, most notably mTOR and BCL-2-associated death promoter^[19]. The activation of mTOR increases cellular proliferation, and inactivation of BAD decreases apoptosis and increases cell survival^[21]. In normal tissue, this pathway is negatively regulated by the tumor suppressor phosphatase on chromosome 10 [phosphatase and tensin homolog (PTEN)], which targets the lipid products of PI3K for dephosphorylation^[21].

Expression of both IGF and the IGF receptor is up-regulated in HCC and cirrhotic liver, resulting in stimulation of the PI3K/AKT/mTOR signaling pathway in addition to activation of the RAF/MEK/ERK and WNT/ β -catenin pathways^[33,34]. Anomalies in PTEN function may lead to overactivation of the PI3K/AKT/mTOR pathway in HCC. PTEN expression is reduced in nearly half of all HCC tumors, resulting in constitutive

activation of the PI3K/AKT/mTOR pathway^[35]. Decreased PTEN expression has been shown to correlate with increased tumor grade, advanced disease stage and reduced overall survival (OS) in patients with HCC^[35]. In a mutation analysis of HCC samples, activation of the IGF pathway, upregulation of EGF, dysregulation of PTEN, and aberrant mTOR signaling were present in half of the samples; inhibition of mTOR activity with a rapamycin analog (everolimus) was effective in improving survival and suppressing recurrence^[36]. These results suggest that mTOR pathway activation plays a crucial role in the pathogenesis of HCC (Figure 2).

The PI3K inhibitor RG7321 and the Akt inhibitor perifosine target the PI3K/Akt/mTOR pathway and are in early stages of clinical development. The mTOR inhibitors everolimus (RAD001), sirolimus (Rapamune) and temsirolimus (CCI-779) have been studied for efficacy and safety in patients with advanced HCC. Everolimus has produced a median progression-free survival (PFS) of 3.8 mo and OS of 8.4 mo in phase I / II testing in patients with advanced HCC^[37]. A phase III study to compare everolimus and placebo and a phase I / randomized phase II study (sorafenib + everolimus *vs* sorafenib alone) to test the efficacy and tolerance of sorafenib in combination with everolimus are underway (NCT01035229). In a phase II study of sirolimus in patients with advanced HCC, sirolimus exhibited some antitumor activity in patients with advanced HCC^[38]. However, larger studies are required to determine the value of this agent.

Temsirolimus, an mTOR inhibitor, has been approved for the treatment of advanced renal cell carcinoma. The efficacy and potential utility of this agent in HCC is currently under investigation (NCT01079767).

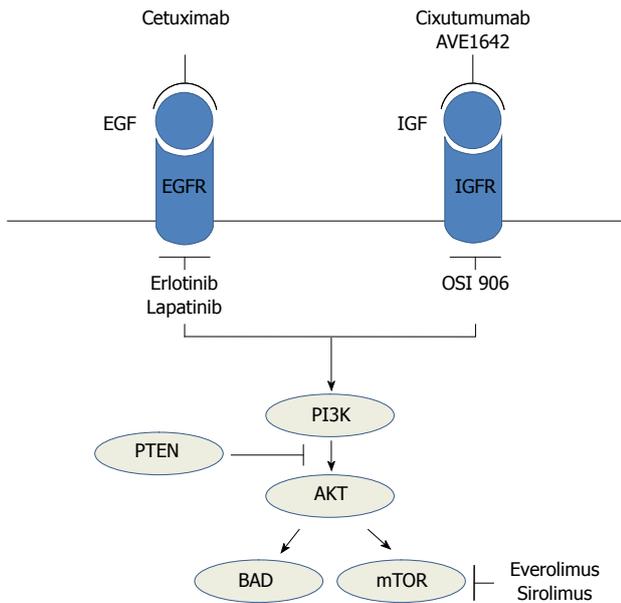


Figure 2 PI3K/Akt/mTOR pathway and the molecular agents targeting this pathway. BAD: BCL-2-associated death promoter; EGF: Epidermal growth factor; EGFR: EGF receptor; IGFR: Insulin-like growth factor (IGF) receptor; mTOR: Mammalian target of rapamycin; PTEN: Phosphatase and tensin homolog; PI3K: Phosphatidylinositol-3-kinase.

VEGF/VEGFR, PDGFR, AND FGFR

Normal angiogenesis is maintained by a balance between proangiogenic and anti-angiogenic factors^[39]. The angiogenic balance is disturbed in HCC. Angiogenesis is important for HCC growth and metastasis and occurs as a result of complex alterations that involve promoting factors [such as VEGF, angiopoietin and fibroblast growth factor (FGF), inhibitory factors, including thrombospondin (TSP) and angiostatin], and the surrounding tissue. A number of angiogenic growth factors, including VEGF-A, angiopoietin-2 and PDGF, have been shown to be upregulated in HCC tumors at the gene expression level and plasma protein level in patients with HCC compared with cirrhotic patients^[40]. The principal angiogenic factors involved are VEGFs, PDGFs, TGF- α and - β , basic FGF, EGF, hepatocyte growth factor (HGF), angiopoietins and interleukin-4 and -8^[39,41]. These growth factors and cytokines induce angiogenic signaling through a variety of mechanisms, including activation of the RAF/MEK/ERK, PI3K/AKT/mTOR and JAK/signal transducer and activator pathways.

Increased VEGF expression has been reported in cirrhotic and dysplastic liver tissue, suggesting a possible role for VEGF-mediated angiogenesis in hepatocarcinogenesis^[42]. VEGF clearly plays an important regulatory role in HCC; high levels of VEGF expression have been linked with HCC tumor grade, poor outcome after resection, disease recurrence, poor disease-free survival (DFS) and OS, vascular invasion and portal vein emboli^[43-46]. Expression of FGF-2 is also elevated in patients with HCC, and FGF-2 expression in HCC correlates with

tumor microvessel density and postoperative recurrence rate^[47-49]. Tumor angiogenin expression correlates with microvascular density in patients with HCC, and high serum angiogenin levels are associated with decreased survival at 5 years^[50].

The VEGF pathway can be targeted through two approaches: anti-VEGF monoclonal antibodies or inhibitors of the receptor tyrosine kinase associated with VEGFR. The anti-VEGF monoclonal antibody bevacizumab was the first angiogenesis inhibitor to be approved as an antineoplastic agent. Bevacizumab has shown encouraging early evidence of efficacy in patients with advanced HCC^[51,52]. The combination of bevacizumab with either cytotoxic agents (gemcitabine, oxaliplatin, and capecitabine) or erlotinib has also shown encouraging results in four phase II trials in patients with advanced HCC^[53-56].

Sorafenib is an orally available multikinase inhibitor that was originally designed to target VEGFR-1, -2, -3, PDGFR and c-kit. In a phase II study of patients with advanced inoperable HCC, sorafenib induced a PR in 2% of the patients. The median time to progression (TTP) was 4.2 mo and median OS was 9.2 mo^[57]. In the phase III SHARP (Sorafenib HCC Assessment Randomized Protocol) trial, sorafenib (400 mg twice daily) significantly prolonged OS compared with placebo in patients with advanced HCC (10.7 mo in the sorafenib group *vs* 7.9 mo in the placebo group)^[58]. The median time to radiological progression was significantly longer in the sorafenib group (5.5 mo *vs* 2.8 mo). In another randomized phase III study performed in the Asia-Pacific region, the OS was 6.5 mo in the sorafenib group compared with 4.2 mo in the placebo group (the hazard ratio in the sorafenib group was 0.68, $P = 0.014$)^[59]. Sorafenib is the only targeted therapy to have been approved for clinical use in several countries, including the United States and in Europe. Although sorafenib improved OS in patients with HCC, the associated toxicities may significantly affect patients' quality of life. High rates of dermatologic side effects have commonly been reported with sorafenib, the most clinically significant of which is hand-foot skin reaction^[60]. Despite initial responses to sorafenib, most HCC patients experience a loss of efficacy. No effective second-line treatment options currently exist for patients who are resistant or refractory to and/or intolerant of sorafenib.

Beyond sorafenib, sunitinib is the most studied multikinase inhibitor targeting VEGFR-1 and VEGFR-2. Sunitinib also displays inhibitory activities against other receptor tyrosine kinases, including PDGFR-a/b, c-KIT, FLT3, and RET kinases. Sunitinib is currently indicated for the treatment of renal cell carcinoma and gastrointestinal stromal tumors^[61-63]. Two phase II studies of sunitinib in patients with advanced HCC have been performed. In the first study, the PR rate was 2.9%, and 50% of the patients achieved stable disease^[64]. In a second phase II study, one (2.7%) patient experienced a confirmed PR and 13 (35%) of 37 patients achieved stable

disease^[65]. A phase III study comparing sunitinib with sorafenib (NCT00699374) was discontinued due to a greater incidence of adverse events in the sunitinib group and because sunitinib failed to demonstrate superiority or non-inferiority to sorafenib in extending the survival of patients with advanced HCC.

Brivanib is a dual inhibitor of VEGFR and fibroblast growth factor receptor signaling pathways. Because FGF signaling may contribute to acquired “resistance” or compensatory signaling during anti-VEGFR therapy, the simultaneous inhibition of these 2 pathways by brivanib may both delay initial progression in response to antiangiogenic therapy (as first-line treatment) and successfully treat tumors that have already progressed during the course of anti-VEGFR therapy (as second-line treatment)^[66,67]. Brivanib has demonstrated a disease control rate of 51% and an OS of 10 mo as first-line monotherapy in a phase II trial of predominantly Asian patients with HCC^[68]. In another phase II trial of brivanib in patients with HCC who had been treated with sorafenib, brivanib caused a tumor response rate of 4.3% and disease control rate of 45.7%^[69].

Large randomized phase III Brivanib Study in Patients at Risk (BRISK) HCC program trials have been conducted to evaluate the role of brivanib in advanced HCC (BRISK-FL, BRISK-PS and BRISK-APS). The BRISK-PS trial evaluated brivanib *vs* placebo in patients who had failed or were intolerant to sorafenib therapy (NCT00825955). This study did not meet its primary end point of improving OS, but treatment with brivanib showed improvements in the response rate^[70]. The BRISK-FL trial (NCT00858871) directly compared the clinical outcomes of brivanib *vs* sorafenib in patients with advanced HCC who received no prior systemic therapy. The median OS was 9.5 mo in the brivanib arm compared with 9.9 mo in the sorafenib arm, which was not a statistically significant difference. No significant survival differences were observed between subgroups based on geographic regions, cause of HCC or disease severity. The study did not meet its primary OS objective based upon a non-inferiority statistical design^[71].

Vatalanib (PTK787) is a potent tyrosine kinase inhibitor that binds directly to the ATP-binding sites of VEGF receptors. Vatalanib inhibits both Flt-1 and Flk-1/KDR and other class III receptor tyrosine kinases, such as PDGFR- β , Flt-4, c-kit, and c-fms^[72]. In a phase I / II study of vatalanib combined with doxorubicin in patients with advanced HCC, the overall response rate was 26.0%, with all of the responding patients achieving PR. Another 20% of the patients achieved SD for at least 12 wk^[73].

Linifanib (ABT-869) is a novel receptor tyrosine kinase inhibitor with potent activity against members of the VEGFR and PDGFR families^[74]. In a phase II study of linifanib in advanced HCC, the estimated objective response rate was 9.1%, the median time to disease progression was 3.7 mo, and the median OS was 9.7 mo^[75]. An open-label, randomized phase III study of the efficacy

and tolerability of linifanib *vs* sorafenib in advanced HCC (NCT01009593) was conducted. The OS of linifanib given as monotherapy once daily was similar to sorafenib given twice daily per standard of care^[76].

TSU-68 is an oral tyrosine kinase inhibitor of FGFRs, VEGFRs and PDGFR and has demonstrated some clinical efficacy in a phase I / II trial of heavily pretreated patients with advanced HCC. Treatment of patients with unresectable or metastatic HCC with TSU-68 was associated with disease stabilization or improvement in 51% of the patients^[77]. A randomized placebo-controlled phase III trial in Japan, South Korea and Taiwan is currently recruiting patients with unresectable HCC and will evaluate transcatheter arterial chemoembolization (TACE) in combination with either TSU-68 or placebo.

Cediranib (AZD2171) is another selective inhibitor of VEGFR-1, -2 and -3. Cediranib also exhibits activity against c-kit, PDGFR- β , and FLT4 at nanomolar concentrations. In a phase II clinical study of advanced HCC, the median OS was 5.8 mo. No patients experienced confirmed response. The median time to progression was 2.8 mo^[78].

EGFR, IGF AND HGF/c-MET SIGNALING

EGFR, a member of the human epidermal growth factor receptor (HER) family, contains an intracellular tyrosine kinase domain which can trigger signal transduction through the MAPK and PI3K/Akt/mTOR pathways. Thus, these receptors contribute to cell growth, differentiation, survival and adhesion^[79]. EGFR overexpression has been reported in HCC. Immunohistochemical analysis by Buckley *et al*^[80] revealed that EGFR was overexpressed in 50 (66%) of 76 HCCs, and fluorescence *in situ* hybridization (FISH) showed additional *EGFR* gene copies in 17 (45%) of 38 HCCs. EGFR-targeting drugs include anti-EGFR antibodies (such as cetuximab and panitumumab) and inhibitors of EGFR tyrosine kinases (such as erlotinib, lapatinib and gefitinib); these drugs have been used widely for the treatment of HCC.

Cetuximab is a recombinant chimeric monoclonal antibody that targets the extracellular domain of EGFR. In a phase II clinical trial of cetuximab in patients with advanced HCC, the median OS was 9.6 mo and the median PFS was 1.4 mo. The treatment was generally well tolerated. No treatment-related grade 4-5 toxicities occurred. Grade 3 aspartate aminotransferase, hypomagnesemia, and fever without neutropenia were each noted in 1 patient^[81]. A randomized trial comparing gemcitabine-oxaliplatin (GEMOX) alone with a GEMOX-cetuximab combination is ongoing to define the real contribution of anti-EGFR therapy.

Erlotinib is a potent and reversible inhibitor of EGFR tyrosine kinase. In an *in vitro* study, erlotinib potentially suppressed the growth of human EGFR-expressing HCC cell lines. Erlotinib has been shown to inhibit the RAF/MEK/ERK signaling pathway and block signal

transducer and activator of transcription-mediated signaling^[82]. A phase III placebo-controlled, double-blind SEARCH (Sorafenib and Erlotinib, a Randomized Trial Protocol for the Treatment of Patients with HCC) trial has been conducted in patients with advanced HCC. Three hundred sixty-two patients received sorafenib plus erlotinib and 358 received sorafenib plus placebo. No significant differences were observed in OS or TTP between the arms. Erlotinib, when added to sorafenib as the standard of care in advanced HCC, did not prolong overall survival^[83].

Lapatinib is a dual inhibitor of EGFR and HER-2/NEU that acts by docking into the ATP binding site of the two receptors^[84]. Phase II results have indicated that lapatinib is well tolerated and have shown preliminary evidence of antitumor activity in HCC^[85]. Among 40 patients with advanced HCC, the response rate was 5%, median PFS was 2.3 mo and median OS was 6.2 mo.

The IGF/IGFR signaling pathway regulates several cellular processes, including proliferation, motility and inhibition of apoptosis^[86]. Ligand binding to IGF-1R triggers rapid receptor autophosphorylation, which in turn initiates downstream cellular effectors, ultimately leading to activation of PI3K, protein kinase B and the RAF/MEK/ERK pathway^[87]. In HCC, dysregulation of IGF signaling occurs predominantly at the level of IGF-2. IGF-2 is overexpressed in 16%-40% of human HCCs, and IGF-2R (an alternative receptor for IGF-2) is underexpressed in approximately 80% of HCCs^[88,89]. Associations have been reported between disease stage, metastasis and survival and the functions of IGF and IGFR in HCC^[90,91]. Several strategies to target this system, including monoclonal antibodies against the IGF-1 receptor (IGF-1R) and small molecule inhibitors of the tyrosine kinase function of IGF-1R, are under active investigation.

Pre-clinical evidence obtained from HCC cells has shown that IMC-A12 (cituxumumab), a human monoclonal antibody that blocks IGF-1R. A phase I study of IMC-A12 yielded a partial response in HCC^[92]. However, a subsequent phase II study in patients with advanced HCC showed that IMC-A12 is inactive as a monotherapy^[93]. Up to 46% of the patients developed grade 3-4 hyperglycemia in this study. Hyperglycemia may be the dose limiting toxicity of IGF-1R monoclonal antibodies.

BIIB022 is an anti-IGF-1R monoclonal antibody that blocks binding of both IGF-1 and IGF-2 to IGF-1R. This agent does not appear to cause hyperglycemia, which is a common side effect of receptor-specific antibodies. A planned phase I / II study comparing sorafenib with or without BIIB022 in patients with advanced HCC was terminated due to a business decision by the sponsor company.

AVE1642 is another monoclonal antibody that specifically blocks IGF-1R signaling. This agent has been evaluated in combination with sorafenib in a phase I study in advanced HCC patients^[94]. Long-lasting disease stabilization was observed in most patients with PD.

OSI-906 is a novel potent dual tyrosine kinase inhibitor of both IGF-1R and insulin receptor. The unique advantage of OSI-906 over the previous class of anti-IGF drugs is its ability to minimize IGF-2 activity in situations in which IGF-1R inhibition alone is not sufficient. The phase II study of second-line treatment for advanced HCC patients who failed first-line treatment with sorafenib (NCT01101906) was terminated because the sponsor decided not to pursue the development of this drug.

The HGF/Met pathway is involved in tumor growth, invasion and angiogenesis in various types of cancer^[95]. c-Met is a tyrosine kinase receptor for the HGF ligand. HGF-induced activation of c-MET ultimately leads to the activation of downstream effector molecules, including phospholipase C, PI3K and ERK^[96]. c-MET overexpression has been observed in 20%-48% of HCC, and overexpression has been linked with decreased 5-year survival in patients with HCC (Figure 3)^[97-99].

Tivantinib (ARQ 197) is a selective, oral MET receptor tyrosine kinase inhibitor with broad-spectrum antitumor activity as single agent. MET overexpression has been shown to be a negative prognostic factor in HCC after sorafenib failure. Tivantinib demonstrated a nearly doubling of PFS and OS in the MET high group compared to placebo in a phase II study as second-line treatment in patients with advanced HCC^[100]. The activity of tivantinib in combination with sorafenib is also promising. Adverse events include hematological toxicity, asthenia and loss of appetite. The initially high incidence of neutropenia in patients with HCC led to dose reduction from 360 mg *bid* to 240 mg *bid*. Currently, a pivotal phase III study in advanced, MET-high HCC after sorafenib failure is planned.

WNT-BETA-CATENIN PATHWAY

A major and early carcinogenic event in the development of HCC seems to be the abnormal regulation of the transcription factor β -catenin, a key component of the WNT signaling pathway.

During normal cell homeostasis, Wnt proteins are absent. Initiation of Wnt signaling leads to a series of events that cause loss of β -catenin phosphorylation, which prevents its degradation. β -catenin then accumulates in the cytoplasm and translocates into the nucleus. Hepatocytes with nuclear translocation of β -catenin display abnormal cellular proliferation and express membrane proteins involved in HCC, metastatic behavior, and cancer stem cells^[101]. A high incidence of β -catenin mutations (nearly 40%) has been observed in HCC cases that occur in patients with HCV. HCC cases that occur in HBV patients display β -catenin activation that is induced in a mutation-dependent manner by the expression of HBx protein^[102,103]. Agents targeting Wnt- β -catenin are under development. Preliminary studies targeting the Wnt- β -catenin pathway have demonstrated a potential space for new novel therapies to treat HCC.

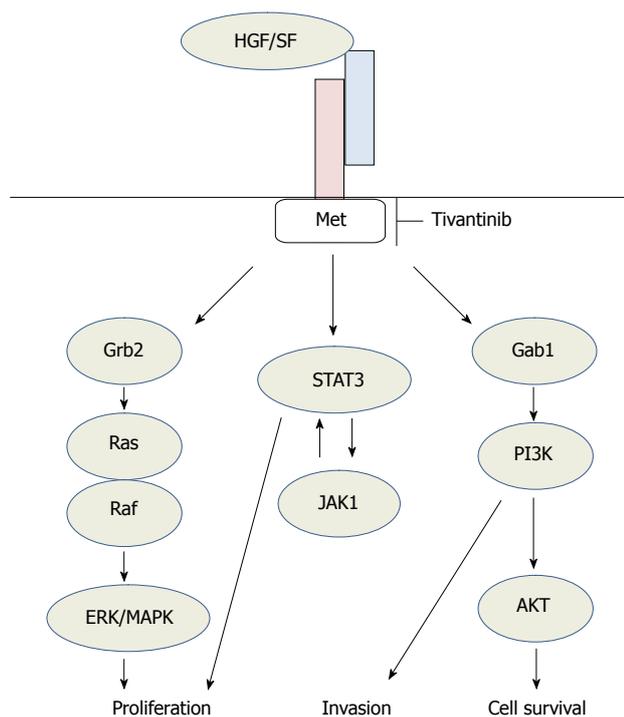


Figure 3 The c-Met signaling pathway suggested in hepatocellular carcinoma. Gab1: GRB2-associated binding protein 1; Grb2: Growth factor receptor-bound protein 2; HGF/SF: Hepatocyte growth factor/scatter factor; JAK1: Janus kinase 1; Met: Met proto-oncogene; PI3K: Phosphatidylinositol-3-kinase; STAT3: Signal transducer and activator of transcription 3; ERK: Extracellular signal-regulated kinase.

JAK/STAT PATHWAY

The Jak/Stat pathway is activated by more than 40 cytokines and growth factors and is involved in multiple cell functions, including differentiation, proliferation, and apoptosis^[104]. In this pathway, cytokines induce phosphorylation of the Janus tyrosine kinases (Jak1, 2 and 3 and Tyk2), which is followed by activation of Stat1-6^[105]. The phosphorylation of Jak1, Jak2, and Tyk2 tyrosine kinases is not detected in normal livers but increases significantly between surrounding non-neoplastic liver and HCCs^[106]. Activation of Stat1, Stat3, and Stat5 has been shown to be significantly higher in tumors than in the respective surrounding livers; pStat3 is higher in HCC with poor prognosis than in HCC with better prognosis^[106]. The levels of Jak/Stat targets, including Bcl-xl, Mcl-1, cyclin D1, and c-Myc, are markedly elevated in the majority of HCCs. A phase I study of the JAK2 inhibitor AZD1480 in advanced solid malignancy (including HCC) is planned (NCT01219543).

FUTURE PERSPECTIVES

Molecular targeted agents that have been introduced into clinical use in recent years have been approved for the treatment of a specific cancer and then frequently used to treat various other types of cancer (Table 1). Genetic alterations clearly play a major role in hepatocarcinogenesis, and abnormalities in several critical molecular

Table 1 Molecular targets and therapeutic agents

Molecular targets	Therapeutic agents
VEGF/VEGFR	Sorafenib
	Bevacizumab
	Vatalanib (PTK787)
	Cediranib (AZD2171)
	Brivanib
	Sunitinib
EGF/EGFR	Linifanib (ABT869)
	Cetuximab
IGF/IGFR	Erlotinib
	Lapatinib
	OSI-906
Ras/Raf/MEK/ERK	IMC-A12
	AVE1642
	BIIB022
	Sorafenib
PI3K/Akt/mTOR	Selumetinib (AZD6244)
	AZD8055
	Everolimus
Wnt-β-catenin	Sirolimus
	Temsirolimus
	PFK118-310
	PFK115-584
MET	CGP049090
	Tivantinib

EGF: Epidermal growth factor; EGFR: EGF receptor; ERK: Extracellular signal-regulated kinase; FGFR: Fibroblast growth factor receptor; IGFR: Insulin-like growth factor (IGF) receptor; VEGF: Vascular endothelial growth factor; VEGFR: VEGF receptor; mTOR: Mammalian target of rapamycin; MET: Met proto-oncogene.

signaling pathways have been identified as contributing to tumor development and progression^[107,108].

Currently, sorafenib is the only effective systemic treatment option for advanced HCC. While the drug is effective for patients with advanced HCC, sorafenib prolongs life expectancy for only approximately three mo. To move beyond sorafenib monotherapy, a potential role for this agent in the adjuvant setting following surgical resection, radiofrequency ablation, or TACE or in combination with other targeted agents or chemotherapy is under investigation.

Several new promising multi-targeted molecules have been developed and are currently under investigation for the treatment of HCC (Table 2). Unfortunately, HCCs are refractory to many targeted therapies. Therefore, resistance to treatment remains the major challenge for targeted therapy. Many resistance mechanisms have been identified, including epigenetic changes, alternative splicing, target inactivation, upregulation of alternative pathways (by cellular adaptation to the pathway being targeted), and a range of mutations. A combination of different agents or a single “unspecific” inhibitor of several pathways may offer advantages to overcome resistance. Combinations of targeted agents with chemotherapy regimens also remain to be further explored. Molecular targeted therapy blocking angiogenesis has demonstrated somewhat promising results, but the efficacy of these agents is limited by survival pathways induced by hypoxia. Thus, the inhibition of hypoxia-induced survival signals

Table 2 Efficacy results of targeted therapies for advanced hepatocellular carcinoma

Molecular targets/agents	Phase	Efficacy	Ref.
VEGF/VEGFR Sorafenib	Phase III SHARP Sorafenib <i>vs</i> placebo	Median OS: 10.7 mo <i>vs</i> 7.9 mo	[58]
Sunitinib	Phase III (Asian) Phase II	Median OS: 6.5 mo <i>vs</i> 4.2 mo Median PFS: 3.9 mo	[59] [65]
	Phase III Sunitinib <i>vs</i> sorafenib	Median OS: 9.8 mo Median OS: 7.9 mo <i>vs</i> 10.2 mo	
Brivanib	Phase II, first-line	Median PFS: 2.8 mo Median OS: 10 mo	[68]
	Phase II, second-line	Median PFS: 2.7 mo Median OS: 9.8 mo	[69]
	Phase III (BRISK-PS) Brivanib <i>vs</i> placebo	Median OS: 9.4 mo <i>vs</i> 8.3 mo TTP: 4.2 mo <i>vs</i> 2.7 mo RR: 12% <i>vs</i> 2%	[70]
	Phase III (BRISK-FL) Brivanib <i>vs</i> placebo	Median OS: 9.5 mo <i>vs</i> 9.9 mo TTP: 4.2 mo <i>vs</i> 4.1 mo RR: 12% <i>vs</i> 8%	[71]
Vatalanib (PTK787)	Phase I / II, combined with doxorubicin	OS: 7.3 mo PFS: 5.4 mo	[73]
Inifanib (ABT-869)	Phase II	TTP: 3.7 mo Median OS: 9.7 mo	[75]
Cediranib (AZD2171)	Phase II	Median OS: 5.8 mo TTP: 2.8 mo	[78]
EGF/EGFR Cetuximab	Phase II	Median OS: 9.6 mo Median PFS: 1.4 mo	[81]
Erlotinib	Phase III (SEARCH) Sorafenib/erlotinib <i>vs</i> orafenib/placebo	Median OS: 9.5 mo <i>vs</i> 8.5 mo TTP: 3.2 mo <i>vs</i> 4.0 mo	[83]
Lapatinib	Phase II	Median PFS: 2.3 mo Median OS: 6.2 mo	[85]
	Phase III Lipatinib <i>vs</i> sorafenib	Median OS: 9.1 mo <i>vs</i> 9.8 mo	
IGF/IGFR Cituxumumab (IMC-A12)	Phase II	Median OS: 8 mo	[93]
Ras/Raf/MEK/ERK Selumetinib (AZD6244)	Phase I / II	11 patients enrolled PR in 3, SD in 6, PD in 2 patients	[31]
PI3K/Akt/mTOR Everolimus	Phase I / II	Median PFS: 3.8 mo Median OS: 8.4 mo	[37]
Sirolimus	Phase II	Median PFS: 15.3 wk Median OS: 26.4 wk	[38]
MET Tivantinib	Randomized Phase II Tivantinib <i>vs</i> placebo ITT population c-Met high	Median TTP: 6.9 wk <i>vs</i> 6.0 wk Median OS: 6.6 mo <i>vs</i> 6.2 wk Median TTP: 11.7 wk <i>vs</i> 6.1 wk Median OS: 7.2 mo <i>vs</i> 3.8 wk	[100]

ITT: Intent to treat; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; PR: Partial response; RR: Response rate; SD: Stable disease; TTP: Time to progression; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; mTOR: Mammalian target of rapamycin; PI3K: Phosphatidylinositol-3-kinase; Met: Met proto-oncogene; EGFR: Epidermal growth factor (EGF) receptor.

might be required for targeted agents to block angiogenesis as an adjuvant therapy following TACE. Additionally, exploring potential markers that can help in identifying the patients who are most likely to respond (or to at least identify those who will not respond) to treatment is critical. Future development of genomic analysis of HCC will aid in the identification of specific biomarkers for patient selection for either single agent or combination molecular targeted therapies.

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