

# Emerging Targeted Strategies in Advanced Hepatocellular Carcinoma

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## Abstract

Treatment of advanced-stage hepatocellular carcinoma (HCC) remains a challenge because of the complex nature of the disease and the lack of available therapies. The antiangiogenic multikinase inhibitor sorafenib is the first therapy to demonstrate a significant overall survival benefit in advanced HCC. However, new agents for both first- and second-line treatment of advanced HCC are needed. The multiple pathways involved in HCC oncogenesis, proliferation, and survival provide many opportunities for the development of molecularly targeted therapies. Many novel agents are under investigation in phase III trials in advanced HCC, including antiangiogenic multikinase inhibitors (e.g., brivanib, sunitinib, linifanib) and inhibitors of the mammalian target of rapamycin (mTOR) pathway (e.g., everolimus). Although these therapies have demonstrated some utility as single agents in advanced HCC, rational combinations of therapies are likely to provide greater success. Current research efforts are directed at combining agents targeting different molecular pathways (e.g., sorafenib in combination with erlotinib) and combining molecularly targeted agents with systemic chemotherapy or transarterial chemoembolization (TACE). Therapies targeting other molecular pathways in HCC are in early development; future research will focus on discovering additional targets for therapy and identifying biomarkers that predict the success of current therapies.

## Keywords

- ▶ hepatocellular carcinoma
- ▶ brivanib
- ▶ angiogenesis inhibition
- ▶ mTOR inhibition
- ▶ combination therapy

Hepatocellular carcinoma (HCC) is a complex and heterogeneous malignancy that arises in the context of progressive underlying liver dysfunction. Given the asymptomatic nature of early disease and the limited use of surveillance, the majority of HCC cases present at advanced or incurable stages. The prognosis of advanced-stage HCC is poor, with an overall survival (OS) rate of < 5%,<sup>1</sup> and in earlier stages, 5-year recurrence rates of over 70% have been reported despite surgical or locoregional therapies.<sup>2–4</sup> The treatment options for patients with recurrent or de novo advanced HCC are limited, and until recently there were no systemic treatment options that provided a clear survival benefit for these patients. Systemic chemotherapy and hormone therapies have not been effective in HCC, partly owing to the inherent hepatic dysfunction and the chemoresistance of the tumor.<sup>5,6</sup> However, in the last decade, a better understanding of the

molecular pathogenesis of HCC has led to the evaluation of molecular targeted therapies in this setting. Although the exact molecular mechanisms for hepatocarcinogenesis have still not been defined, angiogenesis has been found to have an integral role in HCC pathogenesis, making this a rational therapeutic target in this disease.

Sorafenib is an antiangiogenic multikinase inhibitor that targets the vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor- (PDGFR-)  $\beta$ , RAF kinase, and stem cell factor receptor (c-kit). It was the first systemic therapy to demonstrate a significant improvement in OS in patients with advanced HCC. Two positive pivotal phase III trials (the Sorafenib HCC Assessment Randomized Protocol [SHARP] trial and the Asia-Pacific trial), and its subsequent approval represent a major breakthrough in the treatment of advanced HCC.<sup>7,8</sup> However,

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given the limitations of sorafenib therapy, such as resistance and tolerability, there are still unmet medical needs in the treatment of HCC. Our knowledge of the diverse etiologies and the genetic heterogeneity of HCC and the multiple molecular pathways implicated in HCC pathogenesis are now being evaluated as potential targets for therapeutic interventions, including the VEGF, fibroblast growth factor (FGF), PDGFR, epidermal growth factor receptor (EGFR), and mammalian target of rapamycin (mTOR) pathways. This review will examine our current understanding of these pathways, the efficacy and safety data pertaining to the most promising targeted agents beyond sorafenib, and novel treatment combinations in clinical testing for HCC. There are many other novel agents and targets in development, including histone deacetylase inhibitors (HDAC), c-Met inhibitors, MEK kinase inhibitors, insulin-like growth factor receptor (IGFR), arginine deiminase, and the anti-VEGF monoclonal antibody bevacizumab. In this article, we will focus on those agents currently in advanced phase III trials.

### Signaling Pathways Involved in HCC Pathogenesis

Hepatocellular carcinoma is a highly vascularized tumor, and the central role of angiogenesis in its initiation, growth, and subsequent dissemination to other tissues is well recognized. Angiogenesis in HCC is dependent on endothelial cell activation, proliferation, and migration, which occur in response to angiogenic cues (e.g., hypoxia and inflammation) and involves several molecular effectors such as growth factors, extracellular matrix proteins, and proteases.<sup>9,10</sup> Vascular endothelial growth factor and its receptors are known to be key mediators of HCC neovascularization, primarily through their stimulation of endothelial cell growth and induction of vascular permeability.<sup>9,10</sup> Supporting the major role of VEGF in hepatocarcinogenesis are reports of its increased expression from low-grade to high-grade dysplastic nodules to early HCC, which correlates directly with increased neoangiogenesis and cell proliferation activity.<sup>11</sup> Additionally, high serum levels of VEGF have been shown to significantly correlate with advanced tumor stage, recurrence of HCC following resection, and presence of intrahepatic metastasis and venous invasion.<sup>12</sup> Overexpression of VEGF and its receptors in tumor tissue is also reportedly associated with worse OS and recurrence-free survival after surgical resection.<sup>13–15</sup> Similarly, a prospective study showed that pretreatment serum elevations in VEGF were associated with progressive disease and poor survival in patients with inoperable HCC who underwent transarterial chemoembolization (TACE) treatment.<sup>16</sup>

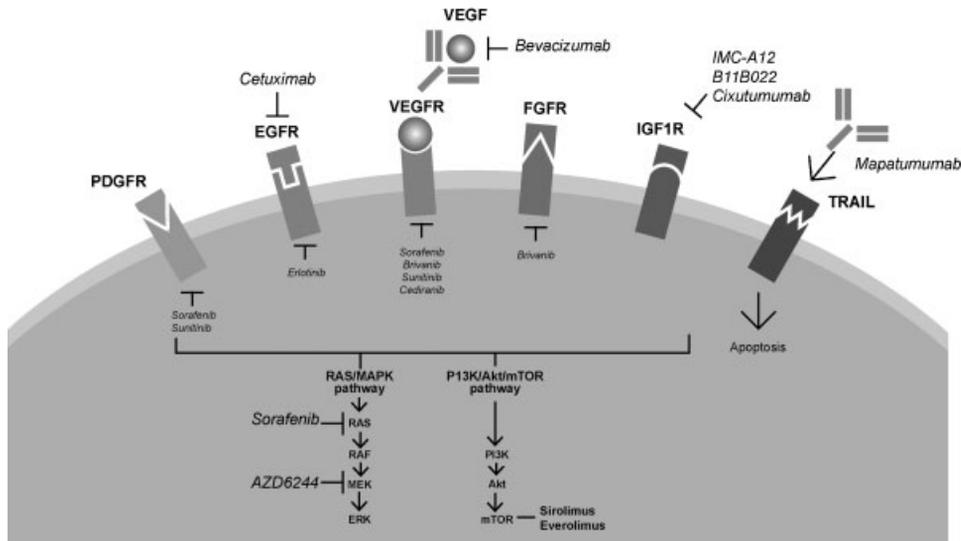
In addition to the VEGF pathway, FGF and its family of receptors have been implicated also in augmenting HCC growth, invasion, and angiogenesis, making it an attractive candidate for therapeutic intervention.<sup>17</sup> Activation of the FGF pathway induces neovascularization through various mechanisms, including stimulation of endothelial cell proliferation, migration, invasion, and capillary formation.<sup>18,19</sup> Increased serum levels of FGF and concomitant activation of FGF receptors are associated with tumor invasion and

recurrence, treatment resistance, and poor prognosis in HCC.<sup>20,21</sup> Synergistic interactions between FGF and VEGF have been shown to drive HCC development and angiogenesis.<sup>22,23</sup> Compelling evidence indicates that induction of the FGF signaling pathways might represent a resistance mechanism to the antiangiogenic effects of VEGF-targeted agents in HCC.<sup>23,24</sup> In addition, alterations in ligand expression has been identified as a potential driver in HCC.<sup>25</sup> Together, these data indicate that concomitant inhibition of both the VEGF and FGF pathways might be more efficient at controlling disease and overcoming resistance to anti-VEGF therapies than targeting either factor alone.

Several other signaling pathways have been shown to be involved in HCC pathogenesis; the most studied are the phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR, EGFR, Ras/Raf/mitogen-activated protein kinase/ERK kinase (MEK)/extracellular-signal-regulated kinase (ERK), and IGFR pathways.<sup>26</sup> The PI3K/Akt/mTOR pathway is a major intracellular signaling cascade that is involved in the regulation of cell growth, proliferation, and survival.<sup>27</sup> Mammalian target of rapamycin is a potent inducer of angiogenesis through upregulation of the hypoxia-induced gene HIF1- $\alpha$ .<sup>28</sup> The mTOR pathway mediates its effects through activation of various tyrosine kinase receptors, such as VEGFR, EGFR, PDGFR, and IGFR.<sup>29</sup> Nearly 50% of patients with HCC have shown activation of the mTOR pathway, which may be partially attributable to activation signals from receptor tyrosine kinases such as IGFR and/or EGFR pathways.<sup>30</sup> The activation of the mTOR pathway in HCC is associated with aggressive tumor behavior and decreased survival, supporting efforts to target this pathway for therapeutic interventions.<sup>31</sup> The Ras/Raf/MEK/ERK signaling cascade is another important intracellular pathway. Ras activation and subsequent downstream signaling may be mediated by hepatitis C virus (HCV) infection. As Raf is a potential target for sorafenib, this observation may be another explanation for sorafenib's clinical activity in HCC.<sup>32,33</sup> In addition, the aberrant activation of the Wnt pathway may also play a role in HCC pathogenesis and is another potential target in HCC.<sup>34</sup>

cMET is a tyrosine kinase receptor, with its ligand hepatocyte growth factor (HGF), that has been implicated in liver cancer. Most recently, randomized phase II data of the cMET inhibitor, tivantinib, has demonstrated activity in a subset of patients with advanced HCC that have progressed on sorafenib and had elevated expression of cMET by immunohistochemistry.<sup>35</sup>

There has been considerable interest in targeting peptide growth factor signaling via the EGFR and IGFR axis, which is suggested by elevated levels of these receptors in HCC.<sup>36,37</sup> The increasing awareness of the association of insulin resistance, diabetes, obesity, and nonalcoholic steatohepatitis (NASH) in the development of cirrhosis and HCC also is evidence that the IGFR pathway might have a causal role in this process.<sup>38</sup> Given the molecular heterogeneity of HCC, the challenge is identifying in which patients any given alteration is critical. It is unlikely that any of these targeted agents will yield clinical success without selecting the patients whose tumors are most dependent on these pathways and therefore



**Fig. 1** Molecular targets and targeted agents in hepatocellular carcinoma.<sup>39</sup> EGFR, epidermal growth factor receptor; ERK, extracellular-signal-regulated kinase; FGFR, fibroblast growth factor receptor; HCC, hepatocellular carcinoma; MEK, mitogen-activated protein kinase/ERK kinase; mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor receptor; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor. (Reprinted with permission from Siegel B et al. *Hepatology* 2010;52:360–369. Copyright John Wiley and Sons).

most likely to benefit, and the identification of predictive markers of response is essential for successful development of new targeted agents.

### Emerging Molecular Therapies in Phase III Development

There are currently a historic number of investigational agents being tested in HCC, most of which are targeting the previously described VEGF axis, FGF, EGFR, and mTOR signaling pathways (►Fig. 1).<sup>39</sup> The most recent clinical data relating to these novel agents, their combinations, and ongoing trials are outlined in ►Tables 1 and 2.<sup>35,40–65</sup>

#### Sunitinib

Similar to sorafenib, sunitinib is an oral, multitargeted inhibitor of several tyrosine kinases, such as VEGF-receptors, PDGFR, and c-KIT, which are involved in regulation of tumor growth, angiogenesis, and metastatic invasion. Sunitinib showed promising antitumor activity in phase II HCC studies, though there were significant toxicities seen, such as bone marrow suppression and a small number of grade 5 events.<sup>40,66</sup> In addition, no one consistent dosing scheme was used in these studies. With this in mind, it may not be surprising that a phase III study comparing sunitinib to sorafenib in patients with advanced HCC was terminated early due to higher incidence of drug-related serious adverse events and failure to demonstrate non-inferiority of OS benefit (median OS in the intent-to-treat population: 7.9 months vs 10.2 months; hazard ratio [HR] = 1.30; 95% confidence interval [CI], 0.99–1.30;  $p = 0.001$ ).<sup>41</sup> In an exploratory analysis, sorafenib substantially improved median OS in comparison to sunitinib in patients with HCV infection (17.6 months vs 9.2 months;

HR = 1.52; 95% CI, 1.09–2.13;  $p = 0.0165$ ), whereas in patients with HBV infection, both agents were equally effective (8.0 months vs 7.6 months; HR = 1.10; 95% CI, 0.92–1.33;  $p = 0.1714$ ).<sup>41</sup> Further analyses of this dataset are ongoing, but the increased toxicity profile of sunitinib as compared with sorafenib likely played an important role in the results.

#### Brivanib

Brivanib is a selective dual inhibitor of the FGF and VEGF receptors that is currently in late-stage clinical development. In preclinical models, brivanib was shown to decrease tumor growth and neovascularization, induce apoptosis, and decrease tumor cell proliferation.<sup>67</sup> Brivanib entered several phase III studies including testing in patients with HCC in both the first-line and second-line settings.<sup>42,68</sup> An initial phase II open-label study evaluated brivanib monotherapy in two patient cohorts with unresectable, locally advanced, or metastatic HCC; 55 patients received brivanib as first-line therapy and 46 patients received brivanib as second-line therapy (having received one prior regimen of antiangiogenic therapy). Patients that received first-line brivanib therapy had a median progression-free survival (PFS) of 2.7 months and a median OS of 10 months (►Table 1).<sup>42</sup> The disease control rate was 47%, including a complete response in 1 patient and partial responses in 3 patients; 22 patients achieved disease stabilization. As second-line therapy, brivanib therapy resulted in a tumor response rate of 4.3% (all partial responses) and a disease control rate of 45.7%. Median OS was 9.8 months and the median time to progression (TTP) was 2.7 months.<sup>68</sup> Most common grade 3/4 adverse events (AEs) were fatigue and hypertension, which were experienced by < 17% of patients, while only < 2% experienced grade 3 hand-foot skin reactions.<sup>42,68</sup>

**Table 1** Early efficacy results of novel targeted therapies in advanced development in hepatocellular carcinoma<sup>35,40–51</sup>

Agent	Phase	N	Efficacy
Tivantinib <sup>35</sup>	Randomized Phase II Tivantinib vs placebo ITT population  c-Met high	71 vs 36  22 vs 15	Median TTP: 6.9 weeks vs 6.0 weeks Median OS: 6.6 months vs 6.2 weeks Median TTP: 11.7 weeks vs 6.1 weeks Median OS: 7.2 months vs 3.8 weeks
Sunitinib	Phase II <sup>40</sup>	34	Median PFS: 3.9 months Median OS: 9.8 months
	Phase III <sup>41</sup> Sunitinib vs sorafenib	1073	Median OS: 7.9 vs 10.2 months;
Brivanib	Phase II <sup>42</sup>	55	Median PFS: 2.7 months Median OS: 10 months
	Phase III (BRISK-PS) <sup>43</sup> Brivanib vs placebo	395	Median OS: 9.4 months vs 8.3 months TTP: 4.2 months vs 2.7 months RR: 12% vs 2%
Linifanib <sup>44</sup>	Phase II	44	TTP: 5.4 months Median OS: 10.4 months
Erlotinib	Phase II <sup>45</sup>	38	Median OS: 13.0 months
	Phase II <sup>46</sup>	40	Median OS: 10.8 months
	Phase III (SEARCH) <sup>47</sup> Sorafenib/erlotinib vs sorafenib/placebo	362	Median OS: 9.5 months vs 8.5 months TTP: 3.2 months vs 4.0 months
Bevacizumab <sup>48</sup>	Phase II	46	Median PFS: 6.9 months Median OS: 12.4 months
Ramucirumab <sup>49</sup>	Phase II	42	Median PFS: 3.9 months Median OS: 14.9 months
Everolimus <sup>50</sup>	Phase I/II	20	Median PFS: 3.8 months Median OS: 8.4 months
Pegylated arginine deiminase <sup>51</sup>	II	80	Mean OS: 15.8 months

Abbreviations: ITT, intent to treat; OS, overall survival; PFS, progression-free survival.

The promising results from the phase II study prompted the BRISK (Brivanib Study in Patients at Risk) HCC program that includes four large randomized phase III trials, three of which evaluate the role of brivanib in advanced HCC (BRISK-FL, BRISK-PS, and BRISK-APS).<sup>55–57</sup> The BRISK-PS trial evaluated brivanib versus placebo in 395 patients with Child-Pugh A or Child-Pugh B HCC for which prior sorafenib therapy had failed or who were intolerant to prior sorafenib therapy (NCT00825955). Although this study did not meet its primary end point of improving OS (9.4 months vs 8.2 months; HR = 0.89; 95.8% CI, 0.69–1.15;  $p = 0.3307$ ), treatment with brivanib resulted in improvements in TTP (4.2 months vs 2.7 months; HR = 0.56; 95% CI, 0.42–0.78;  $p = 0.0001$ ) and response rate (12% vs 2%; odds ratio = 5.75; 95% CI, 1.40–23.62;  $p = 0.0032$ ), which were secondary end points of the study.<sup>43</sup> The toxicity profile of brivanib and median survival for the brivanib group were very similar to that seen in the phase II study in this population. What was surprising and unexpected in BRISK-PS was the median OS of 8.2 months in the control arm. This survival would not be expected based on data from the SHARP or Asia-Pacific sorafenib studies. Although there were some baseline imbalances in the 2:1 randomized study that favored the

control arm (significantly fewer patients with portal vein invasion versus the treatment group, 12% vs 25%, respectively), this number also reflects the changing natural history of HCC in the postsorafenib era. Similar to the BRISK-PS study, the BRISK-APS trial is evaluating second-line brivanib in 252 patients of exclusively Asian ethnicity (NCT01108705).<sup>57</sup> The BRISK-FL trial (NCT00858871) was directly comparing the clinical outcomes of brivanib versus sorafenib in 1050 patients with advanced HCC who received no prior systemic therapy.<sup>55</sup> According to a July 2012 press release, this study did not meet its primary end point of OS.<sup>56</sup>

#### Linifanib

Linifanib is a potent multitargeted receptor tyrosine kinase inhibitor that selectively blocks the activity of the VEGFR and PDGFR families. Preclinical evidence indicates that linifanib inhibits tumor angiogenesis and vascular permeability in HCC experimental models.<sup>69</sup> A phase II study was conducted in 44 patients with Child-Pugh A or Child-Pugh B liver disease to evaluate linifanib activity in advanced HCC in the first-line and second-line settings.<sup>44</sup> Thirty-four percent of patients with Child-Pugh A liver function remained progression-free

**Table 2** Phase III trials in hepatocellular carcinoma<sup>52–65</sup>

Study	Agent	Proposed accrual	Primary end point
First-line therapy			
CALGB-80802 (NCT01015833) <sup>52</sup>	Sorafenib/doxorubicin vs sorafenib	480	OS
BOOST (NCT01405573) <sup>53</sup>	Sorafenib vs placebo (Child-Pugh B only)	320	OS
Linifanib (NCT01009593) <sup>54</sup>	Linifanib vs sorafenib	900	OS
BRISK-FL <sup>a</sup> (NCT00858871) <sup>55,56</sup>	Brivanib vs sorafenib	1050	OS
Second-line therapy			
BRISK-APS (NCT01108705) <sup>57</sup>	Brivanib + BSC vs placebo + BSC	252	OS
EVOLVE-1 (NCT01035229) <sup>58</sup>	Everolimus + BSC vs placebo + BSC	531	OS
REACH (NCT01140347) <sup>59</sup>	Ramucirumab + BSC vs placebo + BSC	544	OS
POLARIS 2009–001 (NCT01287585) <sup>60</sup>	Pegylated arginine deiminase vs placebo	633	OS
Adjuvant targeted therapy following surgical resection or local ablation			
STORM (NCT00692770) <sup>61</sup>	Sorafenib vs placebo	1115	RFS
Targeted therapy in combination or following TACE			
ECOG (NCT01004978) <sup>62</sup>	Sorafenib/TACE <sup>b</sup> vs placebo/TACE	400	PFS
TACE-2 (NCT01324076) <sup>63</sup>	Sorafenib/DEB-TACE vs placebo/ DEB-TACE	412	PFS
BRISK-TA (NCT00908752) <sup>64</sup>	Brivanib vs placebo	870	OS
ORIENTAL (NCT01465464) <sup>65</sup>	Orantinib/TACE vs placebo/TACE	880	OS

Abbreviations: BSC, best supportive care; DEB-TACE, doxorubicin-eluting beads TACE; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; TACE, transarterial chemoembolization.

<sup>a</sup>Did not meet primary end point.

<sup>b</sup>TACE might comprise doxorubicin, mitomycin, and cisplatin; doxorubicin alone; or doxorubicin-eluting beads.

at 16 weeks, with median TTP and OS of 5.4 months and 9.7 months, respectively. Overall survival was comparable to the results achieved in the SHARP study (median OS: 10.7 months).<sup>8</sup> The most common grade 3/4 AEs were hypertension (18%), fatigue (14%), and diarrhea (4.5%). Based on these results, an ongoing randomized phase III study is investigating linifanib as first-line therapy in > 1000 patients with Child-Pugh A advanced HCC (NCT01009593).<sup>54</sup> Although final results are pending, this study was recently terminated by the independent data monitoring committee (IDMC).

### Ramucirumab

Ramucirumab is a recombinant humanized antibody that specifically targets the extracellular domain of VEGFR2. In a phase II study of 42 patients with unresectable HCC who primarily presented with Child-Pugh A disease (74%) and

Barcelona-Clinic Liver Cancer (BCLC) stage C (83%), first-line ramucirumab therapy resulted in a disease control rate of 69%.<sup>49</sup> The median OS for all patients was 14.9 months, and in patients with BCLC C/Child-Pugh A and BCLC C/Child-Pugh B HCC, it was 18.0 months and 4.4 months, respectively. Grade 3/4 toxicities included gastrointestinal bleeding, hypertension, and fatigue. These results may indicate a signal of activity for ramucirumab in the front-line setting, though this was a relatively small population of clinically heterogeneous patients. Despite no clinical data supporting ramucirumab's activity in patients with HCC who have progressed on sorafenib, an ongoing randomized placebo-controlled phase III study (REACH) is evaluating second-line ramucirumab in comparison to best supportive care (BSC) following failure of prior sorafenib therapy in patients with Child-Pugh score <7 (NCT01140347).<sup>59</sup>

### Everolimus

Mammalian target of rapamycin inhibitors, such as everolimus, have demonstrated antitumor activity in several malignancies. In HCC, two early clinical studies have shown that everolimus monotherapy was tolerable and had activity in patients who had received prior systemic therapy.<sup>50,70</sup> Grade 3/4 AEs included lymphopenia, elevations in aspartate transaminase, and hyponatremia. In both studies, the median PFS and OS were 3.8 months and 8.4 months, respectively. Though both studies were single-arm and uncontrolled, their results suggested a potential clinical benefit with everolimus in both patients who had received prior sorafenib therapy and those who did not. An ongoing randomized, placebo-controlled, phase III clinical trial (EVOLVE-1) is evaluating everolimus plus BSC in patients with Child-Pugh A HCC pretreated with sorafenib (NCT01035229).<sup>58</sup>

### ADI-PEG 20

ADI-PEG 20 is arginine deiminase (ADI) formulated with polyethylene glycol (PEG). Its potential as an anticancer agent is based on the hypothesis that HCC is deficient in argininosuccinate synthase and is, therefore, not capable of synthesizing arginine, and the relative arginine deficiency resulting from ADI is toxic to cancer cells. A randomized study comparing two doses of ADI-PEG-20 was performed in a heterogeneous population of patients.<sup>51</sup> Median survival for all patients in this study was 15.8 months and the most common events in this study related to the drug include transient and reversible encephalopathy, skin irritation, or discomfort at the site of injection combined with low-grade fever. A phase III study of ADI-PEG-20 versus placebo in the second-line setting is ongoing (NCT01287585).<sup>60</sup>

### Combination Strategies

Although single-agent therapy has demonstrated some success in the treatment of HCC, intensive research is now focused on enhancing the clinical benefit of many therapies through combination with other agents. The biologic rationale for combination approaches might involve targeting the same pathway at different points to achieve complete blockade of a given pathway or interrupting two different pathways simultaneously in hopes of circumventing feedback loops.

Based on potential interplay between angiogenesis and the EGFR signaling pathways, strategies targeting the VEGF and EGFR axis are being evaluated. In a single-arm, single-institution, phase II study of 40 patients with advanced HCC, erlotinib plus bevacizumab combination therapy was associated with a 16-week PFS of 62.5%, median PFS of 9.0 months, and median OS of 15.65 months.<sup>71</sup> Treatment-related grade 3/4 toxicities were mostly reminiscent of those related to bevacizumab. Despite the lack of similar data with sorafenib and erlotinib, a large phase III study evaluating the combination was launched. However, recently presented results of the SEARCH trial (NCT00901901) demonstrated that the addition of erlotinib to sorafenib did not prolong OS (HR = 0.929;  $p = 0.204$ ), which was the primary end point of the study.<sup>47</sup> A phase I study evaluating the combination of everolimus and sorafenib as front-line therapy in advanced HCC did not move

on to phase II development because of unexpected toxicity (thrombocytopenia), which prevented dose escalation of the mTOR inhibitor.<sup>72</sup>

Although the role of chemotherapy has not been defined in HCC, several strategies combining targeted and cytotoxic agents are being evaluated. In a randomized phase II trial of 96 patients with advanced HCC, most of whom had Child-Pugh A liver disease, the combination of sorafenib plus doxorubicin as first-line therapy yielded a significant improvement in median OS, from 6.5 months to 13.7 months (HR = 0.49; 95% CI, 0.3–0.8;  $p = 0.006$ ), and prolonged PFS (6.0 months vs 2.7 months; 95% CI, 1.4–2.8;  $p = 0.006$ ) compared with doxorubicin alone. Though this study was launched prior to the results of the SHARP study, given sorafenib's proven single-agent activity, the more appropriate control arm would have been sorafenib alone, not doxorubicin. Toxicity profiles were similar to those observed with single agents; however, the combination of sorafenib/doxorubicin increased bone marrow suppression and all grade left ventricular dysfunction (19% vs 2%, respectively).<sup>73</sup> Nevertheless, these results have led to an ongoing Cancer and Leukemia Group B (CALGB) phase III trial evaluating the superiority of sorafenib plus doxorubicin versus current standard of care, sorafenib, in a 480 patients with locally advanced or metastatic HCC (NCT01015833).<sup>74</sup> Several single-arm studies combining bevacizumab with cytotoxic agents, including capecitabine, oxaliplatin/capecitabine, and gemcitabine/oxaliplatin, have shown modest clinical activity; however, bevacizumab-based combinations are not being pursued further in phase III studies at this time.<sup>75–77</sup>

As previously discussed in this supplement, surgical resection and local ablation are curative therapies for early-stage HCC, whereas TACE is the backbone of the management of patients with intermediate-stage HCC. Pre-clinical evidence indicates that TACE increases tumor hypoxic conditions, which then may elicit upregulation of proangiogenic factors, such as VEGF and FGF, and ultimately stimulate angiogenesis.<sup>78,79</sup> It was found that patients with lower plasma VEGF levels following TACE have significantly longer survival compared with those with higher levels following TACE ( $p = 0.008$ ).<sup>80</sup> Taken together, these results suggest that coadministration of an antiangiogenic agents with TACE may block angiogenesis and prevent local recurrence and potentially distant metastasis. Several ongoing clinical trials are testing different combinations of TACE (or other locoregional therapies) and antiangiogenic agents. In a single-center phase II trial, combining TACE with doxorubicin-eluting beads (DEB-TACE) and sorafenib showed promising efficacy with a disease control rate of 95% and objective response of 58%.<sup>81</sup> Toxicity was manageable and mostly related to sorafenib; however, the authors noted increased liver toxicity. Recently presented preliminary efficacy results from the multicenter, randomized, placebo-controlled phase II SPACE trial (Sorafenib or Placebo in Combination with TACE) are less impressive. This trial of 307 patients with intermediate-stage HCC randomized patients to a combination of DEB-TACE/sorafenib or DEB-TACE/placebo and showed a trend toward better objective

response (35.7% vs 28.1%), but did not significantly delay progression with sorafenib (TTP; HR = 0.797; 95% CI, 0.588–1.080;  $p = 0.072$ ).<sup>82</sup> A similar phase III study of sorafenib in combination with TACE versus TACE alone performed in Japan and Korea likewise did not demonstrate any benefit with the combination.<sup>83</sup> This approach is being further evaluated in two ongoing phase III trials (NCT01004978 and NCT01324076).<sup>62,63</sup> Another important phase III trial in this population—with the primary end point of improving OS—BRISK-TA is investigating brivanib versus placebo as adjuvant therapy following TACE in 870 patients with intermediate HCC (NCT00908752).<sup>64</sup> TSU-68 (orantinib) is an oral small molecule inhibitor of VEGFR, PDGFR, and FGFR also currently being evaluated in phase III study in combination with TACE vs TACE alone (NCT01465464).<sup>65</sup>

## Conclusion

Hepatocellular carcinoma is a heterogeneous disease, both in regard to its clinical manifestation with underlying liver disease, and its complex pathogenesis involving aberrant signaling in several molecular pathways. The introduction of sorafenib in the treatment of advanced HCC saw a paradigm shift in its management. Based on new molecular knowledge and recognition of the limitations of sorafenib, novel molecular targeted therapies and combination strategies have been developed. Although early phase data with these agents have looked promising, to date nothing has been shown to be better than sorafenib in the front-line, and studies in the second-line have been disappointing. Looking ahead, concerted research efforts must be focused, not only on identifying new molecular targets and therapeutic agents, but also on understanding mechanisms of resistance to targeted agents. In addition to a better understanding of the natural history of HCC in the postsorafenib era, additional studies aimed at identifying predictive markers for response to novel agents are necessary. Incorporating these new agents into the pre-surgical or adjuvant setting also gives the opportunity for tissue collection and correlative science that is pivotal for increasing our understanding of these agents in HCC. Finally, the best method of assessing the activity of molecular targeted agents in HCC remains to be determined.

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