Current and Emerging Treatment Targets in Advanced Hepatocellular Carcinoma

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INTRODUCTION

Hepatocellular carcinoma (HCC) in men is the fifth most common cancer in the world and the second most common cause of cancer-related deaths [1]. Its incidence is rising both in the United States and worldwide, driven largely by growing cases of hepatitis C and hepatitis B [2]. Most patients present with advanced disease and are therefore not candidates for curative treatment modalities including liver transplantation. In addition, varying degrees of liver dysfunction often make patients ineligible for both liver-directed and systemic therapies.

Sorafenib is the current standard of care for first-line treatment of advanced, unresectable HCC. It is an oral small molecule inhibitor of multiple tyrosine kinases, including Vascular Endothelial Growth Factor (VEGF) receptors 1-3, FLT3, Platelet-Derived Growth Factor Receptor (PDGFR), Raf kinase, FGFR1, c-kit and RET. The SHARP (Sorafenib Hepatocellular Carcinomas Assessment Randomized Protocol) trial was a phase III study which randomized 602 patients with Child Pugh A cirrhosis compared to placebo, with a median overall survival of 10.7 versus 7.9 months [3]. These results led to approval of the drug in the US. Subsequently, the phase III Asia-Pacific study was conducted to obtain regulatory approval of the drug in China. Sorafenib was again shown to be superior to placebo, with a median overall survival of 6.5 versus 4.2 months, respectively with HR 0.68 (p value 0.014) [4]. Lower survival rates in the Asian population were felt to be due to more advanced disease at the time of enrollment in this group. Response rates in both studies averaged less than 5% [4,5]. The efficacy of sorafenib was maintained in a subsequent subset analysis based on HBV status, tumor burden, ECOG PS, LFTs, AFP levels, and prior history of hepatectomy or embolization [6]. Sorafenib has also been studied in patients with Child-Pugh (CP) class B cirrhosis. A phase II prospective study showed that patients with CP class B cirrhosis were able to tolerate sorafenib though outcomes (OS and progression free survival) were inferior compared to patients with CP class A cirrhosis (OS= 3.8 vs. 10 months, p<0.001; PFS 2.1 vs. 4.3 months, p<0.001) [7]. The first and second interim analysis of a large prospective observational study- the global investigation of therapeutic decisions in hepatocellular carcinoma and of its treatment with sorafenib (GIDEON) study -showed that patients with CP class B cirrhosis were not at an increased risk of adverse effects secondary to sorafenib use, compared to patients with CP class A cirrhosis [8,9].

Despite the approval of sorafenib for advanced HCC in 2007, patient outcomes have remained poor given low response rates and problems with toxicities. Furthermore, studies on systemic chemotherapy in patients with advanced HCC have been disappointing. Prior to the approval of sorafenib, doxorubicin was widely used despite its limited activity. A 1988 review by Nerenstone et al evaluated 13 doxorubicin trials and reported an overall response rate of 19% [10]. More recently, a phase III prospective trial randomized patients to a combination of cisplatin/interferon alpha 2b/doxorubicin/5-Fluourouracil (SFU) versus doxorubicin alone. There was no statistically
Signaling pathways and targeted drugs in advanced HCC

Multiple signaling pathways are implicated in HCC pathogenesis, including VEGF, fibroblast growth factor (FGF), PDGFR, epidermal growth factor receptor (EGFR), hepatocyte growth factor (HGF)/c-mesenchymal-epithelial transition factor (c-Met), and mammalian target of rapamycin (mTOR). Tables 1 and 2 list the results from the most recent phase III and phase II studies which have investigated the agents targeting these pathways.

VEGFR inhibitors

Due to the highly vascular nature of HCC, VEGFR is a rational target of therapy. High levels of VEGF correlate with tumor progression, early recurrence following resection, and lower survival rates [13-16].

Sunitinib is a multitargeted inhibitor of several tyrosine kinases, including VEGFR, PDGFR, c-KIT and FLT3 which are involved in tumor growth, angiogenesis and metastasis. Sunitinib was investigated in four phase II studies with varying doses and schedules. The disease control rate ranged from 38-53% and overall survival reported was 8.0 to 9.3 months [17-20]. A first-line phase III study comparing sunitinib to sorafenib in 1074 patients with advanced HCC was conducted but terminated early due to increased toxicities and inability to demonstrate noninferiority in OS with sunitinib (median OS 7.9 vs. 10.2 months; HR 1.3, 95% CI 0.99-1.3, p = 0.001) [21].

Brivanib has been studied for both first- and second-line treatment of HCC. Brivanib is a dual inhibitor of VEGF and fibroblast growth factor (FGF) receptors. FGF signaling is upregulated in HCC and plays an important role in angiogenesis and metastasis. Preclinical studies have shown that FGFR is associated with tumor cell proliferation and anti-apoptosis [22]. Elevated levels of FGFR correlate with invasiveness of HCC and predicts early recurrence following resection [23]. In mouse models of HCC, brivanib inhibited tumor growth and induced apoptosis [24]. A phase II study conducted in 55 patients with advanced HCC reported median progression-free survival of 2.7 months and overall survival of 10 months [25]. The most common adverse events included hypertension, fatigue, and diarrhea. Subsequently, a phase III trial of 395 patients who had failed or did not tolerate sorafenib were randomized to brivanib versus placebo. There was no statistically significant improvement in overall survival (9.4 months vs. 8.2 months; HR = 0.89; 95.8% CI, 0.69-1.15; p = 0.3307) [26]. The BRISK-FL trial compared brivanib versus sorafenib in 1155 patients with advanced HCC in the first-line setting. No survival benefit was seen, with median overall survival of 9.5 months with brivanib and 9.9 months with sorafenib (HR 1.06; 95.8% CI 0.93 to 1.22) [27].

Linifanib (ABT-469), a potent inhibitor of VEGFR and PDGFR, was studied in a phase II trial of 44 patients with advanced HCC [28]. Median overall survival was 9.7 months. The most common adverse events were hypertension, fatigue and diarrhea. A phase III study of 1035 patients evaluating linifanib versus sorafenib as first-line treatment of advanced HCC showed no survival benefit with linifanib [9.1 vs. 9.8 months] [29].

Ramucirumab (IMC-1121B), a fully human monoclonal antibody targeting VEGFR2, has demonstrated antitumor activity and decrease in tumor perfusion and vascularity [30]. A phase II study for patients with unresectable HCC showed a 9.5% response rate and 12 month OS with ramucirumab in the first-line setting [31]. Grade 3-4 adverse events included hypertension, gastrointestinal hemorrhage, infusion-related reactions, and fatigue. A randomized phase III trial (REACH) comparing ramucirumab versus best supportive care as second-line therapy is ongoing (NCT01140347).

Lenvatinib is a multitargeted oral tyrosine kinase inhibitor of VEGFR, FGFR, RET, KIT, and PDGFR. Early clinical studies of lenvatinib in advanced HCC showed antitumor activity with an acceptable toxicity profile [32,33]. A randomized phase III study investigating lenvatinib as first-line therapy in advanced HCC is currently open for enrollment (NCT01761266). Table 4 lists studies currently recruiting patients with advanced HCC.

HGF/c-MET inhibitors

The hepatocyte growth factor (HGF) and its receptor, cellular MET transmembrane tyrosine kinase (cMET) play an important role in HCC pathogenesis via promotion of tumor cell survival, proliferation, invasion, and migration. cMET overexpression has been associated with early tumor recurrence, metastasis, and decreased overall survival [34-38]. C-MET inhibition results in suppression of tumor growth in HCC cell lines and xenograft models [39].

Tivantinib, an oral selective inhibitor of c-MET, was studied in patients with advanced HCC following progression on or intolerance to sorafenib. A randomized phase 2 study showed modest improvement in TTP for patients who received tivantinib compared to placebo [1.6 vs. 1.4 months; p = 0.04] [7]. Patients with MET-high tumors (at least 2+ MET expression by immunohistochemistry in ≥50% of tumor cells) had more pronounced TTP (2.7 vs. 1.4 months, p = 0.03) and median overall survival (7.2 vs. 3.8 months; p = 0.01). The most common adverse events were neutropenia and anemia. A phase III study comparing tivantinib versus placebo is ongoing in patients with MET-high advanced HCC who have failed 1 prior systemic therapy (NCT01755767).

Cabozaantinib, a dual c-MET/VEGFR2 inhibitor, was examined in a phase II randomized discontinuation trial. Median PFS was 4.2 months and overall disease control rate was 68% [40]. The most common grade 3-4 adverse events were diarrhea, hand-foot syndrome, and thrombocytopenia. A randomized placebo-controlled phase III trial comparing cabozaantinib to placebo in the second-line setting is under way (NCT01908426).
Table 1: Completed Phase III studies with targeted therapies in advanced HCC.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Phase</th>
<th>Year</th>
<th>n</th>
<th>OS (months)</th>
<th>Child-Pugh</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib (SHARP) [5]</td>
<td>VEGFR</td>
<td>III</td>
<td>2008</td>
<td>602</td>
<td>10.7 vs. 7.9</td>
<td>A</td>
</tr>
<tr>
<td>Sorafenib (Asia Pacific) [4]</td>
<td>VEGFR</td>
<td>III</td>
<td>2009</td>
<td>271</td>
<td>6.5 vs. 4.2</td>
<td>A</td>
</tr>
<tr>
<td>Sorafenib/erlotinib (SEARCH) [86]</td>
<td>VEGFR, EGFR</td>
<td>III</td>
<td>2012</td>
<td>720</td>
<td>8.5 vs. 9.5</td>
<td>A</td>
</tr>
<tr>
<td>Sunitinib [B7]</td>
<td>VEGFR, PDGFR, c-KIT, FLT3</td>
<td>III</td>
<td>2013</td>
<td>1074</td>
<td>7.9 vs. 10.2</td>
<td>A</td>
</tr>
<tr>
<td>Brivanib (BRISK-FL) [27]</td>
<td>VEGFR, FGFR</td>
<td>III</td>
<td>2013</td>
<td>1155</td>
<td>5.9 vs. 10.1</td>
<td>A</td>
</tr>
<tr>
<td>Linifanib (ABT 869) [88]</td>
<td>VEGFR, PDGFR</td>
<td>III</td>
<td>2012</td>
<td>1035</td>
<td>9.1 vs. 9.8</td>
<td>A</td>
</tr>
<tr>
<td><strong>Second line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brivanib (BRISK-PS) [26]</td>
<td>VEGFR, FGFR</td>
<td>III</td>
<td>2013</td>
<td>395</td>
<td>9.4 vs. 8.2</td>
<td>A or B</td>
</tr>
<tr>
<td>Everolimus (EVOLVE1) [89]</td>
<td>mTOR</td>
<td>III</td>
<td>2013</td>
<td>546</td>
<td>7.6 vs. 7.3</td>
<td>A</td>
</tr>
</tbody>
</table>

OS: Overall Survival; BSC: Best Supportive Care

Table 2: Completed Phase II studies with targeted therapies in advanced HCC.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Phase</th>
<th>Year</th>
<th>n</th>
<th>OS (months)</th>
<th>Child-Pugh</th>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib [7]</td>
<td>VEGFR</td>
<td>II</td>
<td>2012</td>
<td>300</td>
<td>10 (CP A) 3.8 (CP B)</td>
<td>A/B</td>
</tr>
<tr>
<td>Sunitinib [20] (SAKK 77/06)</td>
<td>VEGFR, PDGFR, c-KIT, FLT3</td>
<td>II</td>
<td>2010</td>
<td>45</td>
<td>9.3</td>
<td>A/mild B</td>
</tr>
<tr>
<td>Linifanib [28]</td>
<td>VEGFR, PDGFR</td>
<td>II</td>
<td>2012</td>
<td>44</td>
<td>9.7</td>
<td>A/B</td>
</tr>
<tr>
<td>Vandetanib [90]</td>
<td>VEGFR, EGFR</td>
<td>II</td>
<td>2012</td>
<td>67</td>
<td>5.75 (V100) vs. 4.27 (placebo) 5.95 (V300) vs. 4.27 (placebo)</td>
<td>A</td>
</tr>
<tr>
<td>Bevacizumab/erlotinib [47]</td>
<td>VEGF, EGFR</td>
<td>II</td>
<td>2012</td>
<td>59</td>
<td>13.7</td>
<td>NA</td>
</tr>
<tr>
<td>Bevacizumab/erlotinib [48]</td>
<td>VEGF, EGFR</td>
<td>II</td>
<td>2012</td>
<td>27</td>
<td>9.5</td>
<td>A/B</td>
</tr>
<tr>
<td>Bevacizumab/erlotinib [49]</td>
<td>VEGF, EGFR</td>
<td>II</td>
<td>2013</td>
<td>51</td>
<td>10.7</td>
<td>A</td>
</tr>
<tr>
<td>Bevacizumab/erlotinib [91]</td>
<td>VEGF, EGFR</td>
<td>II</td>
<td>2013</td>
<td>21</td>
<td>8.3</td>
<td>A/B</td>
</tr>
<tr>
<td><strong>Second line</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSU 68 [92] (heavily pre-treated)</td>
<td>VEGFR2, PDGFR, FGFR</td>
<td>I/II</td>
<td>2010</td>
<td>12/35</td>
<td>13.1</td>
<td>A/B</td>
</tr>
<tr>
<td>Cetuximab [93]</td>
<td>EGFR</td>
<td>II</td>
<td>2011</td>
<td>30</td>
<td>9.6</td>
<td>N/A</td>
</tr>
<tr>
<td>Bevacizumab/Erlotinib [94]</td>
<td>VEGF, EGFR</td>
<td>II</td>
<td>2012</td>
<td>10</td>
<td>4.37</td>
<td>A</td>
</tr>
</tbody>
</table>
mTOR inhibitors

The phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway regulates cellular growth, proliferation, and survival. Dysregulation of the PI3K/Akt/mTOR pathway is implicated in the pathogenesis of hepatocellular carcinoma. Preclinical studies have shown aberrant mTOR signaling in approximately half of patients with HCC, and mTOR inhibition with everolimus in vitro and in a xenograft model impeded tumor growth and prolonged survival [41].

Early clinical studies with everolimus demonstrated anti-tumor activity and tolerability in patients with advanced HCC [42,43]. A Phase I/II study with 28 patients showed median PFS and OS of 3.8 months and 8.4 months, respectively. The most common treatment-related grade 3 or higher adverse events included lymphopenia, elevations in aspartate transaminase, and hyponatremia. Unfortunately, a phase III study involving 546 patients showed no survival benefit with everolimus versus placebo following progression on sorafenib in advanced HCC (7.6 months versus 7.3 months [HR=1.05, 95% CI=0.86-1.27; p = 0.675] [44]).

Combination strategies

Although sorafenib seemed to herald the promise of angiogenesis blockade, the lack of efficacy of newer agents solely targeting the VEGF signaling pathway has prompted exploration of novel combination strategies.

Given the modest activity seen with single-agent erlotinib in HCC, dual inhibition of both the EGFR and VEGF pathways have been explored in several studies [45,46]. A phase II study combining erlotinib and bevacizumab in advanced HCC showed median PFS of 7.2 months and median OS of 13.7 months [47]. Common toxicities included fatigue, hypertension, diarrhea, elevated transaminases, and gastrointestinal bleeding. Another phase II trial with 27 patients showed TTP 3.0 months and median OS of 9.5 months [48]. A phase II study conducted in Asia showed median PFS of 2.9 months (95% CI=1.3-4.4) and median overall survival of 10.7 months (95% CI= 6.2-15.2) [49]. A randomized phase II trial comparing bevacizumab-erlotinib versus sorafenib in the first-line setting is ongoing (NCT00881751). The combination of erlotinib with sorafenib was studied in a phase III trial of 720 patients with advanced HCC. However, no survival benefit was seen with the addition of erlotinib to sorafenib (HR = 0.929, p = 0.204) [50].

The combination of targeted therapies with cytotoxic chemotherapeutic agents have been explored extensively. Most of these efforts have concentrated on targeting the VEGF axis with either sorafenib- or bevacizumab-based combinations. A randomized phase II study showed that the combination of doxorubicin plus sorafenib was superior to doxorubicin alone in advanced HCC, with median OS of 13.7 vs. 6.5 months, respectively (p=0.0006) [51]. Nineteen percent of patients who received the doxorubicin-sorafenib combination developed left-ventricular systolic dysfunction versus 2% of those who received doxorubicin alone. A Cancer and Leukemia Group B (CALGB) phase III study-randomizing patients with advanced HCC to sorafenib plus doxorubicin versus sorafenib alone is ongoing (NCT01015833).

The strategy of combining TACE with sorafenib in advanced stage HCC has been utilized in studies including patients with both intermediate and advanced stage HCC with encouraging results [52-57]. VEGF levels are temporarily increased following TACE, reaching peak values one day post-TACE. This has been attributed to tumor ischemia following TACE, leading to upregulation of hypoxia inducible factor-1 alpha, and increase in plasma VEGF levels [58-60]. Thus, using a VEGF inhibitor may be complementary to TACE in patients with advanced HCC [61]. Completed and ongoing studies using a combination of local (TACE) and systemic (VEGF inhibitor) therapies in patients with advanced HCC are listed in Tables 3 and 5, respectively.

Hormonal therapy

Hormone receptors are expressed by liver tumors in varying degrees [62-66]. Immunohistochemical stains performed on tumor specimens from 31 HCC patients showed that 52% were estrogen receptor positive, 84% were progesterone receptor positive, and 68% were androgen receptor positive [66]. Tamoxifen exerts its anti-estrogen effect by binding to the hormone-binding domain of the estrogen receptor [67]. This drug has been extensively studied in patients with advanced HCC [63,98-76]. A systematic review published by Simonnetti showed a minimal survival benefit with tamoxifen [77]. A sensitivity analysis of 7 randomized controlled trials by Mathurin showed a borderline 1-year survival effect of tamoxifen [71]. However, in a more recent meta-analysis of 10 trials, including a total of 1709 patients, tamoxifen had no effect on OS (OR=1.05, 95% CI= 0.94-1.16, p= 0.4) [72].

The unresponsiveness of advanced HCC to tamoxifen was thought to be due to the alteration of the hormone-binding domain of the estrogen receptors (variant estrogen receptors) in the livers of over 30% patients with advanced HCC [67]. This led to the exploration of megestrol, which acts at the post-receptor level, as a therapeutic option in these patients [67,78,79]. In a prospective randomized study of 45 HCC patients with variant estrogen liver receptors, the median survival was significantly higher in the megestrol treated group compared to the placebo group (18 months vs. 7 months, p= 0.0090) [67]. However, a large randomized double-blind trial of 204 treatment-naive advanced HCC patients showed no significant difference in median OS between patients treated with megestrol versus placebo. Furthermore, there was a trend towards a lower OS in the megestrol treated arm (1.88 vs. 2.14 months, HR=1.25, 95% CI =0.92-1.71, p= 0.16) [80].

Somatostatin analogues have also been studied in advanced HCC. Octreotide, a long-acting analogue of somatostatin, [81] binds to somatostatin receptors 2, 3, and 5 [82]. It induces p53-mediated apoptosis of HCC cells (and not hepatocytes which lack SSTR3) via SSTR3 [81,83]. It also inhibits proliferation and decreases the AFP content of HCC cells [81]. In a 2011 meta-analysis including 9 RCTs (759 patients) evaluating the role of octreotide in advanced HCC, patients who received octreotide had a significantly higher OS compared to that of controls (6 month: 54% vs. 42%, RR 1.41, p = 0.008; 1 yr: 29% vs. 18%, p = 0.008). Controls in this analysis included untreated and placebo treated patients. When the control group was limited to placebo treated patients, there was no significant difference in survival rates.
Table 3: Completed studies with Sorafenib/TACE combination in advanced HCC.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Year</th>
<th>n</th>
<th>OS (months)</th>
<th>Child-Pugh</th>
</tr>
</thead>
<tbody>
<tr>
<td>[55]</td>
<td>TACE/Sorafenib vs. TACE/Placebo</td>
<td>2011</td>
<td>458</td>
<td>29.7 vs. not yet reached HR 1.06, p 0.79</td>
<td>A</td>
</tr>
<tr>
<td>[54]</td>
<td>II</td>
<td>2011</td>
<td>35</td>
<td>NA*</td>
<td>A/B BCLC: B/C</td>
</tr>
<tr>
<td>[52]</td>
<td>Retrospective Sorafenib pre- and post- TACE</td>
<td>2013</td>
<td>222</td>
<td>12</td>
<td>A/B score=8 BCLC: B/C</td>
</tr>
<tr>
<td>[56]</td>
<td>Retrospective</td>
<td>2013</td>
<td>355</td>
<td>8.9 vs. 5.9 HR 0.71, p 0.009</td>
<td>A/B BCLC C</td>
</tr>
<tr>
<td>[57]</td>
<td>III Sorafenib post TACE vs. TACE alone</td>
<td>2013</td>
<td>304</td>
<td>7.5 vs. 5.1 HR 0.61, p 0.009</td>
<td>A/B score=&lt;7 BCLC: B/C</td>
</tr>
</tbody>
</table>

NA: Not Available *Disease Control Rate: 95%; Objective Response: 58%

Table 4: Ongoing studies with molecularly targeted therapies in advanced HCC.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Design</th>
<th>Line of therapy</th>
<th>Child-Pugh</th>
<th>NCI trial identifier</th>
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</thead>
<tbody>
<tr>
<td>Sorafenib (BOOST)</td>
<td>VEGFR</td>
<td>III</td>
<td>First</td>
<td>B</td>
<td>NCT01405573</td>
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<tr>
<td>ARQ 197</td>
<td>c-MET</td>
<td>III</td>
<td>Second or Third-line</td>
<td>A</td>
<td>NCT02029157</td>
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<tr>
<td>Brivanib (BRISK-APS)</td>
<td>VEGFR</td>
<td>III</td>
<td>Second</td>
<td>A/B</td>
<td>NCT01108705</td>
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<tr>
<td>Regorafenib</td>
<td>VEGFR</td>
<td>III</td>
<td>Second-line</td>
<td>A</td>
<td>NCT01774344</td>
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<tr>
<td>Ramucirumab (REACH)</td>
<td>VEGFR</td>
<td>III</td>
<td>Second-line</td>
<td>A</td>
<td>NCT01140347</td>
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<tr>
<td>Tivantinib (METIV-HCC)</td>
<td>c-MET</td>
<td>III</td>
<td>Second-line</td>
<td>A</td>
<td>NCT01908426</td>
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<tr>
<td>Cabozantinib (XL 184)</td>
<td>c-MET, VEGFR</td>
<td>III</td>
<td>Second-line</td>
<td>A</td>
<td>NCT01405573</td>
</tr>
<tr>
<td>Sorafenib (BOOST)</td>
<td>VEGFR</td>
<td>III</td>
<td>First-line</td>
<td>B</td>
<td>NCT01761266</td>
</tr>
<tr>
<td>Lenvatinib (E7080)</td>
<td>VEGFR, FGFR, PDGFR, KIT, RET</td>
<td>III</td>
<td>Lenvatinib vs. sorafenib</td>
<td>First-line</td>
<td>A</td>
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<tr>
<td>Sorafenib/doxorubicin (CALGB-80802)</td>
<td>VEGFR</td>
<td>Combination vs. sorafenib</td>
<td>First-line</td>
<td>A</td>
<td>NCT01015833</td>
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<tr>
<td>Sorafenib/Doxorubicin (SoraDox)</td>
<td>VEGFR</td>
<td>IIIB Sorafenib/Doxorubicin vs. Sorafenib</td>
<td>First-line</td>
<td>A/B</td>
<td>NCT01272557</td>
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<td>Sorafenib/Doxorubicin</td>
<td>VEGFR</td>
<td>II</td>
<td>Second-line</td>
<td>A or less</td>
<td>NCT01840592</td>
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<td>Sorafenib/mFOLFOX</td>
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<td>II</td>
<td>First-line</td>
<td>&lt;=A</td>
<td>NCT01775501</td>
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<tr>
<td>Sorafenib/Temozolomide</td>
<td>VEGFR, mTor</td>
<td>II</td>
<td>First-line</td>
<td>A</td>
<td>NCT01687673</td>
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<tr>
<td>Bevacizumab/erlotinib</td>
<td>VEGF, EGFR</td>
<td>Randomized phase II Combination vs. sorafenib</td>
<td>First-line</td>
<td>A</td>
<td>NCT00881751</td>
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<td>INC280</td>
<td>c-MET</td>
<td>II</td>
<td>First-line</td>
<td>A</td>
<td>NCT01737827</td>
</tr>
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<td>PD-0332991</td>
<td>CDK 4/6</td>
<td>II</td>
<td>Second-line</td>
<td>A/B</td>
<td>NCT01356628</td>
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<td>Rafametinib (BAY86-9766)</td>
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<td>Second-line</td>
<td>A</td>
<td>NCT01915589</td>
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<tr>
<td>PF-03446962</td>
<td>ALK-1</td>
<td>II</td>
<td>Second-line</td>
<td>A</td>
<td>NCT01911273</td>
</tr>
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</table>

BSC: Best Supportive Care
between the treatment and control groups [84]. Interestingly, when studies conducted in Western countries alone were included (4 of 9 RCTs), no statistically significant difference in the 6-month, 12-month, and 24-month survival rates was noted [84]. The meta-analysis however, had asymmetry in the funnel plots indicating bias. Also, only 1 of the 9 included RCTs had an SSTR expression status available prior to accrual, enrolling only SSTR positive patients [85]. The authors concluded that octreotide may improve survival in patients with advanced HCC not from Western countries [84].

CONCLUSION

Current and future directions are focused on combining molecularly targeted agents with liver-directed therapies, identifying new relevant targets, and exploring the role of immunotherapy in HCC. Moving the field beyond sorafenib will require continued efforts to improve in our understanding of the mechanisms of HCC carcinogenesis and finding biomarkers to help predict response and resistance.

REFERENCES


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