Role of Systemic Therapy and Future Directions for Hepatocellular Carcinoma

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Abstract
Hepatocellular carcinoma (HCC) is an aggressive tumor that often arises in the setting of liver cirrhosis. Although early-stage disease is often amenable for surgical resection, transplant, or locoregional therapies, many patients are diagnosed at an advanced stage or have poor liver reserve. Systemic therapy is the mainstay of treatment for these patients. At present, the only approved therapy for the treatment of advanced disease is the tyrosine multikinase inhibitor sorafenib. Candidacy for treatment is based on liver reserve. Novel agents for the treatment of this disease are urgently needed. In this article, we review systemic therapy trials and upcoming data for the treatment of HCC.

Keywords
hepatocellular carcinoma, systemic therapy, clinical trials

Received March 21, 2017. Accepted for publication April 13, 2017.

Introduction
Hepatocellular carcinoma (HCC) is an aggressive tumor and is one of the leading causes of cancer-related death worldwide.¹ Around 60% to 80% of patients with HCC have underlying cirrhosis.² Risk factors for the development of HCC include viral and nonviral causes of cirrhosis (hepatitis B or C, nonalcoholic steatohepatitis, and alcohol), inherited errors of metabolism (hereditary hemochromatosis, porphyria cutanea tarda, α-1 antitrypsin deficiency, and Wilson disease), environmental exposures ( aflatoxin), and primary biliary cirrhosis. Because of the pathogenesis of this disease, the treatment for patients with HCC is often complicated by underlying liver dysfunction.

The mainstay of treatment of early-stage disease is surgical; however, many patients are not surgical candidates due to the extent of tumor or underlying liver disease. Patients with poor underlying liver function and/or unresectable disease that is limited to the liver may meet criteria for liver transplantation.³,⁴ Patients who are not candidates for transplantation can be evaluated for liver-directed therapy, including ablation, embolization (bland, chemoembolization, or radioembolization), or stereotactic radiotherapy.

For patients with more advanced disease, systemic therapy is preferred, but there are several challenges to treatment. The etiology of the underlying cirrhosis is often different based on geography and patients may respond differently to treatment. Asian patients tend to have underlying hepatitis B and have well-compensated cirrhosis, whereas Western patients tend to be older with more comorbidities and higher incidence of alcoholic cirrhosis and hepatitis C. Several chemotherapy regimens have been evaluated but have shown very modest efficacy. Targeted therapy has also been tested, and at present, the only Food and Drug Administration (FDA)–approved therapy for the treatment of advanced unresectable HCC is the oral multi-kinase tyrosine kinase inhibitor sorafenib. Objective tumor response rate is limited with this therapy and clinical trials are...
ongoing to develop more effective treatment strategies for this deadly disease. This review will focus on systemic treatment options including chemotherapy, molecularly targeted therapy, and immunotherapy and future directions for the treatment of HCC.

Chemotherapy

Hepatocellular carcinoma presents several challenges to treatment with chemotherapy in that it is generally chemorefractory and patients often have underlying cirrhosis, making it difficult to treat with agents that undergo hepatic metabolism. Chemorefractoriness is suspected to be in part due to high rates of expression of drug-resistant genes, heat-shock proteins, and p53 mutations. Several chemotherapy agents have been investigated.

A study looked at 147 patients with previously untreated HCC, enrolled in phase 2 trials in Japan, to determine predictive factors for tumor response to chemotherapy. Of these, only 10 had a partial response (<10% response rate). Of the patients with poor performance status, ascites, portal vein thrombosis, or serum bilirubin >2, none had any objective response with chemotherapy. However, a more recent study looked at predictive factors in patients undergoing treatment with 5-fluorouracil (5-FU), mitoxantrone, and cisplatin (FMP) therapy and found an objective response rate (ORR) of 22%. Interestingly, the trial found the absence of radiographic intrahepatic disease and ascites to be independent favorable prognostic factors, suggesting that patients with sufficient hepatic function may derive benefit from chemotherapy.

Single-Agent Chemotherapy

Doxorubicin is the most studied chemotherapeutic agent in advanced HCC. Initial studies showed an ORR of 79%; however, subsequent studies have shown ORR of less than 20% with doses of 75 mg/m². Few studies have shown an overall survival (OS) benefit with doxorubicin monotherapy and those that did showed an improvement in survival of about 3 weeks compared to best supportive care (BSC). An open-label trial of doxorubicin in combination with high-dose tamoxifen showed 32% response rate, suggesting that tamoxifen may potentiate the effect of doxorubicin, although it showed progression-free survival (PFS) of only 7 months.

5-Fluorouracil has relatively low toxicity, broad anticancer activity, and despite hepatic metabolism, can still be given in the setting of liver dysfunction. One study showed an ORR of 28% in patients with HCC with good performance status, with no significant toxicities. A retrospective study of capecitabine showed a similar ORR of 25% and median OS of 10.1 months with mostly common toxicities such as hand–foot syndrome and thrombocytopenia and was safe even in the setting of cirrhosis. A phase 2 trial of metronomic capecitabine in patients with HCC enrolled both untreated patients and patients previously treated with sorafenib. Previously untreated patients had a PFS of 6 months and an OS of 14.5 months with stable disease in 50% of patients; previously treated patients had a PFS of 3.2 months and an OS of 9.8 months. A randomized phase 2 trial in previously untreated patients compared single-agent capecitabine to sorafenib and showed 2-month OS and PFS benefit in the sorafenib arm, showing capecitabine to be inferior to sorafenib as a single agent.

Single-agent gemcitabine and irinotecan have also been evaluated and shown to have only very modest activity in HCC (Table 1). Weekly gemcitabine achieved a short partial response in only 17% of patients, while other gemcitabine trials in HCC showed no ORR. Trinotecan showed <10% ORR and progressive disease (PD) in all other patients, with considerable toxicities.

| Table 1. Selected Trials With Single-Agent Chemotherapy. |
|-----------------------------------------------|
| Chemotherapy | Toxicities | Best Response |
|----------------|-----------|---------------|
| Doxorubicin | Myelosuppression, anorexia, nausea/vomiting, alopecia | ORR 79%, median OS of 8 months |
| 5-FU | Mucositis, diarrhea, neutropenia | ORR < 20% |
| Capecitabine | Hand foot syndrome, thrombocytopenia | ORR of 25% |
| Irinotecan | Diarrhea | ORR < 10% |
| Gemcitabine | Cytopenias, hepatotoxicity | 18% PR for median duration of 13 weeks |

Abbreviations: 5-FU, 5-fluouracil; ORR, objective response rate; OS, overall survival; PR, partial response.

Combination Chemotherapy

Chemotherapy combinations have been studied in an attempt to improve response rate and OS compared to single-agent regimens (Table 2). The combination of cisplatin and doxorubicin showed an ORR of 19% and a median OS of 7.3 months. Several other chemotherapy combinations including FMP (infusional 5-FU, mitoxantrone, and cisplatin), ECF (cisplatin, infusional 5-FU, and epirubicin), low-dose FP (continuous 5-FU and low-dose cisplatin), and XELOX (xeloda and oxaliplatin) have been evaluated in phase 2 trials and have shown partial response and stable disease, with ORR ranging from 6% to 18% and OS ranging from 9 to 11 months. A randomized phase 3 trial in Asian patients, with predominantly hepatitis B as the etiology of cirrhosis, compared FOLFOX4 to doxorubicin. Median PFS was significantly better with FOLFOX4 (2.9 vs 1.7 months), and although there was a trend toward improved OS, the primary end point was not met. FOLFOX4 did also have a higher response rate (8% vs 3%) and disease control rate (52% vs 32%), but with some increased rate of neuropathy in the FOLFOX group. Most neuropathy was mild and there was no increase in grade 3 or 4 toxicities in either group.

Several studies have explored gemcitabine-based therapies, with similar ORR as other combinations. A phase 2 study of
Table 2. Selected Trials for Combination Chemotherapy.

| Chemotherapy | Common Toxicities | Best Response |
|--------------|-------------------|---------------|
| FMP          | Leukocytopenia, neutropenia, thrombocytopenia, elevated LFTs | PR in 27% with median duration of 7.6 months, 53% with SD |
| ECF          | GI toxicity, hand-foot rash | Median OS of 10 months and ORR of 14.5% |
| Low-dose FP  | Nausea, vomiting, Thrombocytopenia, neuropenia, neurotoxicity | PR in 47%, TTP 211 days, ORR 18%, SD in 58% |
| GEMOX        | Diarrhea, elevated LFTs, thrombocytopenia, neuropenia, neurotoxicity | ORR 6%, 72% disease control rate, median PFS of 4.1 months, and OS of 9.3 months |
| mFOLFOX4     | Neuropathy, similar toxicity to low-dose doxorubicin | Median PFS of 2.9 months, ORR of 8%, and disease control rate of 52% |
| PIAF         | Hematologic toxicity | Median OS benefit of 2 months, ORR of 20.9% |

Abbreviations: ECF, cisplatin, infusional 5-FU, and epirubicin; FMP, 5-fluorouracil, mitoxantrone, and cisplatin; mFOLFOX, 5-FU, oxaliplatin, leukovorin FP, continuous 5-FU and low-dose cisplatin; GEMOX, gemcitabine plus oxaliplatin; GI, gastrointestinal; ORR, objective response rate; OS, overall survival; PIAF, cisplatin, IFNa, doxorubicin, and infusional 5-FU; PFS, progression-free survival; XELOX, xeloda and oxaliplatin.

Molecularly Targeted Therapy

The molecular pathogenesis of HCC is not well understood; however, several molecularly targeted therapies have been evaluated for activity including inhibitors of vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR), and MEK and MET pathway inhibitors. Mutation profiling of HCC has shown about 30 to 40 mutations, of which 5 to 8 are suspected to be driver mutations—amplifications in several oncogenes such as FGFI9, VEGFA, CCFN1, and TERT have led to several potential targets.

Vascular Endothelial Growth Factor Pathway

Vascular endothelial growth factor inhibition downregulates HGF and therefore decreases proliferation and induces apoptosis. Sorafenib is a multtargeted tyrosine kinase inhibitor that inhibits VEGF, as well as Raf kinase and PDGF receptor, and is currently the only approved therapy for HCC. It was evaluated in the randomized phase 3 SHARP trial which showed a 2.8-month OS benefit of sorafenib compared to BSC (10.7 vs 7.9 months). A second phase 3 trial done in Asia also showed improved median OS with sorafenib compared to placebo. Both of these trials included primarily patients with Child-Pugh (CP) A cirrhosis, and most subsequent trials of other molecular targets have had similar design as the SHARP trial. An exploratory analysis showed the highest survival benefit in patients with hepatitis C, compared to those with hepatitis B or alcohol.

After approval of sorafenib, there were many studies combining sorafenib with chemotherapy and other targeted therapies, but none have shown significant improvement in outcome (Table 3). A phase 2 trial of sorafenib with doxorubicin showed an ORR of 4% but significantly longer TTP with the combination compared to doxorubicin alone (6.4 vs 2.8 months); however, a phase 3 trial (CALGB 80802) failed to show survival benefit of the combination when compared to sorafenib alone. A phase 3 trial of sorafenib with erlotinib also failed to show survival benefit and actually showed worse disease control rate in patients who received the combination.

Other VEGF inhibitors have shown some benefit, although none have been shown to be superior to sorafenib. A phase 2 trial of the anti-VEGF therapy bevacizumab showed 13% ORR...
Table 3. Selected Trials for Targeted Therapies.

| Drug | Common Toxicities | Best Response |
|------|-------------------|---------------|
| Sorafenib | Diarrhea, weight loss, hand–foot skin reaction | Improved OS (10.7 months vs 7.9 months) compared to placebo |
| Sorafenib + erlotinib | Fatigue, diarrhea, elevated LFTs | No OS benefit, lower disease control rate with sorafenib + erlotinib |
| Regorafenib | Hypertension, hand–foot skin reaction, fatigue, diarrhea | Median OS of 10.6 months, ORR 11% and 65% disease control |
| Bevacizumab | Hypertension, thrombosis, major bleed | ORR 13% and median PFS 6.9 months |

Abbreviations: ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

and median PFS of 6.9 months. However, 11% of patients had serious bleeding complications. Other phase 2 trials have combined bevacizumab with erlotinib, with conflicting results (ORR of 24% vs 3%), and a randomized controlled trial of this regimen in second-line patients with HCC is currently ongoing. Another VEGF inhibitor, sunitinib, has been evaluated in several phase 2 studies and has shown a 35% to 45% rate of stable disease. However, a phase 3 study comparing it to sorafenib showed it to be inferior (median OS of 7.9 vs 10.2 months) and the trial was closed prematurely for failure to show superiority and also increased toxicity (encephalopathy and hepatoportal syndrome). A second-line phase 2 trial of the tyrosine kinase inhibitor axitinib showed promising ORR and tumor control rate; however, there was no OS benefit as compared to placebo. Similarly, the anti-VEGFR2 antibody ramucirumab was evaluated in a phase 3 randomized controlled trial in patients with HCC who had previously been treated with sorafenib and showed improvement in median PFS and TTP relative to placebo but no improvement in OS. Linifanib, an ATP competitive inhibitor of VEGF and PDGF receptor tyrosine kinases, was compared to sorafenib in a large phase 3 randomized trial which included 1035 patients. Although there was a greater ORR with linifanib (13% vs 6.9%), there was no survival benefit. Recently, the ongoing randomized, double-blind, phase 3 trial of regorafenib in patients with HCC progressing on sorafenib (RESORCE) trial randomized patients who had progressed on sorafenib to the oral multikinase inhibitor regorafenib versus placebo. The median OS was 10.6 versus 7.8 months. This agent may become the established second-line therapy for advanced HCC. Of note, 68% of patients required dose adjustments of regorafenib for toxicity.

Epidermal Growth Factor Receptor Pathway

Epidermal growth factor receptor is frequently expressed in HCC and may contribute to its aggressive growth. The anti-EGFR/human epidermal growth factor receptor 1 tyrosine kinase inhibitor erlotinib has been studied in combinations as above, as well as a single agent. Per a systemic literature search of 10 phase 2/3 trials (9 phase 2 trial and 1 phase 3 trial), most studies noted a disease control rate of 42.5% to 79.6% and a median OS of 6.25 to 15.65 months. The most frequent grade 3/4 toxicities were fatigue (11.9%), diarrhea (10%), increased alanine transaminase (ALT) and AST (7.3%), and rash (6.9%). Overall, erlotinib is generally well tolerated, but more clinical trials are needed to evaluate the safety and efficacy of the drug.

The anti-EGFR antibody cetuximab has also been studied in advanced HCC. It has shown a 65% disease control rate when combined with gemcitabine and oxaliplatin during a phase 2 trial of 45 patients. Results showed a response rate of 20% with a median PFS of 4.7 and a median OS of 9.5 months. Another phase 2 trial with the combination of capcitabine, oxaliplatin, and cetuximab noted a partial response of 12.5%, stable disease in 75%, and a disease control rate of 83%. Median time to progression was 4.5 months, and OS was 4.4 months. The combination was associated with a modest response rate but a high radiographic stable disease. However, OS and PFS seem shorter compared to historical numbers of the phase 3 trial with sorafenib. This was a generally well-tolerated regimen, and further studies using cetuximab with a chemotherapy backbone have been undertaken but results are not yet available.

Other Pathways

TGF-β has a known role tumor suppression and progression and has been found to be elevated in a subgroup of HCC tumors. A TGF-β selective TKI galunisertib is currently being evaluated in phase 2 studies alone and in combination with sorafenib. Data from one of these studies have shown a trend toward improved TTP in patients with a greater reduction in AFP and TGF-β. This trend also suggests a possible biomarker associated with targeting this pathway.

Fibroblast growth factor is also frequently overexpressed in HCC and plays a role in proliferation, invasion, and angiogenesis in the liver and has been suggested to also have a role in resistance to anti-VEGF therapy. FGFR19 is amplified in 5% to 10% of liver cancers, and preclinical models have shown this amplification to be associated with response to FGFR19-targeted antibodies, suggesting another potential biomarker. Brivanib inhibits both FGFR and VEGFR, but is not FGFR19 specific, and has been evaluated in 2 phase 3 studies, one in the first-line setting with sorafenib (BRISK-FL) and another in the second-line setting compared to placebo (BRISK-PS). Neither study met the primary objective, although in the second-line setting, brivanib did show longer TTP than placebo (4.2 vs 2.7 months). Dovitinib inhibits FGFR, VEGFR, and PDGF receptor and was evaluated in a phase 2 trial comparing it to sorafenib, and although it was well tolerated, it failed to show superior to sorafenib. Studies of FGFR-specific TKIs such as BGJ398 are currently ongoing.

Phosphorylated MEK can be detected by IHC in all HCCs, and increased phosphorylation and expression of MAPK has been shown in over 90% of HCCs. The RAS pathway has an
important role in proliferation, and mutations are common in several different cancers. In vitro treatment with MEK inhibitors has led to growth inhibition and apoptosis, suggesting that the MEK/MAPK pathway plays a role in HCC pathogenesis and could be a therapeutic target.\textsuperscript{25} Several phase 2 trials have looked at MEK inhibitors (selumetinib and refametinib) in HCC and showed median TTP of 122 days and median OS of 290 days; however, no phase 3 trials have been completed to date.\textsuperscript{27}

Dysregulated interaction between the MET receptor and HGF occurs during hepatocyte injury and liver regeneration, with MET activation found in 50% of patients with advanced HCC.\textsuperscript{27} Hepatocyte growth factor inhibitors or MET inhibitors such as tivantinib and cabozantinib have shown promising antitumor activity as monotherapy and in combination with sorafenib. A phase 2 placebo-controlled randomized trial of second-line tivantinib showed improved median time to progression. This was more pronounced in patients with MET-high tumors (as assessed by IHC).\textsuperscript{24} A phase 3 placebo-controlled trials is currently ongoing.\textsuperscript{55} Similarly, second-line treatment with cabozantinib has shown preliminary activity,\textsuperscript{56} and a placebo-controlled phase 3 study is ongoing.\textsuperscript{57}

Molecularly targeted therapies have shown promise in this chemotherapy refractory disease, and current trials may lead to new FDA approvals for this disease, particularly in the second-line setting; however, to date, none have shown superiority to sorafenib, which remains the current standard of care.

**Antibodies, Immunotherapy and Vaccines**

Certain features of HCC suggest that it would be susceptible to immunologic manipulation. An increased ratio of cytotoxic T cells as compared to regulatory T cells has been associated with improved survival.\textsuperscript{58} Initial studies with interferon $\alpha$ (IFN$\alpha$) in advanced HCC were promising with evidence of disease activity,\textsuperscript{59} but a recent randomized controlled trial showed IFN to be poorly tolerated in cirrhotics and showed no survival benefit. As discussed above, IFN has also been combined with chemotherapy as part of the PIAF regimen and showed some benefit, but with significant toxicity.

Checkpoint inhibition has also been evaluated in HCC (see Table 4). A phase 1/2 study of nivolumab was performed in patients with CP A or B who had either progressed on or did not tolerate sorafenib. Preliminary data of 47 patients with expansion cohort at 3 mg/kg dose showed 8 patients with objective antitumor response, 2 with CR, and 48% with stable disease.\textsuperscript{60} The most recent update of this study, a dose expansion cohort, included 206 participants with advanced HCC and CP A. Preliminary data revealed 50% of patients with treatment-related adverse events, 55% of patients with at least 18 weeks follow-up and/or PD, and 6-month OS rate of 69%.\textsuperscript{61} Lastly, a phase 1/2 study of nivolumab investigated patients with advanced HCC who failed, refused, or were intolerant of sorafenib. Forty-eight patients were evaluable for response, and results noted 15% CR, 8% PR, 50% SD, 31% PD with a median OS of 15.1 months.\textsuperscript{62}

| Drug                | Common Toxicities                                      | Best Response             |
|---------------------|--------------------------------------------------------|----------------------------|
| Nivolumab (dose expansion 3 mg/kg) | Fatigue, pruritus, grades 3-4 increased AST/ALT | Preliminary phase 1/2 trial data of 47 patients showed 5% CR, 18% PR, 72% OS at 6 months\textsuperscript{62} |
| Nivolumab (0.1-10 mg/kg for up to 2 years) | Rash, grades 3-4 increased AST/ALT | Initial phase 1/2 study showed 15% CR, 8% PR, 50% SD, 31% PD, median OS 15.1 months\textsuperscript{62} |
| Pembrolizumab (200 mg IV every 3 weeks up to 35 cycles or PD) | Pending study results | Phase 2 study ongoing, pending final results |
| Pembrolizumab (200 mg IV every 3 weeks) + BSC versus placebo + BSC up to 35 cycles or until disease progression | Pending study results | Primary objective is PFS and OS |
| Codirituzumab (1600 mg every 2 weeks after 2 loading doses) | Anemia, increased AST | Secondary objective is ORR, CR, PD |
| Pembrolizumab (200 mg IV every 3 weeks) + BSC versus placebo + BSC up to 35 cycles or until disease progression | Pending study results | Phase 3 study ongoing, pending final results |
| Pexa-Vec (10e9 PFU injections every 2 weeks x 3) + sorafenib (400 mg BID starting at week 6) versus sorafenib (400 mg BID from day 1) | Pending study results | Primary end point is OS Secondary end point is PFS, ORR, CR Safety, biomarkers, and quality of life will be evaluated |

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BID, twice daily; BSC, best supportive care; CR, complete response; IV, intravenously; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFU, plaque forming units; PR, partial response.

There are ongoing checkpoint inhibition trials involving pembrolizumab. A phase 2 trial of pembrolizumab plans to evaluate the drug’s efficacy in 100 patients with previously treated advanced HCC.\textsuperscript{63} Another phase 3 trial compared the efficacy and safety of pembrolizumab with BSC against placebo with BSC in patients with previously treated advanced HCC.\textsuperscript{64} A study of durvalumab (a selective PDL-1 inhibitor) and tremelimumab (a CTLA-4 inhibitor) in patients with or without hepatitis B or C who have progressed on sorafenib is currently ongoing.\textsuperscript{65}
Codrituzumab is a humanized monoclonal antibody against glypican-3, expressed in HCC and involved in antibody-dependent cytotoxicity. A randomized second-line placebo-controlled phase 2 trial did not show clinical benefit (PFS 2.6 vs 1.5 months, OS 8.7 vs 10 months). 56

Pexa-Vec is an oncolytic and immunotherapeutic vaccinia virus designed to selectively replicate in and destroy cancer cells via direct oncolysis with tumor vascular disruption and antitumor immunity. Preclinical and clinical data suggested complimentary effects when combined with sorafenib, and a current phase 3 trial comparing Pexa-Vec + sorafenib to sorafenib alone is currently ongoing. A prior randomized phase 2 trial had shown acceptable safety profile with OS benefit.57

**Future Directions**

While many different treatment regimens have been attempted in HCC, few options have shown significant improvement in outcomes. As in other malignancies, treatment is shifting away from more toxic chemotherapies toward targeted therapy and immunotherapy, although these have also had limited efficacy in HCC. To date, sorafenib remains the only approved systemic therapy, although these have also had limited efficacy in HCC. To date, sorafenib remains the only approved systemic therapy. Future directions are focused on molecular-targeted therapies, especially those with potential biomarkers that may predict or correlate with tumor response.

Several studies have looked at potential biomarkers to determine who will derive benefit from therapy, specifically sorafenib. The response rate with sorafenib is generally low (0.7%-3%), but a small number of cases have demonstrated substantial tumor regression. A study looking at these “responders” found amplification of FGF3 and FGF4, poorly differentiated histology, and multiple lung metastases in 3 of 10 evaluable samples.68 Longer OS is associated with low baseline AFP, low CP score, compensated cirrhosis, and low baseline ALT. Child Pugh score and baseline AST are also independent prognostic factors.69 An analysis of the SHARP trial looked at 10 biomarkers measured at baseline and after 12 weeks of treatment and showed that baseline angiopoietin 2 and VEGF concentrations independently predicted survival. ECOG PFS, baseline AFP, and AP also predicted survival. Although none of the biomarkers tested predicted response to sorafenib, patients with high s-c-KIT or low baseline hepatocyte growth factor concentration in the sorafenib cohort showed a trend towards enhanced benefit.69,70 The ALICE-1 study looked at VEGF and VEGFR genotyping to predict outcomes with sorafenib and identified several polymorphisms (single nucleotide polymorphism [SNPs]) of VEGF that influenced PFS and OS.71 The ALICE-2 study also showed SNPs of hypoxia-inducible factor-1α (HIF-1α) to be significant for PFS and OS.

Other studies have focused on alternative molecular pathways with potential associated biomarkers. Newer molecular therapies have targeted MEK, MET, and MYC. A study looking at expression of mcl-1, pERK½ and pAKT, MYC, and MET in pretreatment specimens of 44 patients with advanced HCC showed poorer OS with pERK expression and mcl-1 expression; however, this did not correlate with TTP.70 A study to look at the prognostic and predictive role of eNOS, Ang2, HIF-1, VEGF, and VEGFR polymorphisms as they pertain to PFS in HCC is currently ongoing and expected to be completed in January 2019. A randomized controlled phase 3 study of tivantinib, an MET inhibitor, in patients with HCC who have failed one line of systemic therapy was currently ongoing and was completed in December 2016. A similar phase 3 randomized, double-blinded study of tivantinib in MET-diagnostic high HCC is also ongoing and expected to complete accrual in March 2017.

Epigenetic modifications have been suggested to drive progression to HCC and include DNA methyltransferases and microRNAs (miRNAs). Histone deacetylase (HDAC) inhibitors act to induce cell growth arrest and apoptosis and have been suggested to have activity in HCC. Preclinical models of a pan-HDAC inhibitor MPT0G009 showed increased apoptotic populations and decreased levels of antiapoptotic proteins, suggesting that it could possibly be a potential HCC therapy.72 A multicenter phase 1/2 study of belinostat in patients with unresectable HCC showed a median PFS of 2.64 months and OS of 6.6 months, which is still inferior to sorafenib; however, HR23B expression was also evaluated as a potential biomarker and was found to be associated with disease stabilization.73 Vorinostat is another HDAC inhibitor that was found to induce NF-kB in vitro, which may actually lead to cancer cell progression. Studies looking at the combination of sorafenib and vorinostat, where sorafenib would act to enhance the cytotoxicity and inhibit NF-kB activity, showed increased efficacy in vitro and in vivo, suggesting another potential new therapy.74 A phase 1 trial of sorafenib and vorinostat in advanced HCC is currently ongoing. MicroRNAs are produced by human cells, released in the blood, and thought to play a role in gene expression and cell proliferation. MicroRNAs have a known role in the pathogenesis of HCC; however, it is unknown whether they can be used as markers for diagnosis and survival. Studies are ongoing to determine the presence of miRNAs in patients with HCC and whether there is a correlation between miRNAs in tumor tissue and blood.75

Immunotherapy has shown promising results in HCC based on small studies as mentioned above. Currently, we are awaiting the results of phase 3 studies to see whether there is benefit of immunotherapy. In addition to check point inhibitors, there are attempts to use vaccines to treat HCC as well. Preliminary data of a phase 2 study of hepcortespenlisimut-L, an oral vaccine made of tumor antigens and pooled alloantigens, showed decreased AFP levels after 2 months of treatment, which correlated with tumor regression or clearance on computed tomography scans. After 10 months, 93.3% of patients were still alive, with 1 patient 57 months out with no evidence of disease.76 This study will be completed in December 2019. A phase 3 randomized, placebo-controlled trial is also currently recruiting. As discussed above, it is suspected that checkpoint inhibition may be enhanced by tumor ablative therapies and there are currently ongoing phase 1/2 trials combining these modalities—these are expected to be completed in 2021.
Further molecular profiling may continue to reveal future drug targets and corresponding biomarkers. Given the heterogeneity of HCC, evaluation of those subsets of patients who respond well to certain therapies may also elucidate potential biomarkers and molecular markers that can more effectively guide treatment recommendations.

Authors’ Note
The remaining authors report no significant relationship with the companies/organizations whose products or services may be referenced in this article.

Declaration of Conflicting Interests
The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Kim is also a consultant for Bayer, Bristol-Myers Squibb, Eli Lilly and Company, and Taiho Oncology.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Dr Kim receives grants/research support from Bayer, Bristol-Myers Squibb, and Eisai Company.

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