Targeting the HGF/c-MET Pathway in Hepatocellular Carcinoma

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Abstract
Hepatocellular carcinoma (HCC) is a significant cause of cancer-related morbidity and mortality worldwide. Despite improvements in local therapies, including surgical resection, liver transplantation, and transarterial embolization, the prognosis remains poor for the majority of patients who develop recurrence or present with advanced disease. Systemic therapy with the tyrosine kinase inhibitor sorafenib represents a milestone in advanced HCC but provides a limited survival benefit. Ongoing efforts to study hepatocarcinogenesis have identified an important role for c-MET signaling in the promotion of tumor growth, angiogenesis, and metastasis. In this review, we summarize the preclinical data from human tissue, cell lines, and animal models that implicate c-MET in the pathogenesis of HCC. We also evaluate potential biomarkers that may estimate prognosis or predict response to c-MET inhibitors for more rational clinical trial design. Finally, we discuss the latest clinical trials of c-MET inhibitors in advanced HCC.

Disclosure of Potential Conflicts of Interest
A.X. Zhu is a consultant/advisory board member for Sanofi-Aventis, Bristol-Myers Squibb, Eisai, Daiichi Sankyo, and Exelixis. No potential conflicts of interest were disclosed by the other authors.

CME Staff Planners Disclosures
The members of the planning committee have no real or apparent conflict of interest to disclose.

Learning Objectives
On completion of this activity, the participant should have a better understanding of c-MET–targeted therapeutics development in advanced hepatocellular carcinoma, their side effects, and the value of c-MET–related prognostic and predictive biomarkers.

Introduction
Liver cancer ranks sixth in incidence and third in mortality among all cancers worldwide (1). The most common primary liver cancer, hepatocellular carcinoma (HCC), accounts for 70% to 85% of the cases (2). Advanced HCC carries a poor prognosis with a 5-year survival rate of less than 10% (3). Although chemotherapy has shown limited efficacy, 2 large randomized trials have shown that the small-molecule tyrosine kinase inhibitor (TKI) sorafenib (Nexavar; Bayer and Onyx) improves survival in advanced HCC compared with placebo, but the median overall survival remains less than 1 year (4–6). As the search for novel and effective treatments continues, the tyrosine kinase receptor c-MET is emerging as a therapeutic target in HCC. In this review, we discuss the role of the c-MET pathway in hepatocarcinogenesis, summarize the preclinical data supporting its potential as a therapeutic target in HCC, and review the prognostic and predictive value of relevant biomarkers. Finally, we will provide an update on c-MET inhibitors currently under investigation in HCC.

The HGF/c-MET Pathway
The c-MET proto-oncogene was originally identified as a fusion gene (tpr-met) in a chemically transformed human osteosarcoma cell line (7). It encodes for the receptor for the ligand hepatocyte growth factor (HGF; ref. 8). In the canonical HGF/c-MET signaling pathway, HGF binding leads to receptor homodimerization, autophosphorylation of tyrosine residues of the carboxy-terminal domain c-MET, and downstream activation of the mitogen-activated protein kinase (MAPK), phosphoinositide-3 kinase (PI3K), and Rac1-Cdc42 pathways (Fig. 1; reviewed in ref. 9). c-MET phosphorylation in the absence of HGF can occur...
through interactions with the EGF receptor (EGFR), cell attachment (10), or binding of the alternate ligand des-gamma-carboxyprothrombin (11). Regardless of the mode of activation, c-MET dimerization, autophosphorylation, and kinase activity seem to be necessary for malignant transformation (12–14).

The HGF/c-MET axis has been shown to exert diverse physiologic effects on cell proliferation, survival, migration, and angiogenesis, with important roles in liver development and regeneration. HGF acts as a potent mitogen for primary hepatocytes (15) and promotes cell motility of epithelial cells in vitro (16). c-Met and HGF knockout mice exhibit analogous phenotypes characterized by embryonic lethality due in part to impaired liver formation (17, 18). Finally, liver HGF expression rapidly increases in rodents following partial hepatectomy (19), and mice subjected to conditional inactivation of c-Met in mature hepatocytes exhibit deficient liver regeneration (20).

### The Role of c-MET and HGF in HCC

#### HGF/c-MET expression in HCC

The discovery that HGF/c-MET signaling promotes hepatocyte proliferation and regeneration has prompted multiple studies of its role in HCC. Surprisingly, HGF expression is decreased in HCC compared with surrounding tissue (21–25). On the other hand, c-MET transcription is increased in 30% to 100% of tumors compared with surrounding liver tissue (22, 25–28). Similarly, c-MET is overexpressed at the protein level in 25% to 100% of HCCs compared with normal liver (26, 28–32), suggesting a potential tumor-promoting role in HCC.

#### HGF/c-MET manipulation in HCC cell lines

In vitro studies have attempted to establish the effect of HGF/c-MET signaling in HCC cells. Rather than acting as a mitogen, recombinant HGF inhibited growth in most HCC cell lines (33, 34). In contrast, c-MET knockdown by RNA...
interference decreased cell proliferation, colony formation, and migration in vitro, and suppressed tumor growth in vivo in multiple HCC cell lines (35–37). Similarly, treatment of c-MET–overexpressing HCC cells with the selective c-MET inhibitor PHA665752 resulted in significant growth inhibition in vitro (IC50 = 50–100 nmol/L) and in subcutaneous xenografts in nude mice (38). Treatment was accompanied by inhibition of c-MET phosphorylation and downstream extracellular signal–regulated kinase (ERK)1/2 and Akt activation. PHA665752 did not have significant activity against 2 low-c-MET–expressing cell lines (38). These data suggest that c-MET may be a promising target in the treatment of HCC and that c-MET overexpression may be a predictive biomarker of response.

**HGF/c-MET manipulation in animal models of HCC**

Studies in animal models of HCC have been consistent with the in vitro data. Carcinogen-induced rat models to which exogenous HGF is administered (39–41) and transgenic mice in which HGF is endogenously overexpressed in the liver revealed both tumor-promoting and tumor-inhibiting effects of HGF (42–45). On the contrary, transgenic models of c-MET overexpression have consistently induced HCC formation in vivo. Liver-specific overexpression of c-Met in mice led to HCC formation in a ligand-independent fashion, and withdrawal of c-Met overexpression promoted marked tumor regression, suggesting a continued role for c-MET in tumor maintenance in vivo (10). Moreover, overexpression of c-Met cooperated with other oncogenes characteristic of HCC, c-myc or mutant β-catenin, to generate HCC with shorter latency and survival in mice (46, 47). These data support the role of c-MET in HCC tumors progression and maintenance, providing a rationale for the clinical development of c-MET inhibitors for HCC.

**Combined inhibition of HGF/c-MET and VEGF pathways in preclinical models**

Several lines of evidence support a significant role for HGF/c-MET in promoting angiogenesis. First, HGF directly promoted the growth of endothelial cells both in vitro and in vivo (48). Second, HGF induced VEGF and suppressed TSP1 (a negative regulator of angiogenesis) expression in cultured breast and leiomyosarcoma cells and in xenografts (49). Third, transgenic mice overexpressing HGF exhibited increased angiogenesis and VEGF transcription in chemically induced hepatic adenomas and HCC (43). Finally, recent work has revealed significant cross-talk between the HGF/c-MET and VEGF/VEGFR receptor (VEGFR) pathways with synergism in enhancing proliferation, cytoskeletal remodeling, and migration in endothelial cells (50). Interestingly, tumor hypoxia, a potential consequence of angiogenesis inhibitors such as sorafenib, led to increased c-MET expression and potentiated the effect of HGF on c-MET activation, cell migration, and invasiveness (51).

Several in vitro and in vivo studies have validated the use of combined c-MET and VEGF/VEGFR inhibition in HCC. The addition of the selective c-MET TKI tivantinib (ARQ197; ArQule, Inc.) to sorafenib promoted additive cytotoxicity in HCC cells (52). Moreover, foretinib (GSK1363089, XL880; GlaxoSmithKline), a multitargeted TKI with activity against c-MET, VEGFR2, RON, AXL, KIT, FLT3, platelet-derived growth factor receptor β (PDGFRβ), and Tie2 (53) impaired growth of patient-derived HCC cell lines in vitro and in vivo (54). Finally, cabozaftinib (XL184; Exelixis), a TKI with activity against c-MET, VEGFR2, and RET, inhibited growth in multiple cancer cell lines, including those of the breast, lung, stomach, and prostate with decreased proliferation, metastatic capability, and angiogenesis in xenografts (55). This preclinical evidence supports the clinical application of combined HGF/c-MET and VEGF/VEGFR pathway blockade for HCC.

**HGF and c-MET as Biomarkers in HCC**

Table 1 summarizes our current understanding of HGF and c-MET as biomarkers in HCC. Although tissue HGF levels have provided little or no prognostic information, plasma HGF levels were consistently higher in patients with HCC compared with normal subjects (26, 56, 57). Moreover, circulating HGF levels were correlated with decreased overall survival in untreated patients (56) and with increased tumor size, grade, recurrence, metastasis, postoperative complications, and worse overall survival after partial hepatectomy (26, 57). A recent biomarker analysis of samples from the pivotal phase III trial of sorafenib showed a trend toward improved survival in patients with a lower pretreatment plasma HGF concentration (58). Elevated circulating HGF levels are observed in many pathologic liver conditions, including hepatitis, and are correlated with more severe liver cirrhosis (59). Thus, it remains unclear whether plasma HGF at diagnosis would be predictive of response to anti-HGF/c-MET therapies, and this possibility needs to be prospectively evaluated in clinical trials of c-MET inhibitors.

Tissue c-MET overexpression has shown prognostic promise with direct correlation to tumor grade (28, 29), portal vein invasion or thrombosis (26, 31), intrahepatic metastases (30, 31), tumor recurrence (26, 31), and worse overall survival (30), although a limited number of samples were examined in each study. A large retrospective study of 194 patients with HCC of less than 5 cm treated with partial hepatectomy or microwave ablation showed that increased c-MET expression was independently associated with worse survival in multivariate analysis (60). Although gene expression profiling of HCC has not consistently shown c-MET overexpression to be an oncogenic driver, a c-MET–positive gene expression signature (identified through comparative microarray analysis of wild-type and c-Met–deficient mouse hepatocytes) has been identified in a subset of human HCCs and was associated with increased vascular invasion and worse outcome (61).

Two major caveats limit the prognostic value of c-MET overexpression in HCC. First, the available data are primarily derived from patients with early-stage disease who have undergone partial hepatectomy (28, 31), and the prognostic value of c-MET overexpression has not been definitively evaluated in advanced HCC. Second, the optimal method for evaluating c-MET protein expression...
remains controversial. One study conducted densitometric analysis on Western blots of tumor tissue using a median cutoff value to delineate high- versus low-cMET-expressing tumors. Five-year survival was significantly lower in the patients with high compared with low c-MET expression (33.5% and 80.3%, respectively; ref. 30). Another study assessed c-MET expression in tumor tissue by immunohistochemistry (IHC) and showed shortened disease-free survival in patients with c-MET expression versus those without c-MET expression (60). c-MET overexpression assessed by IHC in tumor tissue is the only predictive biomarker that has gained supportive evidence in early-phase trials of HGF/c-MET inhibitors (see below; ref. 62). However, the reproducibility and standardization of these approaches to assess c-MET expression need to be addressed in future studies as has been done previously for HER2 evaluation in breast cancer (63).

Tissue and blood markers are increasingly studied as potential pharmacodynamic biomarkers in early-phase clinical trials. The natural choice for c-MET inhibitors is c-MET phosphorylation in tumor tissue. Evaluation of the activity of signaling molecules such as ERK1/2 and Akt (see Fig. 1) is also being pursued, but this analysis may be confounded by the activity of other TKIs, such as sora-

### Table 1. Prognostic and predictive value of HGF/c-MET biomarkers in HCC

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Prognostic value</th>
<th>Predictive value</th>
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<tbody>
<tr>
<td>HGF RNA overexpression in tumor tissue</td>
<td>No correlation with tumor size, grade, proliferation, or OS (23)</td>
<td>Insufficient evidence</td>
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<tr>
<td>HGF protein overexpression in tumor tissue</td>
<td>No correlation with tumor size, grade, or intrahepatic metastases, vascular invasion, or OS (30)</td>
<td>Insufficient evidence</td>
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<tr>
<td>Plasma HGF levels</td>
<td>Level at diagnosis inversely correlated with OS in untreated patients (56); high levels after heptectomy associated with increased complication rate and worse OS (57); high levels correlate with increased tumor size, higher grade, portal vein thrombosis, and postoperative recurrence (60)</td>
<td>Insufficient evidence</td>
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<tr>
<td>c-MET amplification</td>
<td>Rarely observed (31) with insufficient evidence regarding prognostic value</td>
<td>Insufficient evidence</td>
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<tr>
<td>c-MET mutations</td>
<td>Observed in some childhood HCC (69) with insufficient evidence regarding prognostic value</td>
<td>Insufficient evidence</td>
</tr>
<tr>
<td>c-MET RNA overexpression in tumor tissue</td>
<td>Frequent overexpression observed (22, 25–28) but insufficient evidence regarding prognostic value</td>
<td>Insufficient evidence</td>
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<tr>
<td>c-MET protein overexpression in tumor tissue</td>
<td>Correlates with higher tumor grade (poorer differentiation) (28, 29), portal vein invasion or thrombosis (26, 31), increased intrahepatic metastases (30, 31), tumor recurrence (26, 31), and worse OS (30)</td>
<td>IHC overexpression correlates with improved OS and TTP in patients treated with tivantinib (62)</td>
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</table>

Abbreviations: IHC, immunohistochemistry; OS, overall survival; TTP, time to progression.

Clinical Experience

**Clinical trials of single-agent c-MET inhibitors**

In an effort to bring scientific knowledge from the bench to the bedside, several anti-c-MET agents are currently under development and can be broadly categorized into 3 groups: selective c-MET TKIs, multitargeted TKIs with activity against c-MET, and monoclonal antibodies against HGF or c-MET (Fig. 1). Three oral small-molecule c-MET TKIs have shown acceptable toxicity and modest clinical efficacy in phase II trials in advanced HCC: foretinib, cabozantinib, and tivantinib (Table 2). Later, we discuss the unpublished data from conference abstracts that present the clinical experience with these drugs.

**Foretinib.** Foretinib was the first c-MET TKI to be evaluated in clinical trials. It has a broad TKI spectrum,
<table>
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<tr>
<th>Drug/short name</th>
<th>Molecular target (IC&lt;sub&gt;50&lt;/sub&gt; reference)</th>
<th>Phase/arms</th>
<th>Study population</th>
<th>First or second line</th>
<th>Outcomes/endpoints</th>
<th>Most common AEs</th>
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<tr>
<td>Tivantinib/T (62)</td>
<td>c-Met (0.4 μmol/L; ref. 70)</td>
<td>Phase II T, 360 mg orally BID vs. T 240 mg per os BID vs. placebo</td>
<td>n = 107 Childs-Pugh A cirrhosis, geographically unselected</td>
<td>Second ITT population (placebo vs. T):</td>
<td>- TTP (1.4 vs. 1.6 mo, HR = 0.64, P = 0.04)</td>
<td>- Neutropenia (25.4%)</td>
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<td>- PFS (1.5 vs. 1.7 mo, HR = 0.67, P = 0.06)</td>
<td>- Anemia (15.5%)</td>
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<td>c-MET high (placebo vs T):</td>
<td>- OS (3.8 vs. 7.2 mo, HR = 0.38, P = 0.01)</td>
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<td>- TTP (1.5 vs. 2.9 mo, HR = 0.43, P = 0.03)</td>
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<td>- PFS (1.5 vs. 2.4 mo, HR = 0.45, P = 0.02)</td>
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<td>Mixed first and second</td>
<td>- 2/36 with cPR at 12 weeks (RR = 6%) and a third patient randomized at 12 weeks achieved a cPR at 18 weeks</td>
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<td>Cabozantinib/C (65)</td>
<td>VEGFR2 (0.04 nmol/L), c-Met (1.3 nmol/L), RET (5.2 nmol/L), KIT (4.6 nmol/L), Flt-4 (6 nmol/L), AXL (7 nmol/L), Flt-3 (11.3 nmol/L), Flt-1 (12 nmol/L), and Tie2 (1.43 nmol/L; refs. 55, 71)</td>
<td>Phase II C, 100 mg orally daily</td>
<td>n = 41 Childs-Pugh A cirrhosis, geographically unselected</td>
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<td>Most common grade 3/4 AEs:</td>
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<td>- Diarrhea (17%)</td>
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<td>- PPE (15%)</td>
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<td>- Thrombocytopenia (10%)</td>
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<td>Foretinib/F (64)</td>
<td>c-MET (0.4 nmol/L), VEGFR2 (0.9 nmol/L), Tie2 (1.1 nmol/L), Flt-4 (2.8 nmol/L), RON (3 nmol/L), Flt-3 (3.6 nmol/L), KIT (6.7 nmol/L), Flt-1 (6.8 nmol/L), PDGFRβ (9.6 nmol/L), and AXL (11 nmol/L; refs. 53, 71)</td>
<td>Phase II F, 30 mg orally daily</td>
<td>n = 39 Childs-Pugh A cirrhosis Asian</td>
<td>First</td>
<td>- ORR 24% (95% CI, 11%–40%)</td>
<td>- Hypertension (36%)</td>
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<td>- DCR 79% (95% CI, 63%–90%)</td>
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<td>- TTP 4.2 mo (95% CI, 2.7%–7.5%)</td>
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<td>- OS 15.7 mo (95% CI, 7.0%–15.7%)</td>
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<td>Most common SAEs:</td>
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<td>- Hepatic encephalopathy (10%)</td>
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<td>- Ascites (8%)</td>
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Abbreviations: BID, twice daily; CI, confidence interval; cPR, confirmed partial response; CR, complete response; DCR, disease control rate (PR þ SD); ITT, intention to treat; ORR, overall response rate (CR þ PR); RR, response rate; SD, stable disease.
which includes c-MET and VEGFR. Foretinib was tested in a phase I/II trial as first-line therapy for Asian patients with advanced HCC and Child-Pugh A cirrhosis or no cirrhosis. In 38 of 39 patients who were treated at the maximum tolerated dose of 30 mg daily and were evaluable for efficacy, foretinib exhibited an objective response rate (ORR) of 24%, a disease control rate (DCR) of 79%, median time to progression (TTP) of 4.2 months, and median overall survival (OS) of 15.7 months. Foretinib had an acceptable toxicity profile, as the most common adverse events (AE) were hypertension (36%), anorexia (23%), and fever (21%), and the most common serious AEs (SAE) were hepatic encephalopathy (10%) and ascites (8%; ref. 64).

**Cabozantinib.** Cabozantinib is an oral small-molecule multitargeted TKI with activity against c-MET, VEGFR2, and RET. In a phase II randomized discontinuation trial, 41 patients with advanced HCC and Child-Pugh A cirrhosis received cabozantinib, 100 mg daily, for 12 weeks during a lead-in phase. Patients who had a partial response (PR) were maintained on open-label cabozantinib, whereas patients with stable disease were randomized to cabozantinib versus placebo. Patients with progressive disease (PD) discontinued treatment. Two of 36 patients with evaluable disease at 12 weeks had a PR (6%), and a third patient randomized at 12 weeks achieved a PR at 18 weeks. The DCR at week 12 was 68%. A reduction in α-fetoprotein (AFP) by more than 50% from baseline was seen in 26 patients. The median progression-free survival (PFS) was 4.4 months and OS was 15.1 months. Of note, the PFS was similar in patients who were sorafenib naïve (PFS, 4.2 months; n = 20) and who had prior use of sorafenib (PFS, 5.2 months; n = 21). The toxicity profile was acceptable; the most common grade 3/4 AEs were diarrhea (17%), palmar–plantar erythrodysesthesia (PPE, 15%), and thrombocytopenia (10%; ref. 65).

**Tivantinib.** Of the oral c-MET TKIs tested in phase II trials of advanced HCC, tivantinib has gained the most experience. Tivantinib is a selective non-ATP competitive inhibitor of c-MET. A phase Ib study evaluating the use of tivantinib in patients with HCC and Child-Pugh A or B cirrhosis showed preliminary evidence of both safety and efficacy (66). The drug then underwent phase II testing in a randomized, placebo-controlled, multinational, cross-over trial of 107 patients with unresectable HCC who had failed one systemic therapy and had either no cirrhosis or Child-Pugh A cirrhosis (62). Patients were randomized in a 2:1 fashion to tivantinib or placebo. Tivantinib was initially given at 360 mg twice daily, but the dosage was changed to 240 mg twice daily due to a high incidence of neutropenia. The study met its primary endpoint with a modest improvement in TTP in the intent-to-treat population from 1.4 to 1.6 months (HR = 0.64, P = 0.04), favoring the tivantinib group. The safety profile was acceptable, with the most frequent drug-related AEs in the tivantinib group being neutropenia (25.4%) and anemia (15.5%). Grade 3 to 4 neutropenia was seen in 21% of patients at the 360-mg-twice-daily oral dose and 6% of patients at the 240-mg-twice-daily oral dose, so the latter dose was favored.

The most compelling data from this trial came from a subgroup analysis based on tumor c-MET expression. Positive c-MET expression (≥2+ staining intensity in ≥50% of tumor cells by IHC) was associated with improved OS (3.8 vs. 7.2 months, HR = 0.38, P = 0.01), PFS (1.5 vs. 2.4 months, HR = 0.45, P = 0.02), and TTP (1.5 vs. 2.9 months, HR = 0.43, P = 0.03; ref. 62). Despite the early promising results with tivantinib in HCC, it should be cautioned that the sample size was small, the positive signal remained modest, and the data were based on a subgroup analysis (22 patients in the tivantinib arm and 15 patients in the placebo arm for the c-MET high group). Currently, a phase III randomized trial comparing tivantinib, 240 mg twice daily, with placebo in patients with c-MET–positive advanced HCC in the second-line setting is being planned.

**Combination of c-MET inhibition with sorafenib.** On the basis of preclinical data showing the synergy of tivantinib and sorafenib in multiple cell lines (52), a phase I study of 54 patients, including 8 with HCC, was completed and showed preliminary safety and efficacy of the drug combination. An extension cohort of 20 patients with HCC with Childs-Pugh A and B cirrhosis, 10 of whom had received 1 or more systemic therapy, were treated with tivantinib, 240 mg twice daily, and sorafenib, 400 mg twice daily. The combination showed a DCR of 70% with 1 complete response, 1 PR, and 12 patients with stable disease. The toxicities of the combination were manageable, with the most common AEs being rash (40%), PPE (35%), fatigue and diarrhea (30% each), and nausea and anorexia (25% each). Neutropenia was reported in 2 patients (67). These data, along with the preliminary phase II results for foretinib and cabozantinib, support the further development of combined c-MET and VEGF pathway inhibition in HCC.

**Future Development of c-MET Inhibitors in HCC.** The recent failure of several phase III trials with VEGFR TKIs highlights the challenge and need for developing additional targeted agents in HCC. Despite significant preclinical data supporting the role of c-MET as a potential oncogenic driver in HCC, early clinical trials have revealed surprisingly modest benefit of c-MET inhibition. There are several possible explanations. First, HCC is a heterogeneous disease in its predisposing etiologies and tumor microenvironment, which may be insufficiently modeled in cell lines and animal models. Second, no clear consensus exists on how to identify patients whose tumors have high c-MET expression or definitive evidence that this characteristic predicts dependence on c-MET. Third, currently available c-MET TKIs may not be sufficiently selective and potent in vivo. Finally, most patients with advanced HCC have significant underlying cirrhosis, which poses a challenge for the evaluation of targeted therapies. Given the role of the
HGF/c-MET pathway in liver regeneration and the fact that most oral c-MET TKIs are metabolized by the liver, the therapeutic window is likely to be small, and the safety profiles of these agents should be carefully examined. The data from the tivantinib trial are interesting but are based on a small sample size with modest improvement in TTP. Target inhibition by tivantinib has not been shown in vivo in HCC tissues.

Thus, future clinical trials of c-MET inhibitors in HCC should seek to determine and standardize the optimal method for delineating c-MET overexpression and validating its role as a predictive biomarker. In addition, more potent and selective c-MET inhibitors should be tested in HCC, and studies that carefully assess phospho-c-MET inhibition as a pharmacodynamic biomarker should be included in the study design. Despite the rationale, interesting preclinical data for combined c-MET and VEGFR inhibition, and preliminary clinical data on foretinib and caboziotinib, the relative contribution of c-MET and VEGFR inhibition remains to be examined. Finally, successful development of c-MET inhibitors will rely on carefully designed clinical trials with adequate endpoint selection, correct target population, optimal assessment of clinical efficacy, and robust biomarker discovery as previously recommended (68). Despite these challenges, nearly 30 years after its initial discovery, c-MET is emerging as a biologically rational and drug-gable target in HCC.

Acknowledgments

The authors thank Drs. Bruce Chabner and Dan Duda for critical review of the manuscript and helpful suggestions.

Received August 28, 2012, revised December 8, 2012, accepted January 21, 2013; published OnlineFirst February 6, 2013.

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Clinical Cancer Research


