

Recent Developments of c-Met as a Therapeutic Target in Hepatocellular Carcinoma

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Aberrant c-Met activity has been implicated in the development of hepatocellular carcinoma (HCC), suggesting that c-Met inhibition may have therapeutic potential. However, clinical trials of nonselective kinase inhibitors with c-Met activity (tivantinib, cabozantinib, foretinib, and golvatinib) in patients with HCC have failed so far to demonstrate significant efficacy. This lack of observed efficacy is likely due to several factors, including trial design, lack of patient selection according to tumor c-Met status, and the prevalent off-target activity of these agents, which may indicate that c-Met inhibition is incomplete. In contrast, selective c-Met inhibitors (tepotinib, capmatinib) can be dosed at a level predicted to achieve complete inhibition of tumor c-Met activity. Moreover, results from early trials can be used to optimize the design of clinical trials of these agents. Preliminary results suggest that selective c-Met inhibitors have antitumor activity in HCC, with acceptable safety and tolerability in patients with Child-Pugh A liver function. Ongoing trials have been designed to assess the efficacy and safety of selective c-Met inhibition compared with standard therapy in patients with HCC that were selected based on tumor c-Met status. Thus, c-Met inhibition continues to be an active area of research in HCC, with well-designed trials in progress to investigate the benefit of selective c-Met inhibitors. (HEPATOLOGY 2018;67:1132-1149).

Liver cancer was responsible for 745,000 deaths worldwide in 2012.⁽¹⁾ Hepatocellular carcinoma (HCC) is the most common type of liver cancer, typically occurring in patients with chronic liver disease due to hepatitis B/C infection, alcohol abuse, hemochromatosis, or nonalcoholic steatohepatitis.⁽²⁾ The prevalence of HCC is increasing due to the increasing incidence of hepatitis infection, obesity, and metabolic syndrome, as well as increased survival of patients with liver disease. Prognosis is typically poor at diagnosis: the median overall survival (OS) is

approximately 11 months⁽³⁾ for patients with advanced HCC.

Fewer than 25% of patients diagnosed with HCC are candidates for potentially curative surgery. Other therapeutic options are limited, with only two systemic therapies, both nonselective kinase inhibitors, approved for advanced HCC: sorafenib, which inhibits intracellular Raf kinases and a variety of cell surface kinase receptors to inhibit angiogenesis and tumor growth, is approved for first-line use⁽⁴⁾; and regorafenib, which targets kinases involved with tumor

Abbreviations: bid, twice daily; HCC, hepatocellular carcinoma; HGF, hepatocyte growth factor; MTD, maximum tolerated dose; OS, overall survival; PD-1/PD-L1, programmed death 1/PD-1 ligand; RON, receptor originated from Nantes; TKI, tyrosine kinase inhibitor; VEGF/VEGFR, vascular endothelial growth factor/VEGF receptor.

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angiogenesis, oncogenesis, and maintenance of the tumor microenvironment, is approved for second-line use for patients who have progressed on sorafenib.⁽⁵⁾ However, first-line sorafenib and second-line regorafenib each extend the median OS of patients with advanced HCC by <3 months.⁽⁶⁻⁸⁾ Imaging reveals that approximately half the cases of advanced HCC are hypervascular. Inhibition of the vascular endothelial growth factor receptor (VEGFR) by sorafenib and regorafenib might therefore contribute significantly to the benefit each compound confers in this setting.

With efficacy observed with these targeted agents, therapies directed against a number of targets implicated in the development of HCC, including VEGF/VEGFR, fibroblast growth factor and its receptor, platelet-derived growth factor receptor, epidermal growth factor receptor, RAS/RAF, extracellular signal-regulated kinase, phosphoinositide 3-kinase, mammalian target of rapamycin, and c-Met, have been tested or are in development.⁽⁹⁾ The c-Met pathway has gained attention because it is a key pathway in the liver, and targeted therapies have shown signs of promise in the clinic.⁽¹⁰⁻¹³⁾ We critically review the role of c-Met in HCC, reported trials of purported c-Met inhibitors, the properties required of a successful drug, and the features required of trials designed to demonstrate benefit in HCC based on recently reported data from trials of c-Met inhibitors.

c-Met Signaling in Cellular Biology

c-Met is a receptor tyrosine kinase with one known ligand, hepatocyte growth factor (HGF). c-Met is expressed by epithelial cells, endothelial cells, neurons, hepatocytes, and hematopoietic cells.⁽¹⁴⁾ c-Met is

involved in epithelial–mesenchymal transition and plays a critical role in tissue modeling during embryogenesis; postpartum c-Met has a limited role in tissue repair, particularly in the liver.⁽¹⁵⁾

HGF induces c-Met dimerization and activation, leading to stimulation of multiple downstream signaling pathways, including mitogen-activated protein kinase, phosphoinositide 3-kinase, signal transducer and activator of transcription, and nuclear factor kappa-B.⁽¹⁶⁾ These pathways execute the cellular effects of c-Met activation, including increased proliferation, survival, mobilization, invasiveness, and epithelial–mesenchymal transition.⁽¹⁷⁾

c-Met Signaling in Liver Disease and HCC

A complex interplay exists between liver disease, HCC, and c-Met (Fig. 1). Chronic liver diseases such as cirrhosis and those caused by hepatitis B or C infection are well-known triggers of HCC.⁽¹⁸⁾ Liver disease increases demand for hepatocyte proliferation, which in turn promotes the up-regulation of c-Met and/or HGF.⁽¹⁹⁾ In addition, c-Met is transcriptionally induced by hypoxia-inducible factor-1, a transcription factor triggered by hypoxia in advanced bulky HCC tumors, and may induce VEGF-A expression, further enhancing tumor angiogenesis.⁽²⁰⁾ c-Met-induced hepatocyte proliferation, survival, and regeneration are involved in liver repair^(21,22); and c-Met can also affect the development of liver disease by suppressing chronic inflammation and the development of fibrosis.⁽²³⁾ c-Met activity is therefore beneficial in liver disease, potentially promoting wound healing and delaying disease development.⁽²⁴⁾ However, this activity appears to have limitations, with preclinical data suggesting that c-Met activity decreases in the later stages of

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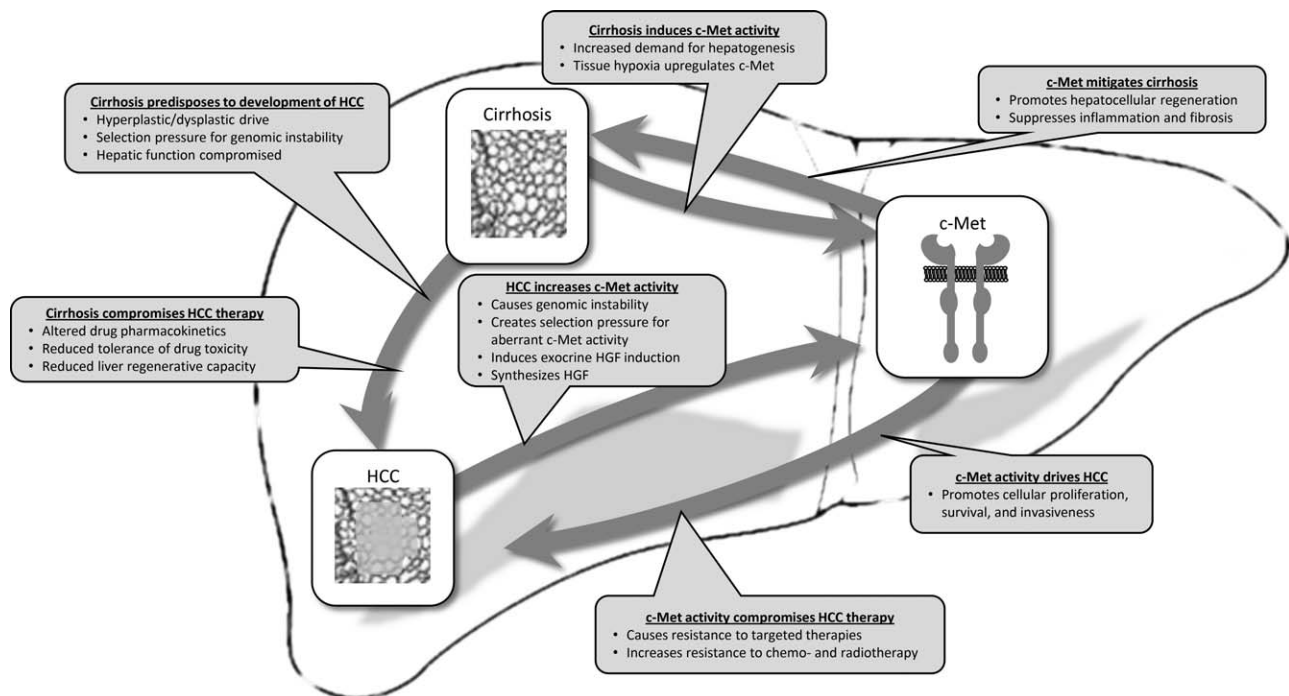


FIG. 1. Interplay between cirrhosis, HCC, and c-Met expression in the liver. Cirrhosis triggers an increase in c-Met activity, which serves to mitigate disease progression by promoting liver regeneration and reducing inflammation and fibrosis. However, c-Met also provides an oncogenic drive which promotes the development of HCC. Cirrhosis further promotes HCC by increasing demand for cellular proliferation, leading to dysplasia which favors oncogenesis. Genomic instability in HCC further promotes c-Met aberrations, leading to increased c-Met activity. Cirrhosis reduces the regenerative capacity of the liver and may exclude patients from therapy by resection. Cirrhosis also reduces tolerance to systemic therapies, particularly those causing substantial hepatotoxicity.

chronic liver disease as regenerative potential becomes exhausted.⁽²⁵⁾

Despite its potentially beneficial effects in chronic liver disease, increased c-Met activity can initiate, drive, or contribute to the development and progression of HCC. Aberrant c-Met activity is associated with rapid tumor growth, aggressively invasive disease, and poor patient prognosis.⁽²⁶⁾ c-Met aberrations occur in approximately 50% of patients with HCC⁽²⁷⁾ and can arise through gene mutation (4%), gene amplification (24%), increased mRNA expression (50%), and receptor overexpression (28%).^(28,29) Constitutively activating mutations in the kinase domain can occur, although these are rare in HCC.⁽³⁰⁾ More frequently, overexpression of c-Met causes receptor dimerization and activation⁽³¹⁾ with reduced dependence on HGF. Overexpression of receptors capable of transactivating c-Met, including receptor originated from Nantes (RON)⁽³²⁾ and insulin-like growth factor receptor 1,⁽³³⁾ can also activate c-Met. Aberrant c-Met activity can also result from the abnormally high HGF levels that are associated with HCC.⁽³⁴⁾

c-Met has thus been identified as an important factor in the modulation of liver disease and as an oncogenic driver of HCC. c-Met activity may also confer resistance to sorafenib therapy in HCC.⁽³⁵⁾

c-Met Inhibitors in HCC

Inhibitors of c-Met/HGF signaling have demonstrated antitumor potential in preclinical models of HCC by decreasing hepatocellular tumor cell proliferation, cell motility, and invasion and promoting apoptosis.⁽³⁶⁾ c-Met inhibitors have also shown signs of efficacy in the treatment of HCC, particularly against c-Met-positive tumors.⁽³⁷⁾

c-Met signaling can be inhibited by several types of agent, principally HGF-neutralizing antibodies, HGF antagonists, and c-Met tyrosine kinase inhibitors (TKIs). Clinically relevant examples of each are identified in Table 1. All types have the potential to inhibit HGF-dependent c-Met signaling. Some HGF

TABLE 1. Clinically Important Inhibitors of the HGF/c-Met Signaling Pathway

Drug Name	Type	Mechanism	Therapeutically Relevant Targets	Phase 2 Indications	Phase 3 Indications
Rilotumumab	mAb	Neutralizing	HGF	Prostate, GBM, ovarian, SCLC, NSCLC, CRC, RCC	Gastric, SCLC
Ficlatuzumab	mAb	Neutralizing	HGF	AML, HNSCC, NSCLC	
Onartuzumab	mAb	Antagonist	c-Met	GBM, NSCLC, TNBC, gastric, CRC	Gastric, CRC
Tivantinib	Nonselective TKI	Non-ATP competitive	c-Met, tubulin	Gastric, CRC, RCC, HNSCC, prostate, breast, pancreas, mesothelioma, myeloma, sarcoma	HCC (failed), NSCLC (stopped)
Golvatinib	Nonselective TKI	ATP competitive	c-Met, KDR	Glioblastoma, melanoma, SCCHN, HCC	
Cabozantinib	Nonselective TKI	ATP competitive	c-Met, KDR, RET, KIT, TIE-2, FLT-3	GBM, NSCLC, breast, cholangiocarcinoma, CRC, pancreas, myeloma, thyroid, ovarian cancer	Prostate, HCC
Foretinib	Nonselective TKI	ATP competitive	c-Met, KDR, TIE-2, RON, FLT-4, FLT-3	Gastric, SCCHN, pRCC, NSCLC, breast	
Crizotinib	Nonselective TKI	ATP competitive	c-Met, ALK	NSCLC, lymphoma, melanoma, gastric, urothelial cancer	
Savolitinib	Selective TKI	ATP competitive	c-Met	pRCC, gastric cancer	
Capmatinib	Selective TKI	ATP competitive	c-Met	pRCC, NSCLC, HCC, HNSCC, CRC, melanoma, GBM	
Tepotinib	Selective TKI	ATP competitive	c-Met	HCC, NSCLC	

Abbreviations: ALK, anaplastic lymphoma kinase; AML, acute myeloid leukemia; ATP, adenosine triphosphate; CRC, colorectal cancer; FLT, Fms Related Tyrosine Kinase; GBM, glioblastoma multiforme; HNSCC, head and neck squamous cell carcinoma; KDR, vascular endothelial growth factor receptor-2; KIT, tyrosine protein kinase kit; mAb, monoclonal antibody; NSCLC, non-small-cell lung cancer; pRCC, papillary renal cell carcinoma; RCC, renal cell carcinoma; RET, rearranged during transfection; RON, receptor originated from Nantes; SCLC, small-cell lung cancer; TIE-2, Tyrosine-protein kinase receptor Tie-2; TKI, tyrosine kinase inhibitor; TNBC, triple-negative breast cancer.

antagonists may also partially inhibit HGF-independent c-Met signaling by inducing c-Met internalization, thereby lowering cell surface expression.⁽³⁸⁾ c-Met TKIs can reliably inhibit both HGF-dependent and HGF-independent c-Met signaling because both mechanisms depend on c-Met kinase activity.

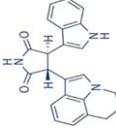
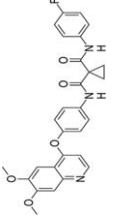
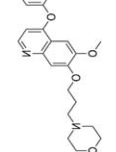
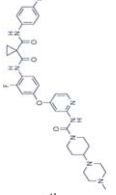
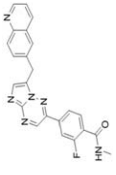
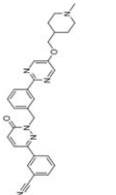
c-Met TKIs can be broadly categorized as nonselective or selective. Selectivity is normally claimed when c-Met is the only kinase inhibited at clinically relevant exposures, nominally requiring agents to be at least 10-fold more potent against c-Met than all other kinases. Selectivity established *in vitro* does not rule out activity against untested kinases or nonkinase targets or the existence of metabolites with nonselective activity. Furthermore, *in vivo* and *in vitro* selectivity profiles may significantly differ. In contrast, nonselective c-Met inhibitors have confirmed activity with similar potency against at least one other kinase.

The antitumor activity of nonselective c-Met inhibitors may be enhanced through inhibition of non-c-Met

targets. However, their selectivity profiles are fixed and thus relevant for a minority of patients with tumors with heterogeneous but specific target expression. Inhibition of targets beyond c-Met is associated with increased toxicity, which may limit the achievable dose so that c-Met cannot be inhibited effectively. This additional toxicity and potential suboptimal target inhibition may outweigh and/or limit the potential benefit of enhanced antitumor activity due to inhibition of multiple targets. Furthermore, the antitumor activity of nonselective c-Met inhibitors may be predominantly due to their activity against non-c-Met targets, making it impossible to ascribe drug effects observed in trials specifically to the inhibition of c-Met.

In contrast, selective c-Met inhibitors are expected to induce fewer toxicities at clinically relevant doses sufficient to produce effective c-Met inhibition. Reduced toxicity supports the use of selective c-Met inhibitors over nonselective c-Met inhibitors in combination with other therapies.⁽³⁹⁾

TABLE 2. Properties of c-Met Inhibitors Intended for Treatment of HCC

Synonyms	Tivantinib	Cabozantinib	Foretinib	Golvatinib	Capmatinib	Tepotinib
ARQ 197	XL 184	GSK1363089	E7050	INC280, INCB28060	MSC2156119J, EMD1214063	
Arqule, Inc.	Exelixis	GlaxoSmithKline	Eisai Co. Ltd.	Novartis	Merck Serono	
Nonselective	Nonselective	Nonselective	Nonselective	Selective	Selective	
(3R,4R)-3-(5-(6-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-1-yl)-4-(1H-indol-3-yl)-2,5-pyrrolidinedione	N-(4-(6,7-dimethoxyquinolin-4-yl)oxy)phenyl)-N-(4-fluorophenyl)-1-cyclopropane-1,1-dicarboxamide	N ¹ -[3-Fluoro-4-[[6-methoxy-7-(3-morpholinopropoxy)-4-quinolyl]oxy]phenyl]-N-(4-fluorophenyl)-cyclopropane-1,1-dicarboxamide	N'-[2-Fluoro-4-[2-[[4-(4-methylpiperazin-1-yl)piperidine-1-carbonyl]amino]pyridin-4-yl]oxyphenyl]-N-(4-fluorophenyl)-cyclopropane-1,1-dicarboxamide	2-Fluoro-N-methyl-4-[7-(quinolin-6-yl-methyl)-imidazo[1,2-b][1,2,4]triazin-2-yl]benzamide	(3-(1-(3-(5-(1-Methylpiperidin-4-yl)methoxy)-pyrimidin-2-yl)-benzyl)-1,6-dihydro-6-oxo-pyridazin-3-yl)-benzotrifluoride	
						
<i>In vitro</i> IC50 for c-Met (nM)	355	1.3	0.4	14	0.13	3
Other known targets (IC50, nM)	Microtubules (unknown), GSK3α (unknown), GSK3β (unknown)	KDR (0.035), RET (5.2), AXL (7), TIE2 (14.3), FLT3 (11.3), c-KIT (4.6)	c-Met (0.4), KDR (0.86), TIE-2 (1.1), RON (3), FLT-4 (2.8), FLT-3 (3.6)	KDR (16)	None (>10,000-fold selectivity in a panel of 57 kinases)	None (1,000-fold selectivity versus 242 human kinases)
<i>t</i> _{max} (hours)		2-5	4	3	1.9	9
<i>t</i> _{1/2} (hours)		55	55	45	3.1	46

Abbreviations: GSK3α/3β, glycogen synthase kinase 3 alpha and beta; IC50, 50% inhibitory concentration, the dose required to inhibit activity by 50%; *t*_{max}, time required to reach maximal inhibition; *t*_{1/2}, time required for half of drug to be eliminated.

TABLE 3. Trials of c-Met Inhibitors in Patients With HCC

Drug	Brief Trial Description	Phase	Status	Trial Registration No.	Region/Country	C-Met Status	ECOG Status	Child-Pugh Class or Score	Exclusion Criteria	Primary Outcome Measure	Secondary Outcome Measures
Tivantinib	Monotherapy versus placebo for advanced HCC after sorafenib failure (METV-HCC)	III	Complete	NCT01755767	USA, Australia, Europe	MET diagnostic-high using archival or recent biopsy	0-1	A	> 1 prior systemic treatment; prior c-Met therapy	OS (every 8 weeks); trial failed to improve OS	PFS
Tivantinib	Monotherapy versus placebo for advanced HCC after sorafenib or chemotherapy failure (JET-HCC)	III	Recruiting	NCT02029157	Japan		0-1	A	> 2 prior systemic therapies; prior c-Met therapy	PFS (estimated 8-12 weeks in PFS)	OS (estimated 24 weeks in OS)
Tivantinib	Monotherapy versus placebo for unresectable HCC after failure of one systemic therapy	II	Complete	NCT00988741	USA, Canada, Europe	Undefined	0-2	A	> 1 prior systemic treatment	TTP compared to placebo (every 6 weeks)	PFS, OS, ORR, DCR compared to placebo (every 6 weeks); safety (every 4 weeks); pharmacokinetics (every 3 months)
Cabozantinib	Monotherapy versus placebo for advanced HCC (not fibrolamellar carcinoma or mixed hepatocellular cholangiocarcinoma) after sorafenib failure	III	Ongoing	NCT01908426	Worldwide	Undefined	0-1	A	> 2 systemic therapies for advanced HCC; any anticancer agent within 2 weeks of randomization; prior cabozantinib	OS (up to 38 months) duration of PFS	ORR (up to 38 months)
Foretinib	Monotherapy for advanced HCC	I	Complete	NCT00920192	Southeast Asia	Undefined	0-1	< 6	Prior nonselective TKI; currently receiving cancer therapy	TTP	

TABLE 3. Continued

Drug	Brief Trial Description	Phase	Status	Trial Registration No.	Region/Country	C-Met Status	ECOG Status	Child-Pugh Class or Score	Exclusion Criteria	Primary Outcome Measure	Secondary Outcome Measures
Capmatinib	Monotherapy versus placebo for advanced HCC after sorafenib failure	II	Suspended	NCT01964235	Worldwide	Confirmed c-Met dysregulation	0-1	A, NE	Previous anti-neoplastic therapy or investigational drug completed <5 half-lives of the agent prior to randomization and not received from clinically significant treatment to <grade 2; received any targeted agent other than sorafenib	TTP	BOR, ORR, DCR, PFS, OS
Golitinib	Combination with sorafenib versus sorafenib alone first-line for advanced HCC	I/II	Ongoing, not recruiting	NCT01271504	USA, Europe	Undefined	0-1	A or B	Previously received E7050 anti-c-Met or antiangiogenic therapy	Undefined	Efficacy parameter
Capmatinib	First-line monotherapy for advanced HCC	II	Recruiting	NCT01737827	Asia (China, Hong Kong, Singapore, Thailand)	Confirmed c-Met dysregulation	0-2	A, NE	Prior treatment with c-Met inhibitor or HGF targeting therapy; previous local therapy completed <4 weeks prior to dosing	TTP	ORR, PFS, OS, DCR

TABLE 3. Continued

Drug	Brief Trial Description	Phase	Status	Trial Registration No.	Region/Country	C-Met Status	ECOG Status	Child-Pugh Class or Score	Exclusion Criteria	Primary Outcome Measure	Secondary Outcome Measures
Tepotinib	Monotherapy for advanced HCC after sorafenib failure	I/II	Recruiting	NCT02115373	Europe, USA	Not defined for phase 1; confirmed c-Met overexpression for phase 2	0-1	A	Prior systemic anticancer treatment for HCC (except sorafenib); prior treatment with any agent targeting HGF/c-Met pathway local/regional therapy within 4 weeks before day; prior history of liver transplant	Phase 1: no. DLTs to define recommended phase 2 dose Phase 2: PFS at 12 weeks	TTP, time to symptomatic progression, response, PFS, OS, AFP response
Tepotinib	First-line monotherapy for advanced HCC, compared to sorafenib in phase 2 part	I/II	Recruiting	NCT01988493	Asia (China, South Korea, Singapore)	Not defined for phase 1; confirmed c-Met overexpression for phase 2	0-2	A, NE	Prior systemic anticancer treatment for HCC; prior treatment with any agent targeting HGF/c-Met pathway; local/regional therapy within 4 weeks before day 1; prior history of liver transplant	Phase 1: recommended phase 2 dose Phase 2: TTP	Phase 1: preliminary antitumor activity Phase 2: antitumor activity

Abbreviations: AFP, alpha-fetoprotein; BOR, best overall response; DCR, disease control rate; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; NE, no encephalopathy; ORR, overall response rate; PFS, progression-free survival; TTP, time to progression.

To date, six HGF/c-Met inhibitors have been investigated in clinical trials in HCC. All are TKIs, four nonselective and two selective (Table 2). The nonselective inhibitors tivantinib and cabozantinib have been assessed in phase 3 studies as second-line therapy for HCC; the remainder are currently being investigated in phase 1b/2 trials of first-line therapy for HCC (Table 3).

Nonselective c-Met Inhibitors

TIVANTINIB

Tivantinib is a non-adenosine triphosphate-competitive inhibitor of c-Met, with an inhibitor constant of 355 nM. Tivantinib inhibits c-Met by stabilizing its nonphosphorylated inactive conformation,⁽⁴⁰⁾ which was expected to confer high selectivity. Preclinical studies have demonstrated that tivantinib is cytotoxic against many cell lines *in vitro*, including three derived from HCC,⁽⁴¹⁾ but that this cytotoxicity is unrelated to c-Met expression. Tivantinib was subsequently shown to inhibit microtubule assembly, explaining its cytotoxicity *in vitro*; and to be active in cell lines resistant to the microtubule disruptors vincristine, colchicine, and paclitaxel because tivantinib is not a substrate for adenosine triphosphate-binding cassette transporters.⁽⁴²⁾ Tivantinib also potently inhibits glycogen synthase kinases 3 alpha and beta, potentially contributing to cytotoxicity by promoting apoptosis.⁽⁴³⁾

A phase 1b study of tivantinib in patients with previously treated HCC and Child-Pugh A or B liver cirrhosis (NCT00802555)⁽⁴⁴⁾ showed that the most common treatment-related adverse events were neutropenia, leukocytopenia, fatigue, and anorexia, a safety profile like that described for cytotoxic microtubule disruptors and therefore likely due to the non-c-Met inhibitory activity of tivantinib. No drug-related worsening of liver function or performance status was observed, although one patient experienced a drug-related bilirubin increase. Antitumor activity was observed.

A subsequent phase 2 study (NCT00988741)⁽⁴⁵⁾ assessed the antitumor activity of tivantinib in tumors of known c-Met status. While the trial was initiated using tivantinib 360 mg twice daily (bid), the dose was amended to 240 mg bid to reduce the high incidence of treatment-emergent grade ≥ 3 neutropenia. Time to progression was significantly longer for patients with c-Met-high tumors versus c-Met-low tumors (1.6

versus 1.4 months, $P = 0.03$), although progression-free survival and OS were not significantly different (progression-free survival, 1.5 versus 1.4 months, $P = 0.06$; OS, 6.6 versus 6.2 months, $P = 0.63$). Although initially taken as evidence that the antitumor activity of tivantinib is mediated by activity against c-Met, it has subsequently been proposed that c-Met expression is a biomarker of susceptibility to cytotoxic therapy and that the observed activity can be accounted for by microtubule disruption.

Separate phase 3 studies of tivantinib in patients with HCC after systemic treatment failure have been initiated in the West and Japan. These trials enrolled patients with c-Met-high tumors. Because tivantinib can be rapidly metabolized by cytochrome P450 2C19, in Japan two doses of tivantinib are being used in trials in other tumor types: 360 mg bid for extensive metabolizers and 240 mg bid for the 20% of patients who are low metabolizers. However, patients with advanced HCC display distinctive tivantinib pharmacokinetic profiles,⁽⁴⁶⁾ leading to a reduced dose of 120 mg bid being used in the phase 3 trial regardless of cytochrome P450 2C19 phenotype, potentially reducing efficacy. The METIV-HCC phase 3 trial conducted in Western patients has been recently reported to have failed to meet its primary endpoint of improving OS.⁽⁴⁷⁾

CABOZANTINIB

Cabozantinib is a nonselective TKI with activity against c-Met, VEGFR2, FLT3, KIT, AXL, and RET, a combination anticipated to provide synergistic antitumor activity.⁽⁴⁸⁾ However, it is debatable whether an agent with such broad-spectrum activity is optimal. Cabozantinib can inhibit the growth of c-Met-positive and c-Met-negative xenografts by decreasing angiogenesis but is more effective in c-Met-positive xenografts, suggesting that c-Met inhibition contributes to antitumor activity.⁽⁴⁹⁾

Cabozantinib has been assessed in a phase 2 study in patients with solid tumors, including a cohort of 41 patients with advanced HCC who had received a median of one prior therapy, with 51% having received sorafenib.⁽⁵⁰⁾ The most common grade 3/4 adverse events were diarrhea (17%), palmar-plantar erythrodysesthesia (15%), and thrombocytopenia (10%), making its safety profile more similar to those of VEGFR TKIs than those of selective c-Met inhibitors. Cabozantinib showed signs of efficacy in patients with advanced HCC, with an overall disease control rate of 68%. However, the relative contribution of

cabozantinib activity against c-Met versus its other targets is unknown. Based on these data, the ongoing CELESTIAL phase 3 trial (NCT01908426) is comparing cabozantinib with placebo in patients with HCC and Child-Pugh A liver function who have progressed following one or two prior systemic therapies.⁽⁵¹⁾ Patients do not appear to be selected for this trial based on tumor c-Met status.

FORETINIB

Foretinib is a potent inhibitor of c-Met, RON, Vascular endothelial growth factor receptor-2 (KDR), receptor tyrosine kinase (AXL), Flt-1, Flt-3, Flt-4, KIT, platelet-derived growth factor receptor, and Tie-2⁽⁵²⁾; the latter targets are involved in angiogenesis. In preclinical patient-derived HCC xenograft models,⁽⁵³⁾ foretinib demonstrated significant antitumor activity and inhibition of angiogenesis. The restoration of sensitivity to lapatinib in non-HCC preclinical models with HER1/2 and *MET* amplification provided evidence that c-Met activity contributes to the antitumor activity of foretinib.⁽⁵⁴⁾

In a phase 1/2 study in advanced HCC (MET111645), foretinib caused dose-limiting toxicities of renal failure and proteinuria, leading to a dose reduction for the part 2 expansion cohort.⁽⁵⁵⁾ At the maximum tolerated dose (MTD), the most common adverse events were hypertension (36%), decreased appetite (23%), and pyrexia (21%), which are not class effects of selective c-Met inhibitors. Antitumor activity was promising and considered sufficient to warrant further investigation in a randomized setting. A phase 1/2 study of first-line single-agent foretinib in patients with advanced HCC subsequently suggested efficacy, with an overall response rate of 22.9% and median time to progression of 4.2 months.⁽⁵⁶⁾

GOLVATINIB

Golvatinib is a dual c-Met and VEGFR-2 TKI that inhibits tumor growth and angiogenesis in xenograft models.⁽⁵⁷⁾ Regression of *MET*-amplified tumor lines required high doses of golvatinib (50–200 mg/kg).⁽⁵⁷⁾ No preclinical studies of golvatinib in HCC models appear to have been reported, but in a phase 1 study of golvatinib plus sorafenib in advanced HCC, the MTD was established at 200 mg/day; the combination was associated with adverse events including nausea and vomiting, diarrhea, hyperbilirubinemia, abdominal pain, elevated liver enzyme levels, and palmar-plantar

erythrodysesthesia.⁽⁵⁸⁾ Confirmed partial responses in 2 of 12 evaluable patients and durable stable disease in 4 of 13 evaluable patients supported evaluation in phase 2 trials. A phase 1/2 trial comparing golvatinib plus sorafenib with sorafenib alone in patients with previously untreated HCC and Child-Pugh A or B disease is ongoing (NCT01271504). Patients eligible for this trial do not appear to be selected based on c-Met status.

LESSONS FROM CLINICAL ASSESSMENT OF NONSELECTIVE C-MET INHIBITORS IN PATIENTS WITH HCC

The completed studies of nonselective c-Met inhibitors raise issues that need to be considered. First, how does activity against targets other than c-Met contribute to efficacy? Second, what is the impact of this broader activity on treatment-related toxicity? Third, how should patients be selected for therapy? Fourth, what are the implications for combination therapy?

Contrary to initial expectations, most or all of the pharmacological activity of tivantinib is likely unrelated to c-Met inhibition; studies of tivantinib therefore have little to contribute to discussion of the role of c-Met inhibition in HCC. Cabozantinib and foretinib have similar selectivity profiles since both target c-Met and receptors associated with angiogenesis. Combined inhibition of angiogenesis and c-Met signaling may be a more effective antitumor strategy than inhibiting c-Met alone as it targets a broader range of the hallmarks of cancer.⁽⁵⁹⁾ Furthermore, inhibition of multiple targets may confer synergistic antitumor activity: c-Met inhibition is postulated to prevent the escape of cancer cells from tumor hypoxia resulting from antiangiogenic activity, reducing the risk of metastases associated with antiangiogenic therapy.⁽⁶⁰⁾ Conversely, tumor hypoxia can induce c-Met expression,⁽⁶¹⁾ potentially reducing the effectiveness of c-Met inhibitors. The contribution made by c-Met activity to the anticancer properties of these drugs has not been addressed in trials and is unknown. Furthermore, c-Met-inhibitory effects may be modified by antiangiogenic effects to an unknown degree. Studies conducted with these drugs to date consequently give little insight into the antitumor activity that may be associated with selective c-Met inhibitors. Unfortunately, too little data to assess the efficacy of golvatinib are available. However, the dual targeting of c-Met and VEGFR-2 is a rational approach given the known efficacy of sorafenib in HCC, and it will be

interesting to see whether this approach can improve on the activity of sorafenib alone.

The toxicity profiles of cabozantinib and foretinib appear similar to those of more selective antiangiogenic agents (hypertension, proteinuria, and palmar–plantar erythrodysesthesia), although cabozantinib is also associated with hematological toxicity. This calls into question whether c-Met inhibition is relevant to their mechanism of action. Tivantinib has toxicity more typical of cytotoxic microtubule disruptors, as expected based on its mechanism of action. In contrast, the adverse events associated with golvatinib seem to be a mix of those associated with VEGFR and c-Met inhibition. As such, the antitumor activity of golvatinib may be due to inhibition of each of these receptors; but whether this is relevant in all patients with HCC is unlikely, and the probability of efficacy would have to be balanced against likely toxicity.

In trials of tivantinib, the c-Met status of tumors was assessed, and the drug showed greater activity in patients with c-Met-high tumors. Based on these results, subsequent phase 3 trials enrolled patients with c-Met-high HCC. However, given that the contribution of c-Met inhibition to the antitumor activity of tivantinib is probably minimal, high c-Met expression may be an incidental biomarker of tumor sensitivity to treatment. No patient selection based on c-Met status or analysis of outcomes based on c-Met status was done in trials of the other nonselective agents. Therefore, it is impossible to evaluate whether the activity of these agents is affected by tumor c-Met, which would help to assess whether c-Met inhibition contributes to their mechanism of action. Consequently, these trials are unlikely to provide any information on which patients are most likely to respond to therapy.

Finally, these trials provide no information regarding whether combination therapy is likely to be effective or tolerable. Some information may be provided by the ongoing phase 1/2 trial of golvatinib, but as one of the targets of this agent (VEGFR-2) is the same as that of sorafenib, with which it is combined, conclusions will depend on the inhibitory activity of sorafenib. If VEGFR-2 is maximally inhibited by sorafenib, additional inhibition by golvatinib is unlikely to cause additional efficacy or toxicity; alternatively, additional VEGFR-2 inhibition by golvatinib could cause further adverse events if physiological processes are more extensively disrupted.

In summary, from the clinical studies of nonselective c-Met TKIs reported to date, it is not possible to draw any conclusions regarding the antitumor activity or toxicity associated with selective c-Met inhibition.

Furthermore, the design of the currently ongoing trials of these agents will not provide significant further insight into whether c-Met inhibition is critical for the activity of these agents or the likely contribution of c-Met inhibition to their activity.

Selective c-Met Inhibitors

Several approaches to selectively inhibit c-Met have been developed. Small interfering RNA knockdown has been used to specifically down-regulate c-Met, resulting in cell cycle arrest and reduced proliferation, motility, and invasiveness *in vitro*⁽⁶²⁾ and inhibition of tumor xenograft growth *in vivo*,⁽⁶³⁾ indicating the therapeutic potential of selective c-Met inhibition. Small interfering RNA has limited clinical utility due to poor delivery to target cells, but other methods of selective c-Met inhibition have been evaluated.

Several antibodies directed against the extracellular domains of c-Met have been developed. Antibody therapies typically minimize off-target toxicities and are suitable for intermittent dosing, but activity may be compromised if tumor cells are inaccessible to antibodies or if antidrug antibodies develop. Most anti-c-Met antibodies developed as potential therapeutics antagonize HGF binding and therefore inhibit HGF-dependent, but not HGF-independent, c-Met activity. This limits their therapeutic potential for the treatment of patients with advanced HCC. Exceptionally, LY2875358 induces significant internalization of c-Met, reducing cell surface c-Met levels to inhibit both HGF-dependent and HGF-independent c-Met activity.⁽³⁸⁾ LY2875358 has shown promising activity against advanced solid tumors⁽⁶⁴⁾; but the focus for development of LY2875358 appears to be non-small-cell lung cancer, and no studies in patients with HCC appear to be ongoing.

Selective c-Met TKIs represent the current most likely clinical candidates. Studies of agents such as PHA665752, AMG 337, RP1400, and tepotinib both *in vitro* and *in vivo* provide consistent evidence that selective targeting of c-Met can inhibit the proliferation of HCC cells and cause xenograft tumors to shrink, with effects greatest when c-Met expression is high.^(36,65–68) Effects on cell motility and migration have also been observed. These observations warrant the clinical assessment of selective c-Met TKIs. We focus on two selective c-Met TKIs, tepotinib and capmatinib, which are in development for HCC (Table 2).

TEPOTINIB

Tepotinib⁽⁶⁹⁾ has an *in vitro* 50% inhibition concentration of 3 nM for c-Met, >1,000-fold selectivity for c-Met over 236 of 241 other kinases tested, and >200-fold selectivity over the remaining five kinases tested. A phase 1 first-in-humans trial established a recommended phase 2 dose of tepotinib 500 mg/day, which is predicted to achieve minimum plasma concentrations of tepotinib ≥ 700 ng/mL in >95% of patients, sufficient to ensure effective inhibition of c-Met phosphorylation and efficacy against tumor growth.⁽⁷⁰⁾ The half-life of tepotinib was estimated to be approximately 46 hours.⁽⁷⁰⁾ No MTD was established, and there were signs of antitumor activity. The rational dose selection for tepotinib, which was designed to ensure complete c-Met inhibition, should enable the effect of c-Met inhibition to be assessed with confidence in tepotinib trials in patients with HCC.

Tepotinib is being assessed in two phase 1b/2 trials in advanced HCC.^(71,72) The first (NCT02115373) is investigating tepotinib as second-line monotherapy for patients with c-Met-positive HCC failing sorafenib treatment. In the phase 1b part, 14 of 17 patients experienced grade ≤ 2 treatment-related adverse events and 5 experienced grade ≥ 3 treatment-related adverse events, included peripheral edema (n = 2), acute kidney injury (n = 2), and lipase increase (n = 1).⁽⁷³⁾ A partial response was seen in 2 patients; 3 patients had stable disease. The maximum duration of response was >57 weeks. Recruitment to the phase 2 part has recently been completed.

The second study (NCT01988493) is comparing tepotinib with sorafenib first-line in Asian patients with HCC.⁽⁷²⁾ In the phase 1b part, the most common treatment-related adverse events of grade ≤ 2 were diarrhea (n = 10), elevated aspartate aminotransferase (n = 7), and elevated alanine aminotransferase (n = 6). Fifteen of 27 patients experienced grade ≥ 3 treatment-related adverse events, the most common being grade 3 increased lipase levels (n = 3) and grade 3 diarrhea (n = 2).⁽⁷⁴⁾ Of 7 patients with c-Met-positive HCC, 2 had a partial response and 2 had stable disease; which compares favorably to outcomes in the group of 18 patients with c-Met-negative disease, in whom the best observed response was stable disease.

The phase 2 parts of both of these trials require that patients have HCC with high levels of c-Met (c-Met 2+ or c-Met 3+ by immunohistochemistry), and, being randomized, the trial in progress in Asia will

demonstrate whether tepotinib is more effective than sorafenib in this selected patient population.

CAPMATINIB

Capmatinib has an *in vitro* 50% inhibition concentration of 0.13 nM for c-Met and >10,000-fold selectivity over 57 other kinases tested.⁽⁷⁵⁾ In a phase 1 trial of capmatinib in patients with c-Met-dependent solid tumors (NCT01072266), 15 of 33 (45%) with HCC, capmatinib 600 mg bid was identified as a dose suitable for further study. The relatively high dose and twice-daily dosing regimen reflect the short plasma half-life of capmatinib (3.1 hours).⁽⁷⁶⁾ Near-complete inhibition of c-Met phosphorylation was reported in paired biopsies from 1 patient with colorectal cancer. The most frequent drug-related adverse events were decreased appetite (33%), nausea (30%), vomiting (27%), and fatigue (27%). The most frequent drug-related grade 3/4 adverse events were fatigue and decreased appetite, and dose-limiting toxicities were fatigue and increased bilirubin. Stable disease in 8 of 33 patients was the best-reported response in this heavily pretreated patient population. Patients with HCC and confirmed c-Met pathway dysregulation are being recruited to a phase 2 expansion trial (NCT01737827). A further phase 1b/2 trial examining capmatinib in combination with PDR001, an anti-programmed death 1 (PD-1) antibody, is also recruiting patients with advanced HCC (NCT02795429); but there is no requirement for tumor c-Met positivity.

The safety profiles of tepotinib and capmatinib are similar and can reasonably be attributed to c-Met inhibition. Importantly, profound inhibition of c-Met has been confirmed at the active doses used, and established without reaching the MTD in the case of tepotinib. These observations suggest that the full antitumor activity of selective c-Met inhibitors can be exploited in the clinic, with a safety profile favorable for use in combination. Both agents have shown promising signs of efficacy in HCC.

Implications for Trial Design

Trials conducted to date in patients with HCC have not been designed to allow the antitumor effects of c-Met inhibition to be fully assessed. In studies of nonselective agents, the contribution of c-Met inhibition to antitumor activity cannot be determined, while

studies of selective c-Met inhibitors in HCC suggest that activity is greatest in tumors with c-Met aberrations, but patient selection according to c-Met status has not been well defined, and reported data are too preliminary for strong conclusions to be drawn.

Conclusive proof that inhibition of aberrant c-Met activity has antitumor activity will require well-designed trials. At minimum, in the first-line setting these would include randomization of patients to a selective c-Met inhibitor versus the current standard of care (sorafenib); dosing of the selective c-Met inhibitor at a level known to inhibit c-Met activity sufficiently to prevent associated signaling, which requires consideration of pharmacodynamic and pharmacokinetic data rather than dose selection based on MTD; appropriate selection of endpoints, although the gold standard in cancer trials remains OS; inclusion of patients with underlying liver disease representative of the general population of patients with HCC; and selection of patients based on known aberrant tumor c-Met activity. In later-line settings, patients would be randomized to a selective c-Met inhibitor versus regorafenib or placebo. In addition, the effective dose may need to be reevaluated because it could differ from that established for first-line treatment due to possible differences in drug pharmacokinetics and tolerability associated with progressive liver disease.

As the inclusion of patients with c-Met-low or c-Met-negative HCC in trials potentially confounds the assessment of efficacy associated with c-Met inhibition, the choice of method for determining aberrant tumor c-Met activity in future trials will be important. Potential assays include HGF immunoassay (ligand overexpression), c-Met immunohistochemistry (receptor overexpression), *MET in situ* hybridization (target amplification), and *MET* gene sequencing (mutation). No single assay can identify all types of aberrant c-Met, and some assays may identify c-Met alterations that do not lead to clinically relevant increased c-Met activity. Furthermore, the relationship between HGF levels, c-Met overexpression, *MET* amplification, and sensitivity to c-Met inhibitors has not been fully established. *MET* amplification in tumors appears to be an effective biomarker of responsiveness to c-Met inhibitors in a range of solid tumors,⁽⁷⁷⁾ possibly because such aberrations are selected during tumor evolution to drive tumor progression through c-Met overexpression. *MET* mutations that cause skipping of exon 14 consistently lead to accumulation of functional c-Met on the surface of tumor cells and sensitivity to c-Met inhibitors.⁽⁷⁸⁾ However, such mutations in HCC have

limited clinical importance because their incidence in HCC is <0.1%.⁽⁷⁸⁾ Other activating *MET* mutations are also rare, detectable only in childhood HCCs⁽⁷⁹⁾; and most HCCs that express high levels of c-Met receptor have neither amplified nor mutated *MET*.⁽²⁸⁾ A proportion of such HCCs appear sensitive to c-Met inhibitors,⁽⁸⁰⁾ and the challenge will be to differentiate those likely to respond from those unlikely to respond, most likely based on criteria other than c-Met status.

The ideal diagnostic for the selection of patients with tumors responsive to c-Met inhibitors must have good predictivity, which depends upon diagnostic sensitivity and specificity. A diagnostic based on assays to detect genomic aberrations of c-Met (fluorescence *in situ* hybridization for copy number gain, next-generation sequencing for mutation) could provide good specificity (most tumors with genomic aberrations are sensitive to c-Met inhibitors) but limited sensitivity because tumors sensitive to c-Met inhibitors but without genomic aberration would not be identified. These assays could therefore be the basis of a good diagnostic, but additional assays are required to identify patients whose tumors have normal *MET* but express aberrant, tumorigenic c-Met. It is reasonable to assume that such tumors can be detected with good sensitivity using c-Met immunohistochemistry, but additional assays would be required to increase specificity by excluding patients whose tumors express high levels of c-Met that are incidental to tumorigenesis. The combination of c-Met immunohistochemistry with additional biomarkers such as gene expression signatures determined by high-content technologies such as RNA sequencing has the potential to improve the predictivity of a single-marker assay by establishing tumor addiction to c-Met at the molecular pathway level. The development of such complex diagnostics will require extensive investigation, followed by validation in carefully designed trials with prospectively selected patients. Diagnostics will become increasingly important as c-Met inhibitors progress to phase 3 trials, and the development of companion diagnostics will be critical.

Although c-Met inhibitors have shown evidence of activity in HCC as monotherapy, combining them with other therapeutic agents may also have potential. Increasingly, personalized health care is enabling key drivers of individual HCCs to be identified and targeted,⁽⁸¹⁾ and the role of nonselective inhibitors in HCC shows that multikinase inhibition can be effective. Use of combinations of selective c-Met inhibitors

with agents selective for other targets has the promise to enable rational combinations of kinases to be inhibited with less toxicity than that associated with the inhibition of therapeutically irrelevant targets using nonselective inhibitors. To date, c-Met inhibitors in combination with sorafenib⁽⁸²⁾ and erlotinib⁽⁸³⁾ have been evaluated in trials including patients with HCC. Early signs of efficacy are promising, but larger trials will be required before firm conclusions can be drawn.

There is growing interest in immune checkpoint inhibitors for the treatment of patients with HCC. Limited data are currently available regarding PD-1 ligand (PD-L1) and c-Met (co)expression, but a direct anti-inflammatory effect of HGF/c-MET on several types of immune cells has been described, suggesting that c-Met inhibitors combined with anti-PD-(L)1 agents may synergize to promote an antitumor immune response.⁽⁸⁴⁾ Phase 1/2 and 3 trials of nivolumab (anti-PD-1 antibody) alone and in combination with the anti-cytotoxic T lymphocyte antigen 4 antibody ipilimumab, pembrolizumab (anti-PD-1 antibody), and durvalumab (anti-PD-L1 antibody) alone and in combination with the anti-cytotoxic T lymphocyte antigen 4 antibody tremelimumab are ongoing⁽⁸⁵⁾ and collectively have demonstrated promising efficacy, safety, and tolerability. Because c-Met and checkpoint inhibitors affect different targets in HCC, synergistic efficacy from combination therapies is an exciting possibility that remains to be tested clinically.⁽⁸⁶⁾

The ability to combine c-Met inhibitors with other targeted therapies will become increasingly important as personalized therapy for HCC becomes more common.

Liver Disease and c-Met-Targeted Therapy

c-Met inhibition may exacerbate underlying liver disease in HCC,⁽⁸⁷⁾ although evidence from clinical trials of c-Met inhibitors is limited, perhaps partly due to the exclusion of patients with poor liver function from trials to date. However, the prognosis of patients with HCC is influenced not only by the status of the tumor but also by the underlying liver function; 90% of patients with HCC have underlying cirrhosis, and 75% have active hepatitis.⁽⁸⁸⁾

Cirrhosis and resection both drive liver regeneration,⁽⁸⁹⁾ which may be compromised by c-Met inhibitors. Cirrhosis additionally leads to hypoxia in the

liver,⁽⁹⁰⁾ promoting the expression of c-Met⁽⁹¹⁾, which may increase the concentration of c-Met inhibitor required to render c-Met inactive. Therapies with an antiangiogenic component, including some nonselective c-Met inhibitors, may compound liver hypoxia.

Liver disease can also affect drug pharmacokinetics and pharmacodynamics.^(92,93) Fibrosis and cirrhosis reduce phase 1 and phase 2 enzyme activity in the liver, impairing hepatic clearance of drugs and altering drug-drug interactions and metabolic profiles.⁽⁹⁴⁾ These effects can alter the dose of drug required to achieve a desired blood concentration and may lead to the emergence of novel toxicities.⁽⁹⁰⁾ Liver disease therefore typically reduces the therapeutic window in patients and may necessitate a reduction in dose to suboptimal levels to avoid dose-limiting toxicity.^(92,93) The larger therapeutic margin of selective c-Met TKIs compared to nonselective c-Met TKIs may be a critical advantage for their use in patients with cirrhosis.

To allow adequate dosing and meaningful assessment of efficacy, most clinical trials of drugs in HCC are conducted in patients with Child-Pugh A disease. Most patients with advanced HCC, however, have Child-Pugh B or C disease and may not tolerate the effective doses of c-Met inhibitors established in trials. Further, c-Met inhibitors may cause disproportionate acceleration of advanced liver disease, precluding their use in these patients.⁽⁸⁷⁾ Increased c-Met inhibitor toxicity may be further confounded when the inhibitors are used as part of combination regimens. Highly selective c-Met inhibitors offer the best hope of effective treatment with acceptable toxicity in these patients.

In summary, greater liver toxicity associated with c-Met inhibition may be anticipated in patients with more severe liver disease. The degree to which underlying disease might restrict the use of c-Met inhibitors for the treatment of patients with HCC has yet to be established and may depend on additional factors including the subtype and grade of HCC,^(95,96) ethnicity, and hepatitis B and C virus infection.⁽⁹⁷⁾

Conclusions

c-Met is a therapeutically relevant target in HCC, with important roles in tumor proliferation, motility, and invasion. Both nonselective and selective inhibitors of c-Met have been developed. Early trials of these inhibitors indicate that c-Met inhibition has activity in HCC and that the safety profiles of nonselective and

selective agents differ, with implications for clinical utility. Furthermore, these trials provide information that can be used to optimize the design of further trials of these agents to ensure that the activity of c-Met inhibition is fully characterized.

It will be important to consider the potential interaction between underlying liver disease and c-Met inhibitor therapy due to the apparent role of c-Met in the repair of liver damage; however, data to date do not indicate any clinically relevant adverse effects of selective c-Met inhibitor therapy on liver function. Selective c-Met inhibitors such as tepotinib have the greatest potential for demonstrating benefit, based on considerations including dose selection, patient selection, and adverse event profile. Ongoing trials and translational research will improve patient selection, enable assessment of antitumor effects, and demonstrate the efficacy of c-Met inhibitors in combination with other therapies.

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