

Emerging molecular targets in oncology: clinical potential of MET/hepatocyte growth-factor inhibitors

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Abstract: The MET/hepatocyte growth-factor (HGF) signaling pathway plays a key role in the processes of embryogenesis, wound healing, and organ regeneration. Aberrant activation of MET/HGF occurs through multiple mechanisms including gene amplification, mutation, protein overexpression, and abnormal gene splicing interrupting autocrine and paracrine regulatory feedback mechanisms. In many cancers including non-small-cell lung cancer, colorectal, gastric, renal, and hepatocellular cancer, dysregulation of MET may lead to a more aggressive cancer phenotype and may be a negative prognostic indicator. Successful therapeutic targeting of the MET/HGF pathway has been achieved using monoclonal antibodies against the MET receptor and its ligand HGF in addition to MET-specific and multitargeted small-molecule tyrosine-kinase inhibitors with several drugs in late-phase clinical trials including onartuzumab, rilotumumab, tivantinib, and cabozantinib. MET frequently interacts with other key oncogenic tyrosine kinases including epidermal growth-factor receptor (EGFR) and HER-3 and these interactions may be responsible for resistance to anti-EGFR therapies. Similarly, resistance to MET inhibition may be mediated through EGFR activation, or alternatively by increasing levels of *MET* amplification or acquisition of novel “gatekeeper” mutations. In order to optimize development of effective inhibitors of the MET/HGF pathway clinical trials must be enriched for patients with demonstrable MET-pathway dysregulation for which robustly standardized and validated assays are required.

Keywords: MET, HGF, colorectal cancer, gastric cancer, NSCLC, renal cancer, hepatocellular cancer, onartuzumab, rilotumumab, cabozantinib

MET signaling pathways and function in healthy tissue

The *MET* proto-oncogene was first identified in a chemically transformed osteosarcoma-derived cell line in 1984, and its protein product was subsequently found to describe a receptor tyrosine kinase the ligand for which was identified as hepatocyte growth factor (HGF; or scatter factor).¹⁻³ Ligand-dependent activation by binding of HGF to MET leads to receptor dimerization and phosphorylation of three kinase-domain tyrosine residues which then initiate the process of autophosphorylation of tyrosine (Tyr) 1349 and Tyr1356 in the bidentate substrate-binding site, facilitating recruitment of cytoplasmic effector proteins and activating transmembrane signaling.⁴ Downstream signaling effects are transmitted via mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)/Akt (protein kinase B), signal transducer and activator of transcription proteins (STAT), and nuclear factor- κ B.⁵⁻⁷ The final output of the terminal effector components of these pathways is activation of cytoplasmic and nuclear

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processes leading to increases in cell proliferation, survival and mobilization, and invasive capacity.⁸

The MET/HGF signaling pathway plays a key role in hepatocyte and placental formation during embryogenesis, and additionally in voluntary muscle and central nervous system formation.^{9–12} The effects of MET/HGF are critical for wound healing and organ regeneration; signaling through this pathway encourages proliferation of keratinocytes and their mobilization into de-epithelized zones, and increased levels of HGF produced in response to injury by hepatocytes and renal epithelial cells leads to mitotic and antiapoptotic activity.^{13–15} These constitutive effects of MET on proliferation, apoptosis, and migration are subverted during the process of tumor growth and metastasis leading to an aggressive MET-addicted tumor phenotype.

MET activation in cancer

Aberrant MET signaling is a hallmark of multiple cancer types, and may occur through gene amplification or mutation, protein overexpression, or abnormal gene splicing which interrupt normal autocrine and paracrine regulatory feedback mechanisms.⁶ Missense mutations of *MET* have been demonstrated in the germ line of families with a history of hereditary papillary renal cell carcinoma (RCC) and in the tumors of a subset of sporadic papillary renal cancers.¹⁶ Production of mouse models with an activating mutation replacing endogenous *MET* yielded diverse cancers including carcinomas, lymphomas, and sarcomas, providing proof of concept of oncogenic activity for the mutated genotype.¹⁷ *MET* amplification on chromosome 7q31 has been described in gastroesophageal, colorectal, and endometrial carcinoma, medulloblastoma, non-small-cell lung cancer (NSCLC), and glioma.^{18–23} Overexpression of the protein receptor tyrosine kinase is more common than amplification, and has been demonstrated in all tumor types with gene amplification in addition to breast, cervical, head and neck, renal, hepatocellular, melanoma, thyroid, and mesothelioma cancer types.²⁴

MET also interacts with other key oncogenic signaling pathways, in particular HER2 (human epidermal growth factor receptor 2) superfamily members epidermal growth-factor receptor (EGFR) and HER-3. For example, cells that express EGFR and MET demonstrate ligand-independent MET phosphorylation and activation through EGFR, whereas in *EGFR*-mutant NSCLC, *MET* amplification leads to escape from gefitinib sensitivity by HER3-mediated activation of PI3K signaling.^{25,26} In Kirsten rat sarcoma (*KRAS*) wild-type colorectal cancer cell lines overexpression of the EGFR ligand TGF α (transforming growth factor- α) leads to MET

activation and cetuximab resistance, and *MET* amplification appears to be a resistance mechanism for colorectal cancer patients treated with anti-EGFR antibody therapy.^{27,28} The MET pathway also increases the malignant potential of tumors through induction of angiogenesis; MET/HGF is a potent inducer of vascular endothelial growth factor (VEGF)-A production and suppressor of thrombospondin-1, and acts synergistically with the VEGF receptor (VEGFR) through common downstream signaling molecules to increase neovascularization activity.^{7,29} Finally, there appears to be an emerging role for MET/HGF signaling in maintaining the stem cell niche in cancer; Wnt activity in colorectal cancer stem cells has been described to be supported by myofibroblast-secreted HGF.³⁰ These interconnected and diverse functions underlie the key role of the MET/HGF axis in driving tumor growth and supporting an intercellular milieu that is conducive to the metastatic spread of the primary tumor.

Development of MET-inhibitor therapies

Greater understanding of the structure, function, and role of MET/HGF in cancer has led to the development of multiple compounds targeting this pathway. These include monoclonal antibodies targeting the receptor and ligand, and small-molecule tyrosine-kinase inhibitors (TKIs) functional at an intracellular level. Monoclonal antibodies in clinical trials include onartuzumab (MetMab; Roche, Basel, Switzerland), rilotumumab (Amgen, Thousand Oaks, CA, USA) and ficlatuzumab (Aveo Pharmaceuticals, Cambridge, MA, USA). Onartuzumab, a human immunoglobulin (Ig)-G₁ antibody with murine variable domains is a potent MET antagonist that competes with HGF for binding at that site.³¹ Rilotumumab and ficlatuzumab are fully humanized monoclonal anti-HGF antibodies that block HGF binding to MET.³² Onartuzumab and rilotumumab bind to the Sema and SPH (serine protease-homology) domains of MET and HGF respectively, and the monovalent binding design of onartuzumab has been demonstrated to prevent activation of the receptor induced by dimerization which may occur with bivalent antibodies.³³

The majority of small-molecule inhibitors of MET may be classified as one of three subtypes each of which impedes adenosine triphosphate (ATP) binding, but of which type II and type III also occupy other distinct binding sites within the MET receptor.⁶ Most type I inhibitors (eg, crizotinib) preferentially bind to the inactive form of the enzyme and are therefore ineffective against tumors harboring an activating Tyr1230H mutation. Type I inhibitors are most

specific for the MET kinase; however, crizotinib has also demonstrated significant efficacy against NSCLC tumors harboring echinoderm microtubule-associated protein-like 4–anaplastic lymphoma kinase (EML4-ALK) fusion and ALK-positive large-cell lymphomas.^{34,35} Type II inhibitors are more promiscuous: in addition to MET, foretinib is an inhibitor of AXL, RON (Recepteur d'Origine Nantais), VEGFR2, PDGFR (platelet-derived growth-factor receptor- β), and KIT.^{36,37} Cabozantinib is a multitargeted TKI with activity against MET, VEGFR2, RET, KIT, AXL, tyrosine kinase with immunoglobulin-like and EGF-like domains (TIE)-2 and FLT, and is active against both the active and inactive conformations of MET.³⁸ Tivantinib, which cannot be accurately classified into any of these subtypes, is a non-ATP competitive MET inhibitor that impedes ligand-dependent and -independent activation.³⁹

MET in lung cancer

In NSCLC overexpression of MET occurs in up to 60% of tumor tissues.⁴⁰ The most common mechanism of MET activation is protein expression secondary to transcriptional upregulation.⁴¹ Although less common, amplification and mutation of the *MET* gene are alternative mechanisms leading to MET activation; *MET* amplification has been reported in 1%–21% of cases, whereas mutations of the *MET* gene occur less frequently and usually lead to activation of the HGF/MET pathway through alternative splice forms deleting the juxtamembrane domain.^{22,42–45} Although MET activation does not appear to be associated with specific clinicopathological characteristics studies have consistently reported an association of both MET amplification/overexpression and intratumoral/plasma HGF levels with poor prognosis.^{43,46–51} Moreover, the HGF/MET pathway also plays an important role in mediating resistance to EGFR TKIs through the activation of both PI3K/Akt and extracellular signal-regulated kinase (ERK) signaling.^{52,53} Preclinical data suggest that combining EGFR TKIs and MET inhibitors is a promising strategy to restore gefitinib sensitivity in cell lines.^{26,54}

In recent years, several inhibitors of the HGF/MET pathway have been investigated in NSCLC, largely in combination with EGFR TKIs. Onartuzumab (the monoclonal antibody that competes with HGF for MET binding) has been examined in a randomized Phase II trial of erlotinib \pm onartuzumab in EGFR-unselected, chemorefractory, NSCLC patients (Table 1). A total of 137 patients were enrolled, and no differences in survival outcomes were observed in the non-molecularly selected intention-to-treat population.⁵⁵ However, in a prespecified subgroup analysis of MET-positive

patients (n=66), the combination of onartuzumab plus erlotinib was associated with a significant improvement in both progression-free survival (PFS; hazard ratio [HR] 0.53, $P=0.04$) and overall survival (OS; HR 0.37, $P=0.002$) compared to erlotinib alone. Outcomes were inferior for MET-negative patients treated with onartuzumab compared to those treated with erlotinib alone (PFS HR 1.71, $P=0.06$; OS HR 2.61, $P=0.004$). A randomized Phase III trial of erlotinib \pm onartuzumab in MET-positive patients was initiated but recruitment was halted for futility following a planned interim analysis.⁵⁶ In contrast, a trial of ficlatuzumab, the humanized IgG₁ antibody, has provided contrasting results in a similar patient population.⁵⁷ Despite promising preliminary activity observed in Phase I trials, a randomized Phase II trial of gefitinib \pm ficlatuzumab in 188 treatment-naïve Asian patients with high incidence of sensitizing *EGFR* mutations failed to demonstrate superiority of the combination therapy.^{58–60} PFS was 5.6 months in the combination arm versus 4.7 months in the gefitinib-alone arm. Interestingly, in contrast to the results reported in the trial with onartuzumab, a subgroup analysis showed that the addition of ficlatuzumab to gefitinib seemed to benefit more those patients with low tumoral MET expression (7.3 versus 2.8 months), and this difference appeared to be more pronounced in the presence of tumors with sensitizing *EGFR* mutations. However, as the patients in this subset analysis were fewer than 20 it is difficult to draw any firm conclusions from these data.

Mixed results have also been demonstrated for tivantinib (ARQ 197; ArQule, Woburn, MA, USA), the non-ATP-competitive small-molecule MET inhibitor that exerts its antitumor activity by stabilizing the inactive conformation of MET.³⁹ A randomized Phase II trial of erlotinib with or without tivantinib in 167 previously treated patients with EGFR TKI-naïve NSCLC failed to meet its primary end point of an improvement in PFS in the intention-to-treat non-biomarker-selected patient population.⁶¹ In this study, a numerically better but not statistically significant improvement in PFS (3.8 versus 2.3 months, HR 0.81; $P=0.24$) was reported for the combination therapy. However, in a prespecified proportional hazards model assessing PFS, this difference was found to be statistically significant (HR 0.68, $P=0.04$). Moreover, in another prespecified exploratory analysis, a significant improvement in PFS was also observed in the group of patients with *KRAS*-mutant tumors (HR 0.18, P -value for interaction =0.006). Based on the evidence of a trend toward an increased benefit from tivantinib in patients with nonsquamous histology and tumors with high *MET* gene copy number, a randomized

Table 1 Selected MET-inhibitor clinical trials with biomarker-selected results if available

Tumor type	Setting	Drug	n	RR	PFS	Biomarker-selected PFS	OS	Biomarker-selected OS
NSCLC								
Mok et al ⁶⁰	1st-line Asian	Gefitinib + ficituzumab Gefitinib	94 94	43% 40%	5.6 months 4.7 months	MET high, 7.4 months MET high, 5.5 months	NR NR	NR NR
Sequist et al ⁶¹	2nd-line EGFR-naïve	Erlotinib + tivantinib Erlotinib + placebo	84 83	10% 7%	3.8 months 2.3 months	MET CNG \geq 5; 5.6 months MET CNG \geq 5; 3.6 months	8.5 months 6.9 months	MET CNG \geq 5; 9.3 months MET CNG \geq 5; 7.5 months
Spigel et al ⁵⁵	2nd/3rd-line advanced	Erlotinib + onartuzumab Erlotinib + placebo	69 68	5.8% 4.4%	2.2 months 2.6 months	MET+, 2.9 m; MET-, 1.4 m MET+, 1.5 m; MET-, 2.7 m	8.9 months 7.4 months	MET+, 12.6 m; MET-, 8.1 m MET+, 3.8 m; MET-, 15.3 m
Colorectal cancer								
Eng et al ⁷⁶	2nd-line KRAS wild type EGFR-naïve	Cetuximab/irinotecan + tivantinib (T) Cetuximab/irinotecan + placebo (P)	60 57	45% 33%	8.3 months 7.3 months	NS difference in PFS for T versus P by MET high expression, inferior PFS for MET low patients treated with T	NR NR	NS difference
Eng et al ⁷³	Chemorefractory KRAS wild type EGFR-naïve	Panitumumab + rilotumumab Panitumumab + ganitumumab Panitumumab + placebo	48 46 48	31% 22% 21%	5.2 months 5.3 months 3.7 months	NS difference in PFS by MET expression Odds ratio (OR) for response to panitumumab + rilotumumab favored MET high (OR 4.97, P=0.028)	NR NR	NR NR
Esophagogastric cancer								
Oliner et al ⁸⁸	1st-line	ECX + rilotumumab	82	38%	5.6 months	MET high, 6.7 months	11.1 months	MET high, 11.1 months
Shah et al ⁸⁷	2nd-line	ECX + placebo Foretinib	39 74	24% 0%	4.2 months 1.7 months	MET high, 4.6 months Two evaluable MET-amplified patients; one SD (2.1 months), one PD	8.9 months 7.4 months*	MET high, 5.7 months
Hepatocellular cancer								
Santoro et al ¹⁰⁰	2nd-line	Tivantinib Placebo	71 36	1% 0%	1.5 months 1.4 months	MET+, 2.2 m; MET-, 1.5 m MET+, 1.4 m; MET-, 1.4 m	6.6 months 6.2 months	MET+, 7.2 m; MET-, 5.0 m MET+, 3.8 m; MET-, 9.0 m
Verslype et al ¹⁰⁶	1st/2nd-line	Cabozantinib	41	5%	4.4 months	NR	15.1 months	NR
Yau et al ¹⁰⁷	1st-line	Foretinib	39	24%	4.2 months	NR	NR	NR
Prostate cancer								
Smith et al ¹¹⁵	1st/2nd-line	Cabozantinib	171	5%	29.4 weeks	NR	NR	NR
Ryan et al ¹²¹	Taxane-refractory	Mitoxantrone-prednisone + rilotumumab Mitoxantrone-prednisone + placebo	93 49	11% 14%	3.0 months 2.9 months	NR NR	12.2 months 11.1 months	MET+, 9.8 m; MET-, 13.4 m MET+, 8.9 m; MET-, not reached
Renal cancer								
Choueiri et al ¹²⁵	2nd-line	Cabozantinib + rosiglitazone	24	28%	14.7 months	NR	NR	NR
Schoffski et al ¹²⁴	2nd-line	Rilotumumab 10 mg/kg Rilotumumab 20 mg/kg	61	2.5% 0%	3.7 months 2.0 months	No correlation between MET expression and PFS	14.9 months 17.6 months	NR NR
Choueiri et al ¹²⁸	1st/2nd-line Papillary renal	Foretinib	74	13%	9.3 months	Germ-line MET mutant 50% ORR, 20% somatic MET mutant	NR	NR

Notes: *intermittent dosing cohort; **continuous dosing cohort.

Abbreviations: RR, relative risk; PFS, progression-free survival; OS, overall survival; NSCLC, non-small-cell lung cancer; NR, not reported; EGFR, epidermal growth-factor receptor; CNG, copy-number gain; KRAS, Kirsten rat sarcoma; NS, no significant; ECX, epirubicin, cisplatin, Xeloda; SD, stable disease; PD, progressive disease; ORR, overall response rate; m, months.

Phase III trial of erlotinib ± tivantinib in pretreated, nonsquamous NSCLC patients was initiated. Although a significant improvement in PFS for the combination treatment was observed, the trial was discontinued early on the advice of the independent data-monitoring committee for futility, as the desired difference in the primary end point of OS would not be reached.²⁴ Other Phase II and III clinical trials investigating tivantinib in combination with erlotinib in NSCLC are ongoing; these include those in the *EGFR* wild-type⁶² and *KRAS*-mutant⁶³ populations.

MET in colorectal cancer

Activation of MET is a common feature in colorectal cancer and upregulation of the HGF/MET pathway, as expressed by MET messenger ribonucleic acid (mRNA) or protein overexpression has been consistently reported in this setting.^{64–66} In contrast and in keeping with other malignancies, ligand-independent MET activation by amplification or mutation has only been reported in a minority of cases.^{41,67} In colorectal cancer MET appears to have an important role in tumor progression and has also been reported to be a negative prognostic indicator.^{23,68–70} Multiple series demonstrate that MET activation in colorectal cancer may provide a selective advantage for the acquisition of an aggressive phenotype that correlates with early stage invasion, liver metastases, and unfavorable clinical outcomes.^{23,68–71}

Preclinical data suggest that HGF-induced MET activation may represent an alternative, RAS-independent mechanism of resistance to cetuximab through the reactivation of the MAPK and Akt pathways. Stimulation with HGF was shown to inhibit the antiproliferative effects of EGFR inhibition, while MET inhibition abrogated this effect.⁷² These preliminary findings of the importance of MET in resistance to anti-EGFR therapy in colorectal cancer have been confirmed in a recent study where *MET* amplification emerged as a novel mechanism of both primary and secondary resistance to EGFR-targeted antibodies, possibly accounting for >10% of cetuximab-resistant cases that are wild type for *KRAS*, *BRAF*, *NRAS* (neuroblastoma RAS), *PIK3CA* (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha), and *HER2*.²⁸ Interestingly, *MET* amplification in patients who progressed on anti-EGFR agents was either a new molecular finding in posttreatment tumor samples or the result of the expansion of a preexisting minor subclonal population of *MET*-amplified cancer cells under the selective pressure of an EGFR-targeted therapy.

Several MET inhibitors have been tested in colorectal cancer or are currently under investigation; however, most

of the available data relate to the monoclonal antibody rilotumumab and the selective, non-ATP-competitive MET TKI tivantinib. In a three-arm, randomized Phase IB/II trial (n=142) of panitumumab (Vectibix®; Amgen) in combination with rilotumumab (anti-HGF antibody), ganitumumab (IGF-1R [insulin-like growth-factor receptor-1 inhibitor]) or placebo, the use of the combination treatment including rilotumumab showed promising activity (overall response rate 31% versus 21%; PFS 5.2 versus 3.7 months) compared to single-agent panitumumab in patients with chemorefractory tumors.⁷³ In a biomarker analysis of 91 of 96 patients allocated to panitumumab ± rilotumumab a correlation between MET expression and activity of rilotumumab was found only when MET-staining intensity (≥2+ versus ≤1+) rather than percentage of MET-positive cells (>50% versus ≤50%) was considered. The anti-MET monoclonal antibody onartuzumab (MetMab) is currently being investigated in a randomized, double-blind, placebo-controlled, Phase II study in conjunction with bevacizumab plus mFOLFOX-6 in chemo-naïve metastatic colorectal cancer patients;⁷⁴ recruitment has completed to this study and results are currently pending.⁷⁵

As a result of promising signals of activity of the anti-MET TKI tivantinib in a Phase IB study in colorectal cancer where four of nine patients had an objective response, a combination study of irinotecan–cetuximab (Eribitux, Merck-Serono) with or without this drug was investigated in a randomized, Phase II trial in a population of *KRAS* wild-type metastatic colorectal cancer patients (n=122) who had progressed on or after one line of systemic therapy.^{76,77} Tivantinib in combination with standard treatment was associated with a higher response rate (45% versus 33.3%) and a slight improvement in PFS (8.3 versus 7.3 months, respectively); however this was not statistically significant (PFS HR 0.85, *P*=0.38). Surprisingly, but in line with what has been observed with ficlatuzumab in NSCLC, a subgroup analysis conducted in a small number of study patients showed a statistically significant improvement in PFS with tivantinib in patients with low-MET-expressing tumors; however this subgroup contained only 23 patients and requires validation in a larger patient cohort. Tivantinib is currently under investigation in conjunction with cetuximab in a Phase II study in advanced colorectal cancer patients who are refractory to anti-EGFR therapy and who demonstrate high MET (immunohistochemistry [IHC] 2+ or IHC 3+) expression.⁷⁴

Esophagogastric cancer

The MET pathway is frequently aberrantly activated in gastric carcinoma with evidence of both overexpression and

amplification demonstrated in multiple series. Overexpression of MET appears to be more common than amplification, and may be membranous or cytoplasmic. In a recent series of 495 Korean patients membranous and cytoplasmic overexpression of MET was demonstrated in 22% of cases and membranous expression alone in 8%. Simultaneous overexpression correlated well with increased MET mRNA expression, copy-number gain, and amplification, and was prognostic with respect to OS and disease-free survival; however, membranous MET expression alone did not significantly correlate with these end points.⁷⁸ In another large Asian series (n=438), Lee et al demonstrated a 24% prevalence of overexpression (IHC 2+ and 3+) combined and a 3.4% rate of copy-number gain using silver in situ hybridization. Almost all (>90%) patients with MET IHC 3+ overexpression demonstrated gene amplification, with the remainder demonstrating high gene polysomy.⁷⁹ Furthermore, all patients with gene amplification demonstrated either IHC 2+ or 3+ overexpression. Therefore it appears that in comparison to overexpression *MET* amplification in gastric cancer is a relatively infrequent event with rates ranging from 2% to 10%.⁷⁸⁻⁸¹ Of note, earlier studies examining levels of amplification are likely to have overestimated the incidence of this event due to methodological considerations as these studies frequently used Southern blot or quantitative polymerase chain-reaction techniques which are unable to distinguish between true gene amplification and polysomy, whereas this poses less difficulty with current in situ hybridization techniques.^{18,19,82}

There is particular difficulty in assessing the consistency of measurement of MET overexpression across studies as different investigators have used either varying percentage of cell staining alone as a measure, whereas others have used both percentage of cells and intensity of staining and various composites of these to yield an H-score.⁸³ This is also true of amplification as the level of copy-number gain which has been designated as MET high is between two and five times the level of a reference gene depending on the series.^{79,80} A recent meta-analysis referencing 15 studies and 2,210 patients attempted to synthesize the prognostic effects of both overexpression and amplification across multiple studies. Both overexpression and amplification were demonstrated to be associated with inferior OS, with HR =2.66 and HR =1.66, respectively.⁸³ This was true for Western and Asian populations, and the prognostic effect of MET was also independent of stage. An additional important consideration when applying these data to potential clinical trial design is the fact that the pattern of *MET* copy-number alteration in gastric cancer (using high-resolution single-nucleotide

polymorphism arrays) appears to be predominantly mutually exclusive of amplification of other relevant receptor tyrosine-kinase genes (*FGFR*, *ERBB2*, *KRAS*, and *EGFR*).⁸⁴

Abrogation of MET-pathway signaling in gastric cancer has been successful using both small-molecule TKIs and monoclonal antibody therapy. In the initial Phase I study of tivantinib (the orally available tyrosine kinase MET inhibitor) in a non-molecularly selected population minor regression was noted in a patient with gastric cancer with stable disease for 15 weeks duration.⁸⁵ Early reports of efficacy of crizotinib in a *MET*-amplified patient cohort were described by Lennerz et al who reported responses in two of four patients treated with crizotinib in a Phase I trial enriched for *MET*-amplified patients.⁸¹ Additionally, a case report detailing a complete and durable response in a female gastric cancer patient with high *MET* polysomy and MET overexpression was reported during the Phase I trial of onartuzumab.⁸⁶ This patient was treated with single-agent onartuzumab at a dose of 20 mg/kg every 3 weeks with a complete response demonstrated following four doses. Unsurprisingly, results of MET inhibition have been less promising in unselected patient populations. Foretinib, a multitargeted TKI targeting MET, RON, AXL, TIE-2, and VEGFR2 failed to demonstrate activity in a largely non-*MET*-amplified gastric cancer patient population previously treated with chemotherapy.⁸⁷ In this Phase II study, 69 evaluable patients were treated with foretinib either on an intermittent (240 mg/day for 5 consecutive days every 2 weeks) or daily dosing (80 mg/day during each 2-week cycle) schedule until progression. No patient in either cohort demonstrated a complete or partial response and 23% and 20% of patients in the intermittent and daily dosing cohorts respectively had a best response of stable disease. Three patients in this study were *MET*-amplified by FISH (fluorescence in situ hybridization): one was unevaluable due to toxicity, one had progressive disease, and one had stable disease of short duration (2.1 months). A Phase II study evaluating the addition of the anti-HGF monoclonal antibody rilotumumab to epirubicin + cisplatin + capecitabine (Xeloda®, Roche) (ECX) chemotherapy in a non-*MET*-selected population has been reported in abstract form. A total of 121 patients with treatment-naïve advanced gastroesophageal cancer were randomized to ECX chemotherapy plus either placebo or rilotumumab at two dose levels (7.5 mg/kg or 15 mg/kg). In the 90 patients with evaluable MET expression, patients with MET-high tumors (>50% cells with MET expression) had superior survival when treated with rilotumumab than those with MET-low tumors (OS 11.1 versus 5.7 months, HR 0.29; *P*=0.012). Conversely, patients with MET-low tumors

treated with chemotherapy plus rilotumumab had a trend toward worse survival.⁸⁸ An exposure–response analysis presented at the same meeting demonstrated that increased exposure to rilotumumab in MET-high patients was associated with improvements in PFS and OS in that patient group.⁸⁹ Both onartuzumab and rilotumumab are currently in global Phase III randomized trials in advanced esophagogastric cancer with MET overexpression: onartuzumab in conjunction with FOLFOX chemotherapy⁹⁰ and rilotumumab with ECX.⁹¹ Multiple MET-targeting TKIs are also currently under evaluation in clinical trials in this setting.

Hepatocellular carcinoma

The MET/HGF pathway has been attributed an important role in the genesis and maintenance of hepatocellular carcinoma, and has emerged as an attractive therapeutic target for this disease. In hepatocellular carcinoma MET overexpression has been reported in 20%–48% of cases.^{92–94} This phenomenon has not been consistently associated with gene amplification, suggesting that for hepatocellular carcinoma alternative mechanisms including autocrine or paracrine HGF-induced activation or epigenetic regulation of expression may account for a significant number of MET-overexpressing tumors.^{95,96} In studies investigating the correlation between MET expression and clinicopathological features or clinical outcome in hepatocellular carcinoma MET has been largely shown to correlate with aggressive tumor phenotype and poor survival in both the early stage and advanced setting.^{97–100} A possible association of MET overexpression with favorable clinical characteristics as suggested by other studies, is likely to be due to the small number of patients analyzed, heterogeneity of the patient populations, or differences in study methodology.^{96,101}

In vitro and in vivo studies demonstrate that MET overexpression is associated with the development of hepatocellular carcinoma, while knockdown of MET leads to the inhibition of tumor growth and regression of advanced tumors.^{102–104} The promising results observed with MET inhibition in preclinical studies of hepatocellular carcinoma raised interest in assessment of MET as a therapeutic target in the clinical setting, in particular because effective systemic treatment options are limited for patients with this disease.^{39,103,104} Several selective MET inhibitors are under development and being tested in early stage clinical trials; however tivantinib (ARQ197; Aveo) is the agent with the majority of clinical data available. In a randomized, double-blind, placebo-controlled, crossover Phase II trial, 74 patients with advanced, Child–Pugh A hepatocellular carcinoma previously treated with

one systemic therapy were randomly allocated in a 2:1 ratio to receive oral tivantinib or placebo.¹⁰⁰ Although clinically marginal, a statistically significant improvement in median time to progression (1.6 versus 1.4 months, HR 0.64; $P=0.04$) was observed in favor of tivantinib. Importantly, a prespecified subgroup analysis indicated that MET overexpression may represent a potential predictive biomarker for tivantinib benefit as the most clinically and statistically significant tivantinib effects in terms of tumor stabilization (50% versus 20%), time to progression (2.7 versus 1.4 months, HR 0.43; $P=0.03$) and OS (7.2 versus 3.8 months, HR 0.38; $P=0.01$) were observed in the group of patients with MET-overexpressing tumors. However, given the modest activity of the drug in the unselected population and the small numbers of patients assessed for MET expression in the subgroup analysis ($n=22$), confirmatory evidence of clinical benefit will be sought in a Phase III randomized trial comparing tivantinib with placebo in pretreated patients with MET-overexpressing tumors.¹⁰⁵

Other multitargeted TKIs with activity against MET have also recently been investigated in hepatocellular carcinoma.^{106–108} In particular, in a Phase II randomized discontinuation trial cabozantinib (an oral inhibitor of MET and VEGFR2), was investigated in 41 patients with hepatocellular carcinoma half of whom had been previously treated with sorafenib.¹⁰⁶ Although only 5% of patients demonstrated a partial response at 12 weeks prior to the randomization, the overall disease-control rate (partial response + stable disease) at this time point was 68%, and 38% of patients with serial α -fetoprotein measurements demonstrated a decline of >50% from baseline. These encouraging results which may in part have been driven also by the antiangiogenic properties of this drug, have led to the development of a large Phase III controlled trial of cabozantinib versus placebo in hepatocellular carcinoma patients previously treated with sorafenib.¹⁰⁹ The monoclonal antibody onartuzumab is also being investigated in conjunction with sorafenib in the first line setting for patients with hepatocellular carcinoma.¹¹⁰

Prostate cancer

MET expression in prostate cancer is associated with high-grade tumors and the presence of metastases, in particular bone metastases, and in prostate cancer cell lines MET expression is inversely correlated with expression of the androgen receptor.^{111,112} The androgen receptor has been demonstrated to be a negative regulator of MET, and accordingly the effect of small-molecule MET inhibitors has been demonstrated to be more potent in androgen-insensitive

prostate cancer cells.^{113,114} Cabozantinib, an inhibitor of MET, VEGFR, and multiple other tyrosine kinases, was investigated in a randomized discontinuation study in advanced castration-resistant prostate cancer at a dose of 100 mg daily; patients with stable disease by response-evaluation criteria in solid tumors (RECIST) at 12 weeks were randomized to cabozantinib or placebo.¹¹⁵ Recruitment was halted following enrollment of 171 patients due to efficacy in the experimental arm of the trial. Although the overall response rate at 12 weeks was 5%, an additional 75% of patients had stable disease, of whom 31 were randomized at week 12. PFS was 23.9 weeks for men treated with cabozantinib, and 5.9 weeks for those receiving placebo (HR 0.12, $P < 0.001$). Bone pain and narcotic use were also significantly decreased in the majority of patients. Dose reductions were frequent (51% at 12 weeks) in this initial study and a subsequent dose-ranging study demonstrated superior tolerability and comparable efficacy for a 40 mg daily dose which was recommended for subsequent randomized clinical trials.^{115,116}

Significant resolution of bone lesions on bone scan has been a notable effect of cabozantinib in prostate cancer trials; it has recently been demonstrated that in addition to direct cytotoxic effects on prostate cancer cells, cabozantinib has an inhibitory effect on osteoclast production and a biphasic dose-dependent effect on osteoblast activity both mediated through MET and VEGFR signaling.¹¹⁷ Therefore, the effects of cabozantinib on bone scintigraphy are as a result of cytotoxicity in addition to direct effects on bone remodeling.

Cabozantinib is currently under investigation in several large randomized studies in metastatic castration-resistant prostate cancer in previously treated patients^{118,119} and in combination with abiraterone in patients who are treatment-naïve.¹²⁰ However, the addition of rilotumumab to mitoxantrone and prednisolone therapy in metastatic castration-resistant prostate cancer patients previously treated with docetaxel did not result in any improvements in PFS or OS when compared to standard therapy (PFS 3.0 versus 2.9 months, OS 12.2 versus 11.1 months, respectively), including in MET-high ($n=38$) patients.¹²¹ Therefore it was not recommended that rilotumumab proceed to a Phase III trial in this setting.

Renal cell carcinoma

The MET pathway is activated through at least two separate mechanisms in RCC of distinct histological subtypes. In clear-cell RCC inactivation of the *VHL* gene is common, and preclinical data suggest that this may induce constitutive phosphorylation of MET leading to enhanced cell mobilization and invasive capacity.¹²² MET expression is com-

mon in RCC and associated with a negative prognosis; in a recent study examining MET expression on 330 RCC cores, expression was highest in papillary and sarcomatoid subtypes and those with a higher Fuhrman grade but was also present on clear-cell RCC, and in an analysis limited to clear-cell subtypes remained a negative prognostic marker.¹²³ In MET-activated clear-cell RCC cell lines treatment with tivantinib led to inhibition of cell proliferation providing a clinical rationale for targeting MET-activated clear-cell RCC with these agents.

A Phase II study with the anti-HGF monoclonal antibody rilotumumab was conducted in 61 patients with metastatic RCC of varying histologies (clear-cell 75.4%, papillary 11.5%), the majority of whom had previously received antiangiogenic therapy.¹²⁴ Although one partial response was maintained for 2.5 years no other responses were seen, median PFS was 3.7 months at 10 mg/kg and 2.0 months at 20 mg/kg rilotumumab doses and tumoral MET expression was not associated with response or survival outcomes. As a result, further development of rilotumumab has not been pursued in this disease.

The antiangiogenic properties of the TKI cabozantinib make this an attractive agent for treatment of RCC. Promising results in clear-cell RCC patients were seen in a drug–drug interaction study examining the effects of rosiglitazone on cabozantinib pharmacokinetics; of 25 patients treated with a median of two prior treatments, 24% had a confirmed partial response by RECIST, and 86% experienced some tumor regression.¹²⁵ These encouraging results have led to the development of multiple clinical trials investigating cabozantinib in clear-cell RCC: in comparison to everolimus in a Phase II randomized study for patients who have previously progressed following TKI therapy,¹²⁶ and in comparison to sunitinib in previously untreated patients.¹²⁷

A second mechanism of MET activation is seen in the papillary subtype of renal cancer, with activating mutations of *MET* found in the germ line of families with hereditary papillary RCC and in a proportion of sporadic noninherited cases. In a nonrandomized study assessing the effect of the nonselective MET inhibitor foretinib 74 patients with papillary RCC were recruited, eleven of whom had germ-line and five of whom had somatic *MET* mutations.¹²⁸ Two patients demonstrated *MET* amplification with no mutation. Median PFS was 9.3 months and 1-year survival was 70% with median OS not reached. Of the ten patients with a germ-line mutation, half had a partial response and half had stable disease, whereas only one of five patients with a somatic mutation had a response and no *MET* amplified

patient did. Although the trial failed to meet its primary end point of a response rate of >25% the response rate in germ-line-mutant patients is noteworthy, and MET inhibition would appear to be worthwhile in this patient group.

Toxicity of MET inhibition

The extracellular inhibitors of the MET pathway (onartuzumab, rilotumumab, and ficlatuzumab) appear to be well tolerated, with relatively few treatment-related serious adverse events reported in clinical trials to date. In the Phase I studies for both onartuzumab and rilotumumab, the maximum tolerated dose was not reached.^{129,130} Peripheral edema appears to be a class effect of these compounds, and increased rates of neutropenia have been demonstrated when rilotumumab is used in conjunction with chemotherapy.⁸⁸ Activation of the MET pathway has been associated with dysregulation of the clotting cascade in preclinical models; however, with the caveat of relatively small control groups treated to date, significant differences in the incidence of thromboembolic disease have not been noted with these drugs.¹³¹ Class-effect toxicities associated with nonselective tyrosine kinase inhibition (fatigue, gastrointestinal upset, hepatotoxicity) are frequent but usually mild.^{87,115} However, awareness of toxicity related to off-target effects, such as those on VEGFR (hypertension, hemorrhage, perforation) is also necessary as these may be significant.¹¹⁵ Additionally, tivantinib appears to have cytotoxic effects that are independent of its MET-inhibitory activity and significant rates of neutropenia and neutropenia-related deaths have been documented with the use of this compound.^{100,132}

Resistance to MET inhibition

Acquisition of novel mutations, redundancy in intracellular signaling pathways, and downregulation of inhibitory feedback mechanisms have been demonstrated to be responsible for de novo and acquired resistance to other TKIs, such as those inhibiting EGFR, BRAF and mitogen-activated protein-kinase kinase (MEK). The mechanisms by which resistance to MET inhibition may occur have recently begun to emerge, and preminent among these is the interplay between the MET and the EGFR pathways. In *MET*-amplified gastric cancer lines treated with the MET inhibitor PHA-665752, EGF, and heregulin-dependent activation of EGFR and HER3 led to downstream effects on the MAPK and PI3K pathways and abrogation of the effects of MET inhibition.¹³³ However, combined blockade of MET and EGFR using gefitinib or with MEK and Akt inhibitors led to reversal of MET resistance. In a separate experiment,

resistance to MET therapy in SNU6838 cells was mediated through TGF α expression and EGFR activation.¹³⁴ Similarly, activation of the EGFR pathway has been demonstrated to be responsible for acquired resistance to the MET inhibitor PF2341066 in *MET*-amplified NSCLC lines and while combination therapy with PF2341066 and the EGFR inhibitor erlotinib did not result in decreased cell proliferation, it did suppress emergence of MET resistance.¹³⁵

Alternative escape mechanisms from MET inhibition include increased amplification of *MET*, acquisition of mutations affecting binding-site conformation, and upregulation of non-EGFR-signaling pathways. In *MET*-amplified gastric (GTL16) and NSCLC (EBC-1) cell lines when initially sensitive cells were treated with either of two MET inhibitors (PHA-665752 or JNJ38877605), the *MET* gene acquired further amplification with subsequent increased levels of protein expression leading to adequate levels of phosphorylation which successfully maintained enzymatic activity.¹³⁶ However, at higher levels of drug which overcame the increased *MET* amplification, amplification and overexpression of KRAS emerged and this remained sensitive to downstream inhibition of MAPK elements using U0126 and PD0325901. An additional pathway by which *MET* amplified gastric cancer cell line GTL16-acquired resistance to MET inhibition with PF04217903 is the emergence of a novel SND1 (staphylococcal nuclease domain 1)-BRAF fusion protein that uses activated BRAF to escape MET suppression.¹³⁷ Again, the activity of this resistance mechanism could be suppressed through combined MET and BRAF or MEK inhibition. Further evidence of the efficacy of combination therapy in overcoming resistance is demonstrated by NSCLC cell lines resistant to erlotinib and the MET inhibitor SU11274, which display upregulation of both mTOR (mammalian target of rapamycin) and Wnt pathway components and restoration of sensitivity to EGFR/MET inhibition by the addition of everolimus.¹³⁸

A final mechanism of resistance in gastric cancer cell lines has been demonstrated when *MET*-amplified SNU6838 gastric cancer cell lines were treated with the MET inhibitors PHA-665752 and PF2341066; a novel mutation occurred in the activation loop of *MET*, causing a conformational change that blocked inhibitor binding analogous to the gatekeeper mutations seen in *EGFR* (*T790M*) following erlotinib treatment and in *ABL* (*T315I*) following imatinib.¹³⁴ Although the *MET* *Y1230H* mutation renders cancers insensitive to type I MET inhibitors, conformational differences between these and type II compounds may allow treatment of *MET* *Y1230H* mutant cancers or prevent the emergence of resistance due to the mutation.^{139,140}

Conclusion and future directions

The ubiquity of MET-pathway activation in cancer and the malignant phenotype that it confers on MET-mutated, -amplified, or -overexpressed tumors ensure that this is an attractive therapeutic target for many cancers. Pharmacological inhibition of this pathway has clear benefits in terms of response and survival, albeit in limited numbers to date. It is clear that to optimize these benefits clinical trials must be enriched for patients with demonstrable MET-pathway dysregulation; what is less clear is the best means by which to achieve this. Robust standardization and validation of assay methodology for MET expression is essential in order to confidently address the benefit of MET inhibition across distinct patient populations, and assessment of the correlation between gene amplification, protein expression, and treatment efficacy is also mandated. With respect to clinical trial development, treatment with anti-MET/HGF antibodies and chemotherapy and/or other antibodies appears to be an attractive option given the lack of significant additive toxicities seen for combination regimens, whereas the small-molecule TKIs may potentially be combined with other similar drugs targeting other relevant pathways. These combinatorial approaches may be designed in order to delay or prevent the emergence of resistance to MET inhibition via intimately connected pathways, such as EGFR, HER3, and RAS. Ultimately, collaborative clinical trials and serial tissue collection will be required in order to fully evaluate the impact of inhibition of this promising target on oncology outcomes.

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