c-Met as a Target for Personalized Therapy

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Supplementary Issue: Pharmacodynamic Biomarkers of Response and Resistance

ABSTRACT: MET and its ligand HGF are involved in many biological processes, both physiological and pathological, making this signaling pathway an attractive therapeutic target in oncology. Downstream signaling effects are transmitted via mitogen-activated protein kinase (MAPK), PI3K (phosphoinositide 3-kinase protein kinase B)/AKT, signal transducer and activator of transcription proteins (STAT), and nuclear factor-κB. The final output of the terminal effector components of these pathways is activation of cytoplasmic and nuclear processes leading to increases in cell proliferation, survival, mobilization and invasive capacity. In addition to its role as an oncogenic driver, increasing evidence implicates MET as a common mechanism of resistance to targeted therapies including EGFR and VEGFR inhibitors. In the present review, we summarize the current knowledge on the role of the HGF-MET signaling pathway in cancer and its therapeutic targeting (HGF activation inhibitors, HGF inhibitors, MET antagonists and selective/nonselective MET kinase inhibitors). Recent advances in understanding the role of this pathway in the resistance to current anticancer strategies used in lung, kidney and pancreatic cancer are discussed.

KEYWORDS: MET, HGF, drug resistance, targeted therapy, NSCLC, renal cancer, pancreatic cancer

SUPPLEMENT: Pharmacodynamic Biomarkers of Response and Resistance

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Introduction

Receptor tyrosine kinases (RTKs) are high-affinity cell surface receptors for polypeptide growth factors, cytokines, and hormones. RTKs regulate many intracellular signal transduction pathways involved in multiple normal and pathological biological processes, including cancer initiation, progression, invasiveness, metastasis and resistance to therapy.[1] The Mesenchymal Epithelial Transition (MET) receptor belongs to a family of RTKs. Dysregulation of the MET signaling pathway occurs in a wide range of human cancers.[1,2]

Increasing evidence indicated that MET may be a common mechanism of resistance to anticancer treatment. In the present paper we review the mechanisms underlying this resistance and possible solutions to restore the sensitivity to several anticancer therapies, including targeted therapy (EGFR inhibitors, VEGFR inhibitors, anti-HER2 drugs, B-RAF inhibitor, ALK inhibitors), chemotherapy (gemcitabine, taxanes, cisplatin, capecitabine) and radiotherapy. The above mentioned drugs are currently used in the treatment of the most frequent solid tumors, including lung, renal and pancreatic cancer. For these tumors the mechanisms of resistance are specifically discussed.

Discovery, Structure and Function of MET and HGF/SF

The MET proto-oncogene is located on chromosome 7q21–31 and encodes the receptor tyrosine kinase MET. In 1984, TPR-MET oncogenic fusion protein from human osteosarcoma tumor cells was first discovered.[3] The MET receptor is a 190 kDa glycoprotein heterodimer consisting of an extracellular α-subunit linked to transmembrane β-subunit by a disulfide bond. The extracellular portion includes the semaphorin (Sema) domain, the PSI domain (Plexin, Semaphorin and Integrin cysteine-rich) and four IPT domains (immunoglobulin plexins transcription).[4] The intracellular domain includes a juxtamembrane sequence, a catalytic region and a carboxy-terminal multifunctional docking site. The juxtamembrane domain contains both Ser975 and Tyr1003 residues, that are involved in MET downregulation.[5] A catalytic region positively modulates the kinase activity. Finally, a carboxy-terminal multifunctional docking site is responsible for the recruitment of many intracellular transducers and adaptors (Fig. 1).[5,6]

The MET receptor is expressed on the surface of epithelial and endothelial cells, where it can be bound specifically by its only known ligand, the hepatocyte growth factor

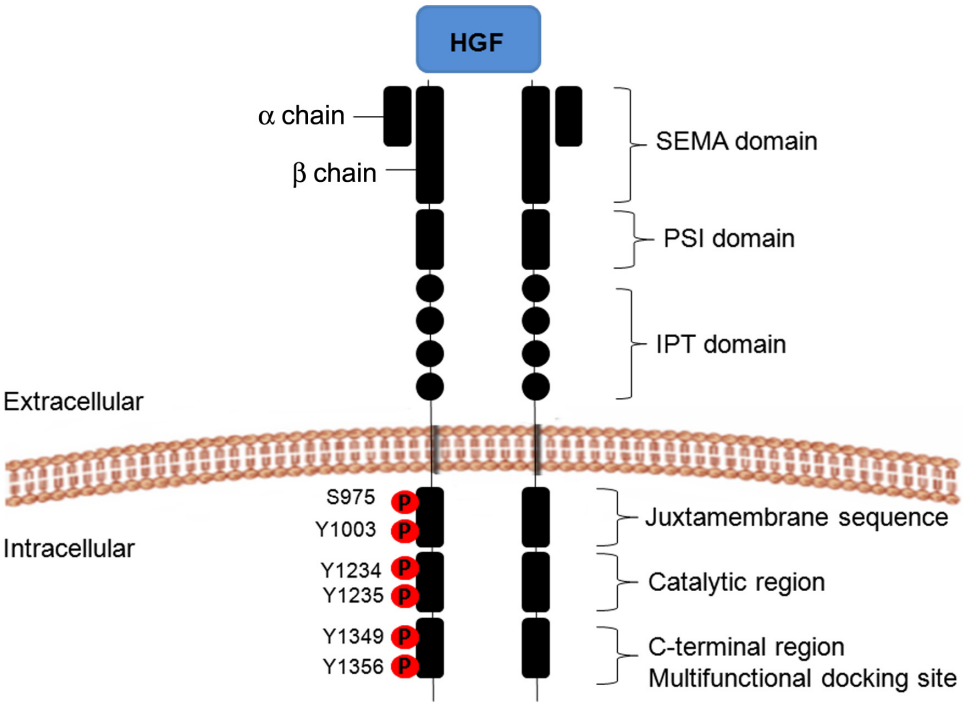

Figure 1. Structure of the c-MET receptor. Extracellular portion include SEMA domain, PSI domain and IPT domain. Intracellular portion include juxtamembrane sequence, catalytic domain and C-terminal region with multifunctional docking site.

(HGF), also called the scatter factor (SF). HGF/SF is a protein belonging to the serine protease family and produced in cells of mesenchymal origin. It is secreted as a single chain, biologically inactive, and converted into its mature form by a cleavage process catalyzed by extracellular proteases.[6–8] Its biologically active form consists of a disulfide-bond heterodimer containing an α-chain and a β-chain. The first contains an amino-terminal hairpin loop (HL) domain followed by four peculiar domains, known as kringle domains; the latter contains a serine proteases homology (SPH) domain that lacks proteolytic activity,[6–8] as shown in Figure 2. MET has two binding sites for HGF. Firstly, the IPT3 and IPT4 domains that bind the N domain of HGF/SF with high affinity, independently of HGF maturation. Secondly, the SEMA domain will bind the SPH domain of HGF/SF with low affinity but only when HGF is active.[9–10]

MET and its ligand HGF are involved in many normal and pathological biological processes, such as fetal development

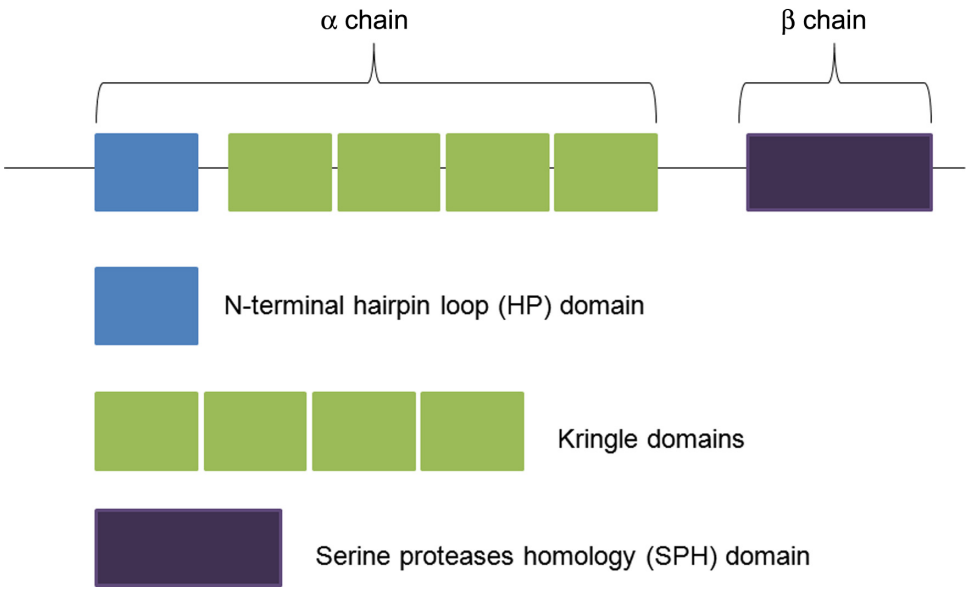

Figure 2. Structure of HGF. Its biologically active form consists of a disulfide-bond heterodimer containing an α-chain and a β-chain.

where it plays an important role in liver, placenta and muscle formation, as well as development of the nervous system.[11–13] After birth, activation of the HGF-MET pathway appears to be involved in epithelial-mesenchymal transition (EMT),[14] as well as hepatic, renal and epidermis regeneration.[11] Furthermore, MET signaling is also involved in tumor growth, invasion, resistance to therapy, angiogenesis and specially in the generation and maintenance of cancer stem cells (CSCs).[15–17]

Activation of MET Signaling Pathway

Activation of the MET signaling pathway can result from various molecular mechanisms, including germline or somatic mutations, chromosomal rearrangement, MET amplification, increased MET protein expression, increased HGF expression or by alteration of other pathways affecting MET activation.[2] These modifications can be observed in a tissue-specific manner alone or combined in different proportions.[1]

The initiation of MET signaling begins with the binding of HGF to the MET receptor at the plasma membrane leading to the stable dimerization of two molecules of MET. Subsequent activation of its intracellular domain is through a process of trans-phosphorylation of the two tyrosine residues in the catalytical regions Y1234 and Y1235, followed by trans-phosphorylation of two docking tyrosines (Y1349 and Y1356) in the carboxy-terminal site. These two tyrosines form the multifunctional docking site which is unique to members of the MET subfamily and essential for MET signaling. It enables MET to bind to multiple substrates and activate a variety of signaling pathways either through direct interaction with signaling molecules or through adaptors such as growth factor receptor-bound protein 2 (Grb2) and Grb2-associated-binding protein 1 (Gab1). Subsequent activation of different intracellular signaling pathways (MAPK, PI3K-AKT cascades, STAT and NF-κB signaling pathways) is responsible for driving proliferation, cell survival, migration and invasiveness (Fig. 3).[18–22]

MAPK signaling pathways. The Mitogen-activated protein kinases (MAPK)s are a group of serine/threonine protein kinases that are activated in response to a variety of extracellular stimuli and mediate signal transduction from the cell surface to the nucleus. They are involved in the regulation of normal cell proliferation, survival and differentiation.[23]

These cascades consist of three protein kinases: a MAPK kinase kinase (MAPKKK), a MAPK kinase (MAPKK) and a MAPK that are partially controlled by protein phosphorylation.[20,24] The MAPKs represent the final effectors of the cascade. There are several groups of MAPKs in mammalian cells: the Extracellular signal-regulated kinases (ERKs), the p38MAPKs and the c-Jun NH2-terminal kinases (JNKs).[7] The ERK pathway is the best studied of the mammalian MAPK pathway, and is deregulated in approximately one-third of all human cancers.[25] The ERKs are mainly triggered by tyrosine kinase-dependent stimulation of RAS.[7] MET activates RAS through the GRB2–SOS complex which can interact directly with carboxy-terminal multifunctional docking site of MET or can be associated indirectly through the SHC adaptor protein.[18,26] Moreover, the tyrosine phosphatase SHP2 dephosphorylates the binding site on the

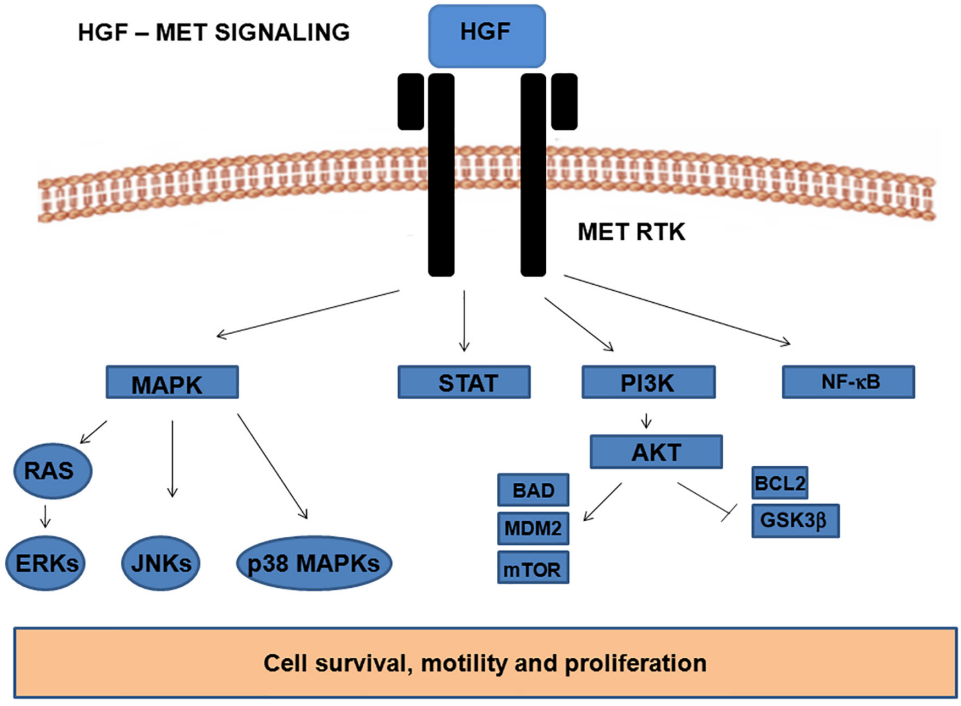

Figure 3. HGF-MET signaling pathway with its downstream effector components (MAPK, STAT, PI3K-AKT cascades and NF-κB) leading to increases in cell survival, motility and proliferation.

adaptor protein GAB1; this will also result in RAS-ERK activation.[27,28] In this pathway, ligand-mediated activation of receptor tyrosine kinases triggers guanosine triphosphate (GTP) loading of the RAS GTPase which can then recruit RAF kinases to the plasma membrane for activation.[25] When RAF translocates to the membrane, it becomes activated which leads to phosphorylation of the dual specificity kinases MEK1 and MEK2. Finally, the activated MEKs phosphorylate the terminal effectors ERK1/ERK2.[7]

PI3K–AKT signaling pathway. The PI3K-AKT pathway is highly conserved and its activation is tightly controlled via a multistep process.[29] PI3K can be activated directly by MET and/or indirectly by RAS.[18] In response to the activation of the MET tyrosine kinases domain, the lipid kinase PI3K phosphorylates phosphatidylinositol (4,5)-bisphosphate (PIP2) to synthesize the second messenger phosphatidylinositol (3,4,5)-triphosphate (PIP3). PIP3 recruits AKT to the plasma membrane where it is phosphorylated and activated by phosphoinositide-dependent kinase-1 (PDK-1). Activated AKT subsequently phosphorylates numerous substrates that promote tumor genesis, including the mammalian target of rapamycin (mTOR), pro-apoptotic protein BAD, anti-apoptotic protein BCL2, E3 ubiquitin-protein ligase MDM2 (which promotes the degradation of the pro-apoptotic protein p53)[7] and glycogen synthase kinase 3β (GSK3β). These targets interfere with important cell cycle regulators such as myc, cyclin D1.[7]

STAT signaling pathway. The Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway consists of the seven members of the STAT protein family from which STAT3 and STAT5 have been demonstrated to be the most important for cancer progression.[30–32] Boccaccio et al found that phosphorylation of the docking site of MET is followed by phosphorylation of STAT3 which causes STATs to dissociate from the receptors.[33] STAT3 is mainly considered to be a direct transcription factor, though many other functions have been described, including gene expression regulation via epigenetic mechanisms, mitochondrion functions regulation, angiogenesis and CSCs regulation. This signaling pathway is able to promote tumor cell proliferation, survival and tumor invasion which highlights its function in cancer.[30]

NF-κB signaling. Nuclear factor-kappaB (NF-κB) is present in almost all cell types and tissues where it regulates gene expression by binding to promoters/enhancers of a host of genes. The NF-κB family consists of five proteins, p65 (RelA), RelB, c-Rel, p105/p50 (NF-κB1) and p100/52 (NF-κB2) that form homo- and heterodimeric complexes by associating with each other to transcriptionally regulate target genes.[34] The NF-κB system is inactive in the cytoplasm due to the action of the inhibitor of κB (IκB).[35] NF-κB activation generally occurs through either classical or alternative pathways.[34] In the classical pathway, c-MET stimulation activates the inhibitor of nuclear factor kappa-B kinase (IKK) complex resulting in the phosphorylation of two N-terminal serine residues of IκB proteins leading to ubiquitin-mediated degradation of IκB and NF-κB activation. In the alternative pathway, IKKα is phosphorylated by NF-κB inducing kinase, which phosphorylates p100 leading to polyubiquitination and degradation of the inhibitory molecules by the proteasome. The result of both pathways is the destruction of IκBs which unmask the nucleus localization signal (NLS) resulting in the release of NF-κB. NF-κB translocates to the nucleus and transactivates target genes by binding to gene promoter/enhancer regions.[21,22,36,37]

In conclusion, the final output of the terminal effector components of these pathways is the activation of cytoplasmic and nuclear processes leading to increases in cell proliferation, survival, mobilization and invasive capabilities.

HGF and MET Dysregulation in Cancer

In human malignancies, genetic alterations of the MET proto-oncogene are relatively rare. In a recent study MET amplification was detected in 2.5% of 1,115 patients with advanced solid cancers. The prevalence was highest in renal cell (RCC, 14%) followed by adrenocortical tumors (15%), gastroesophageal (6%), breast (5%) and ovarian cancers (4%).[38] Generally, in genetically altered MET tumors, MET oncogene behaves as a cell-autonomous selectable driver of tumor growth.[17] The role of MET in tumors is not only restricted to relatively rare genetic alterations but relies on the frequent overexpression of the wild-type gene.[4,7,39] In the CSCs, the wild-type form of MET helps to maintain the phenotype 'inherent' in the stem/progenitor cell of origin.[17]

Indeed, activation of the HGF-MET pathway is currently associated with aggressive pathologic features, poor prognosis, and treatment resistance in several different tumor types.[38,40,41] Lorenzato et al noted that activating somatic MET mutations were infrequent in primary tumors but commonly present at metastatic sites, suggesting that MET mutations are associated with progression rather than initiation of tumorigenesis.[42] Cancers of unknown origin (CUPs) are characterized by upfront metastatic dissemination, a highly undifferentiated, stem-like phenotype and lacking histological markers of the tissue of origin.[43] Interestingly, in these tumors MET activating mutations are present more frequently (30%) in comparison to other solid tumors.[43] A more aggressive biologic behavior of tumors overexpressing MET is also reflected in the inferior survival outcomes found in some studies,[40,41] however, there are some contradictory results on this issue.[44] The frequency of MET dysregulation is higher in adenocarcinomas compared to squamous cell tumors. In gastro esophageal tumors, MET amplification has been reported in only 1% of esophageal squamous cell carcinoma, whereas it ranges from 2% to 10% in adenocarcinomas.[41,45,46] Moreover, some interesting association of MET dysregulation and BRAF mutation or PTEN loss have been described.[47] Finally, MET overexpression has been associated with treatment resistance in radiotherapy, anti-EGFR TKI, VEGFR/BRAF/mTOR inhibitors and anti-HER2 therapy.[48–51]

In summary, alterations in MET and/or HGF are frequently observed in a wide range of cancers and their presence appears to confer an increased propensity for a more aggressive clinical behavior manifested by invasion, metastasis and resistance to the therapy. However, it is possible, that in some specific histological types and in the presence of some molecular aberrations, there is no correlation between MET overexpression and survival outcome.

HGF and MET Inhibitors for Cancer Therapy

RTK pathways have proven to be attractive drug targets allowing the development of novel treatment strategies. One such promising target is the HGF-MET pathway. The HGF and MET targeting agents can be categorized into those that target the HGF ligand or those that target the MET receptor. Agents targeting the ligand can further be categorized into either HGF activation inhibitors (preventing the cleavage of pro-HGF into the active form) or HGF inhibitors (blocking the direct binding of HGF to the MET receptor).[4] Agents targeting the MET receptor can further be categorized into either MET antagonists (binding the receptor) or MET tyrosine kinase inhibitors (TKIs) targeting MET intracellularly[4] (Fig. 4, Table 1).

HGF and MET-targeting agents can be classified as either monoclonal antibodies or small molecules and they differ in terms of pharmacological properties as well as their underlying mechanism of action. They can be used either as a monotherapy, in combination with chemotherapy or in combination with other targeted therapy.[15] Most of the HGF and MET inhibitors showed promising results when used in drug combinations, most likely due to the complexity of tumor biology. Regarding side effects, HGF and MET inhibitors have demonstrated few adverse effects when administered to patients and any combination treatment has been well tolerated. The most frequent adverse events seen in clinical trials included fatigue, anorexia, nausea, vomiting, fever, hypersensitivity reactions, peripheral edema, proteinuria, hematuria, hypertension and bleeding.[1,15]

Inhibition of HGF activation. The activation of HGF from its inactive precursor pro-HGF is a critical step in HGF function[52] and depends on the balance between the activators (HGFAs) and the inhibitors (HAIs).[53,54] Hu et al.[55] investigated the role of HAI-1 in patients with prostate cancer and benign prostate hyperplasia. It was observed that a high level of HAI-1 protein and mRNA expression was present in patients affected by benign disease compared to the more aggressive prostate cancer specimens. Low HAI-1 correlated with a high Gleason score, a more advanced pathological stage and was a predictor for poor prognosis. Therefore, high HAI-1 might be used as a favorable prognostic marker for prostate cancer and a therapeutic target for the treatment of this malignancy.[55] In another study, Tsai et al.[56] investigated the role of HAI-2 in human prostate cancer progression. In this study, a human prostate cancer progression model consisting of cancer cells with increasing invasion capability was used, as well as xenograft models. The expression of HAI-2 decreased throughout the progression in cell invasion capability, and was accompanied by an increased activation of matriptase, an extracellular matrix (ECM)-modulating protease which contributed to tumor genesis and metastasis.[56] Therefore, HAI-1 and HAI-2 might represent novel prognostic markers as well as therapeutic targets. The development of HAIs in cancer is still in the early stages and up to date, no available clinically tested HAIs are available.

Inhibition of HGF binding to the MET receptor. HGF inhibitors bind to HGF and block binding to the MET receptor, effecting downstream activation of the pathway. Several monoclonal antibodies against HGF have been tested

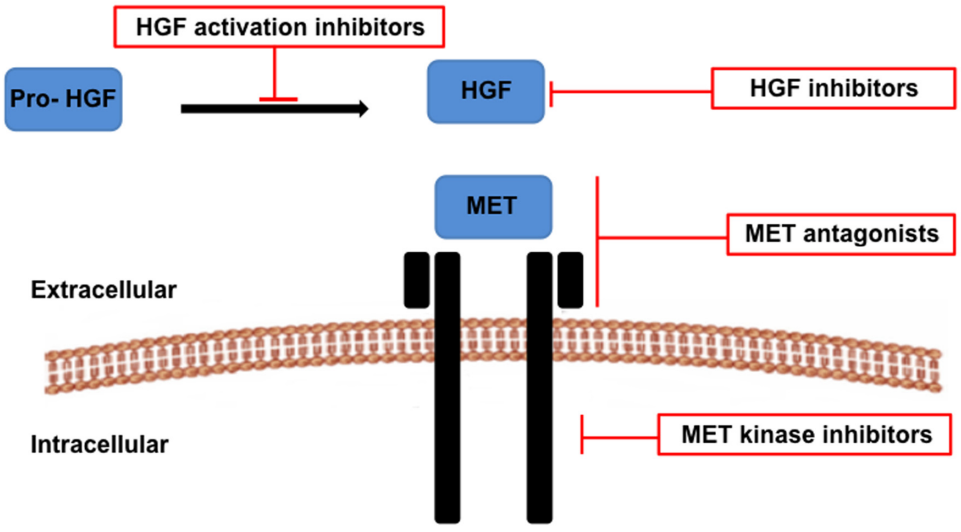

Figure 4. Therapeutic strategies targeting the HGF-MET signaling pathway in cancer include HGF activation inhibitors, HGF inhibitors, MET antagonists and MET kinase inhibitors.

Table 1. Drugs targeting HGF-MET signaling pathway.

	DRUG	MOLECULAR TARGETS
HGF activation inhibitors	HGFAs (activators)	Pro-HGF
	HAIs (inhibitors)	Pro-HGF
HGF inhibitors	Rilotumumab (AMG102)	HGF
	Ficlatuzumab (AV-299)	HGF
	TAK701	HGF
MET antagonists	Onartuzumab	MET
	CE-355621	MET
	DN-30	MET
	LA480	MET
MET kinase inhibitors		
Selective	Tivantinib	MET
	Savolitinib	MET
	AMG 337	MET
	INC 280	MET
Nonselective	Crizotinib	MET, ALK, ROS, RON
	Cabozantinib	MET, VEGFR2, KIT, RET, AXL, FLT3

preclinically, such as rilotumumab, ficlatuzumab and TAK701. Rilotumumab is a fully humanized IgG2 monoclonal antibody.[57] Preclinical data showed synergistic cytotoxicity when acting in combination with temozolomide and docetaxel.[58,59] The efficacy of rilotumumab was evaluated in a phase 2 study in patients affected by gastric or oesophagogastric junction tumors. The patients were randomized to receive rilotumumab plus capecitabine or placebo plus capecitabine. Interestingly, improved median progression-free survival (PFS) and overall survival (OS) in patients treated with rilotumumab plus capecitabine was seen only among the patients with MET overexpression[60] which underlines the growing importance of stratifying the patients for target treatment. Ficlatuzumab is a humanized anti-HGF IgG1 monoclonal antibody that was evaluated in a phase I study in solid tumors as a single agent or in combination with erlotinib.[61] TAK701 is a humanized monoclonal antibody directed against HGF.[62] Okamoto et al described that the addition of TAK-701 to gefitinib treatment is a promising strategy to overcome EGFR TKI resistance induced by HGF in non-small-cell lung cancer (NSCLC) with an activating EGFR mutation.[63]

MET antagonists. MET antagonists compete with HGF for MET binding, resulting in the degradation of MET and subsequent inactivation.[1] Several MET antagonists have been synthesized, including onartuzumab, CE-355621, DN-30, and LA480.

Sano et al.[64] engineered the human NSCLC cell line PC-9, resulting in variants with MET/HGF overexpression and EGFR mutations (exon 19). The combination of onartuzumab and erlotinib was tested *in vitro* and *in vivo* in xenograft models. A PC-9 cell line with HGF overexpression was less sensitive to erlotinib than the parental PC-9 cell line without HGF overexpression; the addition of onartuzumab to erlotinib suppressed the proliferation of parental cells *in vitro*. In PC-9/HGF xenograft tumors, onartuzumab or erlotinib alone minimally inhibited tumor growth; however, combining onartuzumab and erlotinib markedly increased tumor suppression. The authors concluded that patients with NSCLC with EGFR mutations who express high levels of HGF may benefit from onartuzumab and erlotinib combination therapy while HGF expression could be a potential novel biomarker for patient selection.[64] In clinical practice, onartuzumab showed significant survival benefits in combination with erlotinib in NSCLC patients with MET overexpression in a randomized phase II study.[65]

MET kinase inhibitors. Another approach for inhibiting the MET pathway is through MET kinase inhibitors which target intracellular MET. Several small molecule MET kinase inhibitors have entered clinical development over the past decade, including selective MET kinase inhibitors, such as tivantinib (ARQ 197), savolitinib (AZD6094, HMPL-504; volitinib), AMG 337, INC 280 and nonselective MET kinase inhibitors (crizotinib (PF02341066), cabozantinib (XL 184) and foretinib.

Tivantinib (ARQ 197) is a selective, oral, small molecule inhibitor of the MET RTK.[66] It has demonstrated antitumor activity in a wide range of human tumor cell lines and in human xenograft models.[66,67] Recently, a phase I study investigating the combination of tivantinib and sorafenib in patients with advanced solid tumors has been published.[67] Preliminary evidence of anticancer activity was observed in patients with renal cancer, hepatocellular cancer and melanoma, including patients refractory to sorafenib and/or other anti-VEGF pathway therapies. Therefore this combination treatment was

considered to have therapeutic potential treatment a variety of solid tumors. The combination of tivantinib plus erlotinib has been investigated in a phase 3 trial for the treatment of patients with advanced or metastatic NSCLC[68] and in a phase 2 trial of tivantinib as a single agent for the treatment of hepatocellular carcinoma.[69] The combination treatment in NSCLC patients did not show statistically significant differences in OS between the arm of tivantinib plus erlotinib compared to the erlotinib alone arm,[68] although a significant improvement in PFS was observed in the group of patients with KRAS-mutant tumors ($P = 0.006$). Similarly, in HCC patients, a significant improvement in OS was observed in patients with high tumor MET expression.[69]

Savolitinib (AZD6094, HMPL-504) is a novel, selective MET inhibitor.[70] In preclinical studies, savolitinib displayed nanomolar *in vitro* activity against MET and its downstream signaling targets. *In vivo*, savolitinib induced antitumor activity, particularly in tumor models with high MET gene amplification, including papillary renal cell carcinoma xenografts.[71] In an early clinical dose escalation study, savolitinib demonstrated partial responses in 3 papillary renal cell cancer patients, with a fourth patient still on study reaching 27% tumor reduction. Analysis of pre-treatment tumor samples showed that the responders had either a high MET gene copy number or a high MET protein expression.[72]

Crizotinib is a small molecule inhibitor of the anaplastic lymphoma kinase (ALK) with additional activity against the MET, ROS, and RON receptors. Crizotinib was approved for use in ALK-rearranged advanced NSCLC in Europe and US.[73–75] The efficacy of crizotinib has been demonstrated in two randomized trials limited to patients whose tumors had the ALK rearrangement. The first study is a phase 3 trial which randomly assigned 347 pre-treated patients (all one prior platinum-based chemotherapy regimen) to either crizotinib or single agent pemetrexed or docetaxel.[76] In this study, PFS, the primary endpoint of the trial was significantly increased with crizotinib compared to traditional chemotherapy (median 7.7 versus 3 months), the objective response rate (ORR) was also significantly increased (65 versus 20 percent). Responses were achieved more rapidly than with chemotherapy (median time to response 6.3 versus 12.6 weeks) and were of longer duration (32 versus 24 weeks). In this study, no significant difference was observed in OS (median 20.3 versus 22.8 months). The absence of an OS benefit presumably reflects subsequent treatment since 64 percent of chemotherapy-treated patients had crossed over to crizotinib after progressing on chemotherapy. The second study is a phase 2 trial which randomly assigned 343 chemotherapy naïve patients to crizotinib or chemotherapy with pemetrexed plus either cisplatin or carboplatin.[77] PFS, the primary endpoint of the trial, was prolonged with crizotinib compared to chemotherapy (median 10.9 versus 7 months, HR 0.45, 95% CI 0.35–0.60). The ORR was also increased (74 versus 45 percent), although again OS was not significantly different. However, a recently published meta-analysis of six clinical trials revealed extended survival and improved response rates in NSCLC patients treated with crizotinib.[75] The ORR, partial response and complete response rates were 61.2%, 59.8% and 1.5%, respectively. The proportion of patients achieving stable disease was 42.6%.[78]

Cabozantinib is a small molecule inhibitor of MET, VEGFR2, KIT and RET followed by AXL and FLT3[79] and is approved by the US Food and Drug Administration for the treatment of progressive, metastatic medullary thyroid cancer. In a randomized trial, 330 patients with progressive, metastatic or unresectable locally advanced medullary thyroid cancer were randomly assigned to receive either cabozantinib or placebo.[80] A significant prolongation in PFS was observed for cabozantinib treatment compared to placebo (11.2 versus 4.0 months). Partial responses were observed in 28 versus 0 percent. Currently, multiple phase 3 trials in a variety of solid tumors are undergoing.

Targeting HGF-MET in Solid Tumors to Overcome the Drug Resistance

In addition to its role as an oncogenic driver, increasing evidence implicates MET as a common mechanism of resistance to targeted therapies including approved EGFR and VEGFR inhibitors.[48,49] Moreover, MET is involved in resistance to anti-HER2 therapies (trastuzumab and lapatinib)[51,81] and a BRAF inhibitor (vemurafenib)[82] has been described. In the following paragraphs, we describe how targeting of the HGF-MET signaling pathway can overcome the drug resistance in NSCLC, RCC and pancreatic cancer (PDAC) and we summarize clinical studies (Table 2). The expression of MET and HGF is high in these tumors: in NSCLC 40% and 50%, in RCC 70% and 60% and in PDAC >70% and >35%.[83]

Targeting HGF-MET in NSCLC to overcome drug resistance. Lung cancer is the leading cause of cancer-related death for both men and women worldwide. The most prevalent mutated or rearranged oncogenes identified in NSCLC are KRAS, epidermal growth factor receptor (EGFR) and ALK. This knowledge has been translated into clinical practice with the introduction of targeted therapies that have led to the improvement of NSCLC patients' outcome: EGFR TKIs (erlotinib, gefitinib) for NSCLC patients harboring activating mutations in the EGFR TK domain and crizotinib for NSCLC patients carrying ALK translocations.[84–86]

Nevertheless, many patients acquire resistance to anti-EGFR therapy after 6–12 months.[87] Acquired resistance to EGFR TKIs can occur as a result of secondary EGFR mutations or parallel activation of downstream signaling pathways, including MET. Approximately 5%–22% of NSCLC patients with secondary resistance to EGFR TKIs had evidence of amplification of the MET oncogene.[88,89]

Functional crosstalk of MET with EGFR has been reported in lung and colorectal cancer[85,87] and has emerged as a major mechanism for cancer progression as well as resistance to anti-EGFR targeted therapy (see Fig. 5). The therapy of

Table 2. The frequency of the most common MET alterations in selected human cancers.

CANCER	POINT MUTATIONS	GENE AMPLIFICATION/HIGH COPY NUMBER	REF.
NSCLC	4%	2–21%	188–191
Kidney	100% hereditary pRCC	46% type II pRCC, 81% type I pRCC	192
	13%–21.6% sporadic pRCC		
Gastric	NA	16–30%	162
HCC	0%	4–5%	193
CRC	NA	10%	194,195
Head and neck	3–9%	NA	196

lung cancer with EGFR TKI leads to MET amplification which subsequently activates PI3K–AKT signaling.[88,89] In this way, MET signaling can compensate for EGFR inhibition. The resistance can be prevented by combined inhibition of EGFR and MET, as has been shown in human lung tumor xenografts.[90,91] Conversely, the treatment of tumor cells with MET TKIs may lead to the selection of tumor cell populations that escape growth inhibition via the EGFR or SRC kinases.[92]

Several MET inhibitors have been tested in combination with EGFR inhibitors. However, no difference in OS was observed with the combination of either tivantinib with erlotinib,[68] or onartuzumab with erlotinib.[65] When analyzing the subgroups of the patients, a significant improvement in PFS was observed in the group of patients with KRAS-mutant tumors ($P = 0.006$) treated with tivantinib and erlotinib. Similarly, subgroup analysis of NSCLC patients revealed that tumors which overexpressed MET, the combination of onartuzumab

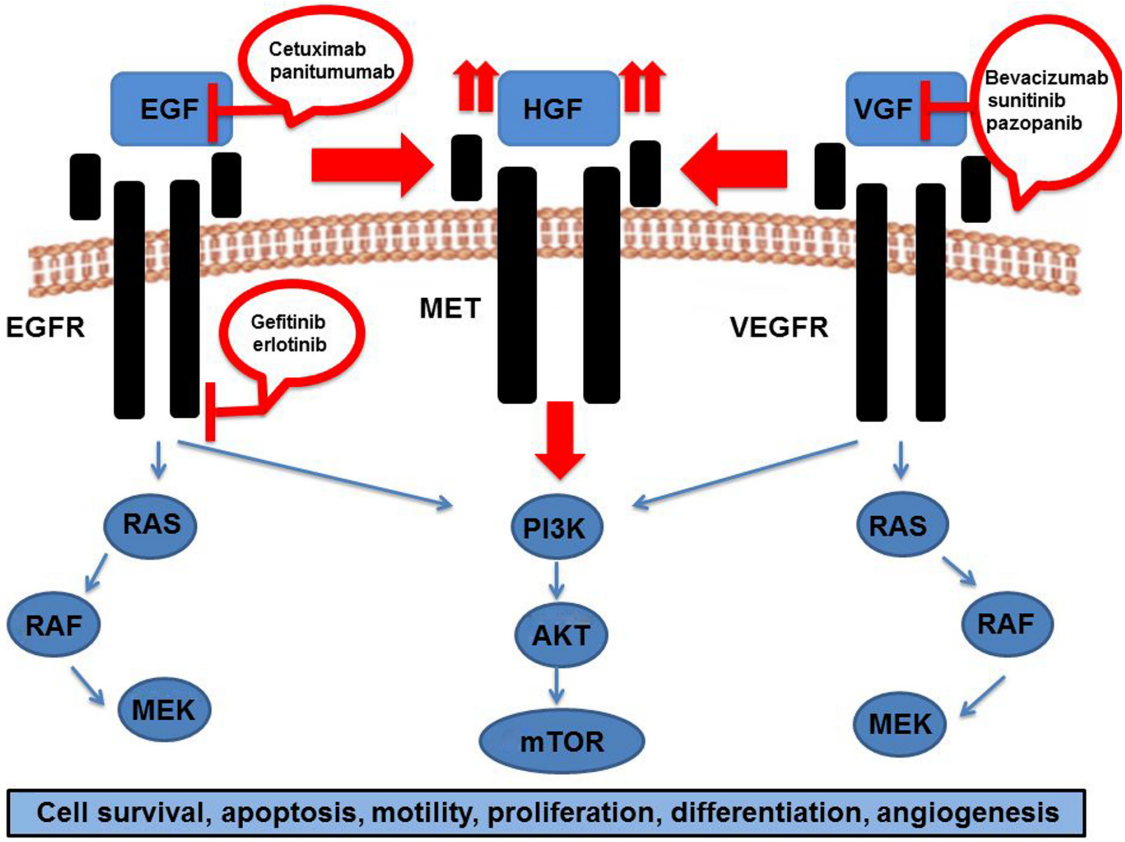

Figure 5. Functional crosstalk of HGF-MET signaling pathway with EGFR and VEGFR signaling pathway.
Notes: The anticancer treatment with EGFR antibodies (cetuximab, panitumumab) or EGFR TKIs (gefitinib, erlotinib) leads to MET amplification with subsequent activation of PI3K-AKT signaling. The resistance can be prevented by dual inhibition of EGFR and MET. Similarly, MET-HGF signaling pathway activation help evade VEGFR inhibition induced by bevacizumab, sunitinib or pazopanib and dual inhibition with VEGFR and MET inhibitor might overcome the resistance to anticancer treatment.

plus erlotinib was associated with a significant improvement in both PFS and OS ($P = 0.04$ and 0.002, respectively).

Another type of MET-targeted therapy available in clinical practice is crizotinib, the first clinically available ALK inhibitor for ALK-rearranged NSCLC in the world.[93,94] This drug was initially designed as a MET inhibitor and indeed, Ou and colleagues showed that patients with NSCLC with MET amplification, but without ALK rearrangement, experienced a rapid and durable response to crizotinib. This demonstrated its therapeutic role also as a MET inhibitor.[95] Kogita et al investigated the role of the MET signal in ALK-positive NSCLC demonstrating that HGF mediated resistance to alectinib (selective ALK inhibitor), but not to crizotinib.[96] It was observed that alectinib activated the MET signal even in the absence of HGF and that the inhibition of the MET signal enhanced the efficacy of alectinib.[96] Moreover, MET expression was significantly increased in ALK- rearranged NSCLC.[97]

Crizotinib showed remarkable responses in NSCLC patients harboring CD74-ROS1 rearrangement; however, crizotinib resistance eventually developed due to acquired mutations such as G2032R in ROS1. As the result of high-throughput drug screening, the authors found that the cabozantinib effectively inhibited the survival of CD74-ROS1-mutant Ba/F3 cells and crizotinib-resistant patient-derived cancer cells (MGH047) harboring G2032R-mutated CD74-ROS1. Cabozantinib was therefore identified as a potential therapeutic strategy to overcome this form of resistance to crizotinib.[98,99]

Actually, several clinical trials targeting HGF-MET signaling in NSCLC are ongoing, using several different monotherapy drugs targeting HGF-MET, such as cabozantinib (NCT01639508) or PF-02341066 (NCT00585195) and combinations with EGFR TKI (gefitinib, erlotinib) (NCT01610336, NCT01911507, NCT01982955, NCT01822496, NCT01887886), nivolumab (NCT02323126) or pemetrexed (NCT02134912).

Therefore, in conclusion, HGF-MET signaling plays an important role in acquired resistance to EGFR TKIs in NSCLC and studies demonstrated that combined inhibition of EGFR and MET can overcome resistance to EGFR inhibitors. Therefore, it seems reasonable to prefer combination therapies that target both signalling pathways that are primarily responsible for the cancer phenotype. In this way, the rescue pathways are targeted simultaneously.

Targeting HGF-MET in renal cancer carcinoma to overcome the drug resistance. RCC is the third most frequent cancer originating from the genitourinary organs.[100] It originates from either the proximal tubule of the kidney or the collecting duct and is classified into four major histological types: clear cell (ccRCC, 75–85% of tumors), papillary (pRCC, 10–15% of tumors), chromophobe (5–10%), and collecting duct tumor (rare). pRCC can be further divided into two morphological subtypes; type 1 consists of predominantly basophilic cells and type 2 of mostly eosinophilic cells. In general, metastatic pRCC has a worse prognosis than ccRCC.[98] Moreover, type I and type 2 of pRCC have different clinical features. Type I is characterized by an indolent clinical course, and type II by a more aggressive clinical behavior.[101]

In ccRCC tumors, mutations or functional inactivation of the von Hippel-Lindau (VHL) gene occur in the majority of cases, resulting in the loss of function or reduced levels of the VHL protein.[102] The subsequent transcriptional hyperactivation of HIF-targeted genes, such as VEGF, PDGF, TGFa, HGF, MET drives tumor progression and hypervascularization.[103,104] Albiges and colleagues[105] reported that MET expression was higher in pRCC than in ccRCC, and higher in type I pRCC compared to type II pRCC. In pRCC, several activating missense mutations of the MET gene have been described, both in sporadic and hereditary forms.[106] The trisomy of chromosome 7, in which MET is located, has been seen to be a common occurrence in pRCC.[107]

Currently, first-line treatment of patients affected by RCC include several anti-VEGF agents (sunitinib, pazopanib and bevacizumab) and an mTOR inhibitor (temsirolimus).[108] VEGF-targeted therapies have a survival benefit in RCC patients, but fail to produce enduring clinical responses in most patients. Inevitably, the disease progresses following a transient 9–11 month period of clinical benefit.[108] It is now well established that crosstalk between the MET and VEGFR pathways supports tumor vascularization and progression but is also implicated in the resistance to anti-VEGFR therapies (Fig. 5). Gene expression studies comparing primary glioblastoma to bevacizumab-treated tumors revealed MET as one of the most upregulated genes.[109] Thus, MET activation is implicated in the upregulation of alternate pathways that help evade VEGFR inhibition.[110,111]

Recently, Ciamporcero et al.[103] evaluated the effects of either monotherapy or combination strategy targeting the VEGF (axitinib) and MET pathways (crizotinib) in ccRCC models (SCID mice). The authors tested these drugs in a human ccRCC patient–derived xenograft, in both sunitinib-sensitive and -resistant models. The combination therapy increased the antitumor effect of both drugs, independently from MET expression. It was concluded that, clinical testing of a combined VEGF and HGF-MET pathway blockade could improve the outcome of patients affected by RCC. Similarly, Shojaei et al.[49] observed increased HGF expression in mouse models resistant to sunitinib. The addition of a MET inhibitor was able to overcome sunitinib resistance.[49] Choueiri and colleagues[112] conducted a phase II clinical trial to investigate the role of foretinib, a dual inhibitor of MET and VEGF in pRCC. Interestingly, pRCC harboring the germline MET mutations were highly predictive of foretinib response, with 50% of patients with mutations having an objective response compared with 9% of patients without mutations.[112] Another MET inhibitor, savolitinib, is currently in clinical development for various indications, including pRCC.[72,113] In a recent

study pharmacodynamic and antitumor activity of savolitinib were tested using a dose response up to 25 mg/kg daily, representing clinically achievable exposures and comparable with the activity of sunitinib or crizotinib.[71] Savolitinib treatment resulted in tumor regressions, whereas sunitinib or crizotinib resulted in unsustained growth inhibition. Evaluation of the pharmacodynamic effects of savolitinib showed that this drug can suppress the MET signalling pathway and the duration of target inhibition is dose related. Interestingly, continuous dosing of savolitinib for approximately 5 weeks showed antitumor activities with no signs of developing resistance, in contrast to sunitinib,[114] which suggested that savolitinib could be of therapeutic potential in sunitinib-resistant pRCC patients.[71]

Temsirolimus is an mTOR inhibitor and is used in RCC patients with poor prognosis.[108] mTOR, a serine/threonine kinase, is a downstream target of the PI3K and AKT pathways, similar to EGFR, MET and VEGF. It plays a critical role in cell survival and proliferation.[115,116] Ishikawa et al.[115] demonstrated that mTOR inhibitors (temsirolimus and everolimus) can overcome HGF-dependent resistance to EGFR-TKIs in EGFR mutant lung cancer cells. Moreover suppression of tumor angiogenesis has been observed.[115]

Actually, several clinical trials targeting HGF-MET in RCC are ongoing, both as a monotherapy (crizotinib in NCT01524926, AZD6094 in NCT02127710, INC280 in NCT02019693) or in combination therapy (axitinib and crizotinib in NCT01999972).

Targeting the MET and VEGFR pathways simultaneously represents a promising approach for RCC treatment since this will target multiple pathways involved in angiogenesis, tumor survival and metastasis.

Targeting HGF-MET in pancreatic ductal adenocarcinoma to overcome the drug resistance. PDAC is a highly aggressive malignancy and fourth leading cause of cancer-related death in developed countries.[117] The median survival after diagnosis is 2–8 months and only 3–6% of all patients with PDAC survive 5 years after diagnosis. Surgical resection remains the cornerstone of management of PDAC, but this is only feasible for a limited number of patients. The average survival of successfully resected patients is between 12 to 20 months, with a high probability of relapse. Since symptoms are not very clear in early stages, 80% of PDACs are diagnosed when already advanced, and no curative therapy is currently available.[117] Chemotherapy prolongs life by only a few months, and PDAC chemoresistance renders most drugs ineffective. Nowadays, there are three different therapeutic options for PDAC in the metastatic setting, gemcitabine as monotherapy, gemcitabine in combinations with nab-paclitaxel or the combination of 5-FU, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX).[117–118]

MET overexpression was significantly associated with TNM stage and lymph node invasion, poor tumor differentiation, increased abnormal angiogenesis and poor OS of PDAC patients.[119–121] There are different mechanisms by which MET overexpression confers chemoresistance in PDAC. MET has been identified as a marker of pancreatic CSCs which have been associated with PDAC aggressiveness, metastatic behavior and intrinsic resistance to chemotherapy.[122] Another mechanism involves the mesenchymal support network. Stroma is the predominant source of HGF, suggesting MET activation is, at least in part, a result of paracrine signaling.[123] Interestingly, HGF has been shown to not only increase VEGF production by stromal cells, but also to act synergistically with VEGF to induce endothelial cell tube formation and proliferation.[124] Inhibition of HGF could therefore represent a potentially useful antiangiogenic approach in PDAC. Additionally, preclinical studies have demonstrated that overexpression of MET has also been associated with EMT-like changes in acquired-gemcitabine-resistant PDAC cells.[125]

Avan et al.[126] showed the ability of crizotinib to specifically target CSC-like-subpopulations, interfere with cell-proliferation, induce apoptosis, reduce migration and synergistically interact with gemcitabine, supporting further studies on this novel therapeutic approach for PDAC. Moreover, the same group showed that crizotinib decreased tumor dimension, prolonged survival, promoted gemcitabine uptake but reduced gemcitabine catabolism. These effects were mediated by an increased activity of the human equilibrative and concentrative nucleoside transporters (hENT1 and hCNT1), and a decreased cytidine deaminase (CDA). The synergism of gemcitabine and crizotinib in an orthotopic mouse model of primary PDAC warrants clinical evaluation for PDAC treatment.[127]

Also cabozantinib enhanced the effect of gemcitabine in a human pancreatic cancer model growing orthotopically in NOD SCID mice. Alone and in combination the tumor growth was inhibited and the population of CSCs was decreased.[119] Hage et al.[128] demonstrated that cabozantinib altered the expression of apoptosis molecules and shifted the balance to antiapoptotic signaling. In parallel, cabozantinib inhibited SOX2, MET and CD133 expression in addition to the self-renewal potential. Most importantly, cabozantinib increased efficacy of gemcitabine even in high-gemcitabine-resistant PDAC, suggesting that cabozantinib can overcome gemcitabine resistance.

Several clinical trials in advanced cancers, including PDAC are currently ongoing including combinations with crizotinib (dasatinib, pazopanib/pemetrexed, vemurafenib, axitinib) or the combination cabozantinib and gemcitabine (NCT01744652, NCT01548144, NCT01531361, NCT01999972, NCT01663272).

Targeting HGF-MET in other tumors. Aberrant MET signaling is a hallmark of multiple cancer types. For metastatic medullary thyroid cancer, cabozantinib is approved by the US Food and Drug Administration.[129] The MET pathway is frequently aberrantly activated in colorectal cancer, esophagogastric cancer, hepatocellular carcinoma, prostate cancer, sarcomas and several studies have shown promising activity of HGF-MET targeting drugs in these tumor

types.[130–138] Moreover, targeting the HGF-MET axis opens new therapeutic possibilities for liquid cancers. For example, HGF expression is critical in acute myeloid leukemia (AML) pathogenesis. Kentsis et al.[139] demonstrated that leukemic cells treated with crizotinib can develop resistance due to compensatory upregulation of HGF expression, leading to restoration of HGF signaling. In cases of AML where MET is coactivated with other tyrosine kinases, such as fibroblast growth factor receptor 1 (FGFR1), concomitant inhibition of FGFR1 and MET blocked compensatory HGF upregulation resulting in sustained logarithmic cell kill both *in vitro* and *in vivo* xenograft models *in vivo*.[139]

Biomarkers for MET Inhibitors

In the era of personalized therapy with more frequent use of targeted agents, it is important to identify biomarkers which can predict response to a specific class of agents, including MET inhibitors. A number of predictive biomarkers to HGF-MET inhibitors are currently being evaluated, such as circulating HGF and MET, MET protein overexpression, MET gene amplification and mutation. However, none of them has been validated yet.

Circulating HGF and MET. Treatment with HGF inhibitors (ficlatuzumab and rilotumumab) can result in an increase in plasma total HGF and soluble MET concentrations from baseline, but no association with clinical outcomes was demonstrated.[140–144] In another clinical trial, administration of the MET antagonist onartuzumab resulted in an increase in HGF, but this elevation was independent of dose, drug exposure, dose duration or tumor type. In addition, the evaluation of the relationship between changes in HGF levels and clinical outcomes in MET-positive patients was inconclusive.[145] In contrast, MET kinase inhibitors (tivantinib) did not show obvious changes in HGF in phase I clinical studies.[146]

MET protein overexpression. Currently, high MET protein expression levels in tumor tissues may be associated with poor prognosis in selected cancer types. In a phase 2 trial with patients that had positive MET expression in tumor tissues, a longer survival was found in patients who received the HGF inhibitor rilotumumab plus ECX (epirubicin, cisplatin, capecitabine) than patients who received ECX alone.[147] However, the results could not be reproduced in the confirmatory phase 3 RILOMET-1 study[148] and OS were statistically significantly worse with rilotumumab ($P = 0.016$). Exploratory biomarker analyses performed on patients with advanced NSCLC receiving the MET antagonist onartuzumab in combination with erlotinib demonstrated an OS benefit in MET-positive patients ($P = 0.002$).[149] A subgroup analysis suggested that MET expression by IHC was a more sensitive predictor than MET amplification measured by FISH.[149] However, mRNA expression of MET did not predict survival in patients treated with onartuzumab.[149] Furthermore, phosphorylated MET, a marker for MET pathway activation, and serum MET did not appear to be a suitable biomarker for NSCLC.[151]

A multicenter Phase II randomized controlled trial, investigated the role of tivantinib in the second-line setting in patients with unresectable hepatocellular carcinoma.[152] The patients were randomized 2:1 to receive either oral tivantinib in two different drug dosages (360 mg twice-daily or 240 mg twice-daily) or to receive placebo. Better PFS was observed in the tivantinib arm in comparison with the placebo arm (HR 0.45, $P = 0.02$) but no detrimental effect in MET-expression-negative patients wasfound.[152,153] A retrospective analysis of patients with NSCLC tumors treated with tivantinib plus erlotinib failed to demonstrate a predictive value for MET protein overexpression.[154] In subgroup analyses, it was shown that MET expression could have predictive potential only in MET-positive patients with nonsquamous histology, suggesting that the clinical relevance of MET biomarker for tivantinib may vary among tumor types.[155]

MET gene amplification and mutation. Amplification of the MET gene locus with overexpression of the receptor on the cell surface is a well-characterized aberrancy as well as MET gene mutations. The latter leads in most cases to a constitutively active form of the molecule. The frequency of these molecular changes differs among tumor types (see Table 2).

In preclinical studies MET amplification predicted sensitivity to multiple MET targeted agents including crizotinib; this was also found in several clinical case reports.[156–157] In a subset of esophagogastric adenocarcinoma patients, a high level of MET amplification as measured by FISH, correlated with responsiveness to crizotinib, although this response was transient.[156] A durable response to crizotinib was observed in a NSCLC patient with de novo MET amplification.[157] In a Phase II trial of foretinib in pRCC, germline mutations of MET were predictive of clinical response.[112] Patients carrying a MET germline mutation experienced partial response (5/10) or stable disease (5/10), compared to only 9% (5/57) of patients with no MET mutations.[112] Moreover, in newly diagnosed multiple myeloma, patients carrying four MET gene copies (9.8%) had a short PFS.[159]

MET phosphorylation/activation. In clinical pre- and post treatment patients' biopsies, changes in MET phosphorylation and activation of downstream signaling effectors were observed in response to several anti-MET agents.[160–161] Treatment with foretinib or tivantinib led to a decrease in the level of MET phosphorylation and activation of ERK and AKT pathways in post treatment biopsies, although it remains unclear whether changes in these markers are predictive of clinical responses.[153,162]

Conclusions. Circulating HGF and MET were evaluated as a pharmacodynamic biomarker of MET inhibition in different clinical trials and it seems that their potential as predictive biomarkers to response depends on the type of MET inhibition (HGF inhibitors, MET antagonists, MET kinase inhibitors). To date their predictive value for clinical response has not been shown. MET protein expression levels in tumor

tissues may be prognostic biomarkers of survival in selected cancer types with specific molecular aberrations. MET gene amplification, copy number, and mutations appear to be relatively conservative biomarkers, but they may be associated with rare events in cancer development.

Future Directions

The HGF-MET axis seems to be one of the most functional signaling pathways involved in tumor genesis, progression and resistance to anticancer treatment.

Several studies demonstrated both *in vitro* and in xenografts that the inhibition of the MET signaling pathway by using selective MET inhibitors correlated with cell growth arrest and apoptosis. Furthermore, the combination strategy resulted in an additive antitumor effect and also restored chemosensitivity in MET-overexpressed resistant cells. Unfortunately, there is a discrepancy between preclinical and clinical studies, which can often be attributed to inappropriate patients' selection and missing circulating biomarkers.[2] In fact, one of the key challenges in the development of targeted therapeutics is the identification of patients likely to obtain clinical benefit by having potentially sensitive tumors. It is essential to develop biomarker assays that have good specificity and sensitivity, and should be included in both early stage and registration-enabled clinical trials to determine their clinical utility.[163] In accordance with Hack et al.[163], possible biomarker strategies to identify MET-driven tumors might be at the DNA level (MET gene amplifications/mutations), at the RNA level (MET-RNA overexpression, microRNA associated with response/resistance to therapy), or at the protein level (MET protein overexpression, MET posttranslational modifications ie, phosphorylation).[163]

Molecular heterogeneity exists both between patients and intra-patient. These molecular changes occur throughout the disease process, in response to treatment and as a consequence of resistance to therapy. Protein markers are often used to assess and predict disease progression and drug response, but gene expression markers may provide more reliable results.[163] MicroRNAs may also represent novel markers of MET activity. For example, three candidate microRNAs that are involved in the modulation of MET expression, miR-449a, miR-340, and miR-409–3p are down regulated in NSCLC, aggressive breast cancer cell lines, and bladder cancer cells, respectively.[164–165] In breast cancer cell lines, expression of miR-340 was inversely correlated with MET expression.[166] Hence, the identification of small sets of gene signatures based on mRNA expression profiles may be helpful in predicting drug response.[167]

Thus, in future clinical trials emphasis on biomarker identification and development should be prioritized, which will allow a better prediction of response to MET inhibitors.

Another challenge in the effective use of HGF/MET-targeted agents for cancer treatment, is the identification and testing of rational drug combinations. Since solid malignancies are comprised of highly heterogeneous groups of cells, the use of targeted inhibitors may select a malignant clone of cells, which are inherently resistant to blockage of the HGF-MET pathway. Acquired resistance to HGF/MET inhibition in cancer cells can develop by point mutations, by increased amplification of MET or by activation of a compensatory signaling pathway which can bypass the effects of targeted agents. Strategies to overcome HGF-MET resistance would involve the targeting of multiple compensatory pathways simultaneously either by using multitargeted agents such as cabozantinib (MET, VEGF), crizotinib (MET, ALK), or by combining targeted agents such as onartuzumab or ficlatuzumab with erlotinib/gefitinib (MET/HGF and EGFR inhibitors, respectively).

Inhibitors of heat shock protein 90 (HSP90), a molecular chaperone to MET, and of other key cellular proteins may offer another approach to overcome resistance to MET inhibition.[168]

A better understanding of the toxicities associated with HGF-MET pathway inhibition is necessary. Peripheral edema due to an attenuation of HGF-mediated signaling in the vascular endothelium, has been associated in multiple tumor types after treatment with all monoclonal antibodies targeting HGF or MET, combined either with various cytotoxic or targeted therapies.[2] This could also explain the increased incidence of venous thromboembolism with HGF/MET inhibition. HGF/MET signaling has been implicated in physiological processes such as tissue growth/repair, hematopoesis and glucose metabolism; therefore it is possible to expect additional toxicity signals such as myelosuppression, mucosal injury, wound healing complications or disturbances in glucose homeostasis.[143–144]

Another challenging topic includes the potential of gene therapy for c-MET overexpression. As a potential therapeutic strategy to inhibit tumor growth Stabile et al.[169] constructed U6 expression plasmids for delivery of sense or antisense sequences into lung tumor cells. These should target the translation start site of the human c-MET gene.[169] These constructs have been examined both *in vitro* and an *in vivo* tumor xenograft model. The c-MET protein was downregulated by 50–60% in two lung cancer cell lines that were transiently transfected with the c-MET antisense versus U6 control. Tumor cells treated with the c-MET antisense construct also showed decreased phosphorylation of c-MET and MAP kinase when exposed to exogenous HGF. The treatment of patient with lung tumors with c-MET antisense versus U5 control plasmid resulted in the downregulation of the c-MET protein expression, a 50% decrease in tumor growth over a 5-week treatment period and an increased rate of apoptosis.[169]

Conclusions

c-MET encodes a versatile RTK involved in many physiological, and pathological and biological processes. The downstream effectors activated by HGF-MET signaling pathway

Table 3. An overview of cancer patients' clinical outcome after treatment with c-MET inhibitors within clinical studies.

TUMOR TYPE	PHASE	DRUG	RESPONSE RATE	PFS	OS	REF.
NSCLC	III	Tivantinib + erlotinib vs. placebo + erlotinib	8.4% vs. 6.5%	2.9 mo vs. 2 mo	12.9 mo vs. 11.2 mo	68
NSCLC	III	Onartuzumab + erlotinib vs. placebo + erlotinib	NA	2.6 mo vs. 2.7 mo	6.8 mo vs. 9.1 mo	65
NSCLC	III	Crizotinib *vs.* CT (pemetrexed or docetaxel)	65% vs. 20%	7.7 mo vs. 3 mo	20.3 mo vs. 22.8 mo	90
NSCLC	III	Crizotinib vs. CT (pemetrexed + cisplatin or carboplatin)	74 vs. 45%	10.9 mo vs. 7 mo	NA	94
NSCLC	II	Erlotinib vs. cabozantinib vs. erlotinib + cabozantinib	NA	1.9 mo vs. 3.9 mo vs. 4.1 mo	4.0 mo vs. NA vs. NA	96
NSCLC	II	Ficlatuzumab + gefitinib vs. gefitinib	43% vs. 40%	5.6 mo vs. 4.7 mo	NA	170
RCC	II	Foretinib	13.5%	9.3 mo	NA	106
RCC	II	Rilotumumab 10 mg vs. 20 mg	2.5% vs. 0%	3.7 mo vs. 2.0 mo	14.9 mo vs. 17.6 mo	171
RCC	I	Cabozantinib	PR 28%, SD 52%	12.9 mo	15 mo	172
RCC	III	Cabozantinib + rosiglitazone	28%	14.7 mo	NA	173
Solid tumors (mainly RCC and colorectal cancer)	I	Savolitinib	3 RCC pts achieved PR, 1 pt CRC achieved PR	NA	NA	72
Prostate cancer	III	Cabozantinib vs. prednisone	41% vs. 3%	5.5 mo vs. 2.8 mo	11 mo vs. 9.8 mo	174
Prostate cancer	II	Mitoxantrone + prednisone + rilotumumab vs. mitoxantrone + prednisone + placebo	11% vs. 14%	3.0 mo vs. 2.9 mo	12.2 mo vs. 11.1 mo	175
Colorectal cancer	I/II	Cetuximab + irinotecan + tivantinib vs. cetuximab + irinotecan + placebo	45% vs. 33%	8.3 mo vs. 7.3 mo	NA	176
Colorectal cancer	I/II	Panitumumab + rilotumumab vs. panitumumab + ganitumumab vs. panitumumab + placebo	31% vs. 22% vs. 21%	5.2 mo vs. 5.3 mo vs. 3.7 mo	NA	177
Esophagogastric cancer	II	Epirubicin + cisplatin + xeloda + rilotumumab vs. epirubicin + cisplatin + xeloda + placebo	38% vs. 24%	5.6 mo vs. 4.2 mo	11.1 mo vs. 8.9 mo	178
Gatric cancer	II	Forentinib (intermittent vs. daily cohort)	0% vs. 0%	1.7 mo vs. 1.8 mo	7.4 mo vs. 4.3 mo	179
Hepatocellular cancer	II	Tivantinib vs. placebo	1% vs. 0%	1.5 mo vs. 1.4 mo	6.6 vs. 6.2 mo	153
Hepatocellular cancer	II	Cabozantinib	5%	4.4 mo	15.1 mo	180
Hepatocellular cancer	I/II	Foretinib	24%	4.2 mo	NA	181
Uveal melanoma	II	Cabozantinib	NA	4.8 mo	12.6 mo	182
Melanoma	II	Cabozantinib	PR 5%, SD 57%	4.2 mo	NA	183
Breast cancer	II	Cabozantinib	PR 14%, SD 57%	4.3 mo	NA	184
HNSCC	II	Foretinib	NA	3.65 mo	5.59 mo	185
Germ cell tumors	II	Tivantinib	PR 0%, SD 20%	1.0 mo	6.0 mo	186
Glioblastoma	II	Rilotumumab (10 vs. 20 mg/kg)	0% vs. 0%	4.1 mo vs. 4.3 mo	6.5 mo vs. 5.4 mo	144
Sarcoma	II	Crizotinib	PR 0%, SD 58.3%, PD 41.7%	5.25 mo	NA	187
Thyroid cancer	III	Cabozantinib vs. placebo	28% vs. 0%	11.2 mo vs. 4.0 mo	NA	188

Abbreviations: HNSCC, head and neck squamous cell carcinoma; mo, months; NA, not available; NSCLC, non small cell lung cancer; OS, overall survival; PFS, progression free survival; PR, partial response; RCC, renal cancer carcinoma; SD, stable disease.

are involved in cell survival, motility and proliferation. The HGF-MET axis is frequently dysregulated in cancer, especially in advanced or metastatic disease and is responsible for tumor growth, invasion and resistance to anticancer therapy.

Clinical trials of MET-targeted drug monotherapy have shown promising results in terms of antitumor efficacy and improvement of clinical outcomes in various tumor types (Table 3). However, in our opinion, the potential of MET

Table 4. MET inhibitors combination therapy to overcome the drug resistance.

DRUG	CANCER	POSSIBILITY TO OVERCOME RESISTANCE TO ANTICANCER TREATMENT	REF.
TARGETED THERAPY			
EGFR inhibitors			
Erlotinib	NSCLC, K-RAS mut	Erlotinib and tivantinib	68
	NSCLC, MET overexpression	Erlotinib and onartuzumab	65
	NSCLC, EGFR mut	mTOR inhibitor	115
Gefitinib	NSCLC	Butein (dual EGFR and MET inhibitor)	150
	NSCLC, EGFR mut	Gefitinib and TAK701	63
Cetuximab	CRC, MET overexpression	Cetuximab and MET inhibitor	198
Panitumumab	CRC, MET overexpression	Panitumumab and MET inhibitor	198
VEGFR inhibitors			
Sunitinib	ccRCC	Axitib and crizotinib	103
	pRCC	Savolitinib	71
		Foretinib (dual MET and VEGF inhibition)	112
Sorafenib	RCC, HCC, melanoma	Sorafenib and tivantinib	67
	HCC, MET overexpression	Tivantinib	69
Anti-HER2 therapies			
Trastuzumab	Breast cancer, HER2 positive	Trastuzumab and MET inhibitor	51
Lapatinib	Esophageal squamous cell carcinoma	Lapatinib and MET inhibitor	81
B-RAF inhibitor			
Vemurafenib	Melanoma, B-RAF activating mutation V600E	Vemurafenib and MET inhibitor	82
Selective ALK inhibitors			
Alectinib	NSCLC with ALK rearrangement and MET overexpression	Crizotinib	93–97
Non-selective ALK inhibitors			
Crizotinib	NSCLC, G2032R-mutated CD74-ROS1	Cabozantinib	98, 99
CHEMOTHERAPY			
Gemcitabine	PDAC	Gemcitabine and crizotinib	126
	PDAC	Gemcitabine and cabozantinib	127
Capecitabine	Gastric or oesofagogastric junction, MET overxpression	Capecitabine and rilotumab	60
Cisplatin	Head and neck cancer, MET overexpression	Cisplatin and MET inhibitor	199
	Cervical cancer	Cisplatin and MET inhibitor	200
Taxanes	Ovarian cancer, MET overexpression	Taxane and MET inhibitor	201
RADIOTHERAPY	Cancer cell lines	Radiation and MET inhibitor	202

targeted agents might be in combination approaches whereby both molecular drivers and mechanisms of resistance are inhibited (Table 4).

In future, an accurate stratification of patients' population and rational mechanism-based treatment combinations are critical for success of MET targeted therapy in the clinical practice.

Abbreviations

ALK: anaplastic lymphoma kinase
CDA: cytidine deaminase
CUP: cancer of unknown origin
Gab1: Grb2-associated-binding protein 1
Grb2: growth factor receptor bound protein 2
HGF: hepatocyte growth factor
HL domain: hairpin loop domain
IPT1-4 domain: four immunoglobulin plexins transcription domains
ccRCC: clear cell renal cancer carcinoma
CSCs: cancer stem cells
EGFR: epidermal growth factor receptor
EMT: epithelial-mesenchymal transition

ERK: extracellular signal-related kinase
GSK3β: glycogen synthase kinase 3β
GTP: guanosine triphosphate
HAI: HGF inhibitor
HGFA: HGF activator
JAK: Janus kinase
JNKs: c-Jun NH2-terminal kinase
MAPK: mitogen-activated protein kinase
MET: mesenchymal epithelial transition receptor
mTOR: mammalian target of rapamycin
NF-κB: nuclear factor kappaB
NSCLC: non small cell lung cancer
OS: overal survival
PDK-1: phsphoinositide-dependent-kinase-1
PDAC: pancreatic ductal adenocarcinoma
PIP2: (4,5)-bisphosphate
PIP3: (3,4,5)-triphosphate
PFS: progression-free survival
pRCC: papillary cell renal cancer carcinoma
PSI domain: plexin, semaphorin and integrin cystein-rich domain
RCC: renal cancer carcinoma
RTKs: receptor tyrosine kinases
SEMA domain: semaphorin domain
SF: scatter factor
SPH: serine proteases homology domain
TKI: tyrosine kinase inhibitor
VEGFR: vascular endothelial growth factor

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Author Contributions

Wrote the first draft of the manuscript: GP, IG. Contributed to the writing of the manuscript: EG, GB. Agree with manuscript results and conclusions: EG, GB. Jointly developed the structure and arguments for the paper: GP, IG. Made critical revisions and approved final version: GP, EG, GB. All authors reviewed and approved of the final manuscript.

Short Overview of Anticancer Therapy

VEGFR inhibitors. Bevacizumab, axitinib, sunitinib, pazopanib.

EGFR inhibitors. EGF receptor inhibitors (cetuximab, panitumumab) or EGFR TKIs (erlotinib, gefitinib).

B-RAF inhibitor. Vemurafenib.

Anti-HER2 therapy. Trastuzumab, lapatinib.

mTOR inhibitor. Temsirolimus.

Gemcitabine. Nucleoside analog used as chemotherapy.

Pemetrexed. Folate antimetabolite used as chemotherapy.

FOLFIRINOX. Chemotherapy schedule that consist of 5-fluorouracil, leucovorin, irinotecan and oxaliplatin.

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