Published in final edited form as:
Eur J Cancer. 2010 May ; 46(7): 1260–1270. doi:10.1016/j.ejca.2010.02.028.

Targeting the HGF/Met Signaling Pathway in Cancer

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Abstract

Under normal conditions, hepatocyte growth factor (HGF)-induced Met tyrosine kinase (TK) activation is tightly regulated by paracrine ligand delivery, ligand activation at the target cell surface, and ligand activated receptor internalization and degradation. Despite these controls, HGF/Met signaling contributes to oncogenesis and tumor progression in several cancers and promotes aggressive cellular invasiveness that is strongly linked to tumor metastasis. The prevalence of HGF/Met pathway activation in human malignancies has driven rapid growth in cancer drug development programs. Pathway inhibitors can be divided broadly into biologicals and low molecular weight synthetic TK inhibitors; of these, the latter now outnumber all other inhibitor types. We review here the basic properties of HGF/Met pathway antagonists now in preclinical and clinical development as well as the latest clinical trial results. The main challenges facing the effective use of HGF/Met-targeted antagonists for cancer treatment include optimal patient selection, diagnostic and pharmacodynamic biomarker development, and the identification and testing of optimal therapy combinations. The wealth of basic information, analytical reagents and model systems available concerning HGF/Met oncogenic signaling will continue to be invaluable in meeting these challenges and moving expeditiously toward more effective disease control.

Keywords

Hepatocyte growth factor; Met; cancer drug development

1. Introduction

The *MET* oncogene was first isolated from a human osteosarcoma-derived cell line on the basis of its transforming activity *in vitro*, caused by a DNA rearrangement where sequences from the *TPR* (translocated promoter region) locus on chromosome 1 were fused to *MET* sequence on chromosome 7 (*TPR-MET*) (1). A similar gene rearrangement was later found in patients with gastric carcinoma (2, 3). Isolation of the full-length *MET* proto-oncogene sequence revealed that it encoded a receptor tyrosine kinase (TK) (2). The subsequent identification of hepatocyte growth factor (HGF) as the natural ligand for the Met receptor protein (4), and the identity of scatter factor (SF) and HGF united a collection of findings demonstrating that a single receptor transduced multiple biological activities including motility, proliferation, survival and morphogenesis (5–8).

Both HGF and Met proteins are processed proteolytically from single chain precursors into mature disulfide linked heterodimers. Both are widely expressed early in development and deletion of either gene lethally disrupts embryogenesis (5, 6, 8). The widespread expression

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of both *MET* and *HGF* genes persists throughout adulthood and upregulation of *HGF* expression after kidney, liver or heart injury suggests that pathway activation protects against tissue damage and promotes tissue repair and regeneration (9–13). The strong interaction between HGF protein and cell surface heparan sulfate (HS) proteoglycans is broadly relevant to HGF biology and HS can be thought of as an HGF co-receptor, modulating HGF binding, Met activation and cellular responses (14–19). Similar to fibroblast growth factor (FGF) signaling, which requires not only FGF-HS binding, but also FGF receptor-HS interaction (20), evidence suggests that HS may facilitate HGF signaling through interactions with both HGF and Met (21). Upon HGF binding, Met autophosphorylation occurs on tyrosine residues Y1234 and Y1235 (numbered according to GenBank J02958) within the activation loop of the TK domain, inducing kinase activity, while phosphorylation on Y1349 and Y1356 near the carboxyl terminus forms a docking site for intracellular adapters that transmit signals downstream (6, 8). An intact docking site is required for transformation and metastasis (8). Critical signaling mediators in this pathway include Grb2, Gab1, phosphatidylinositol 3-kinase (PI3K), phospholipase C-gamma (PLCγ), Shc, Src, Shp2, Ship1 and STAT3 (6, 8).

2. Oncogenic HGF/Met Signaling

Under normal conditions, hepatocyte growth factor (HGF)-induced Met tyrosine kinase (TK) activation is tightly regulated by paracrine ligand delivery, ligand activation at the target cell surface, and ligand activated receptor internalization and degradation. Despite multiple controls, pathway deregulation occurs in a variety of neoplasms. Among the hundreds of genes upregulated by HGF are those encoding proteases required for HGF and Met processing, as well as *MET*, creating the potential for its overexpression through persistent ligand stimulation (6). Indeed, *MET* overexpression is characteristic of several epithelial and mesenchymal cancers and is an independent prognostic factor associated with adverse outcome (22). *MET* gene amplification is thought to be an important driver of metastasis in a subset of lung cancers that acquire resistance to agents targeting epidermal growth factor family members (23). Other mechanisms of oncogenic pathway activation include aberrant paracrine or autocrine ligand production, constitutive kinase activation in the presence or absence of *MET* gene amplification, and *MET* gene mutation (5, 24, 25). Missense *MET* mutations occur in several cancers; the earliest reported mutations were found exclusively in the Met TK domain and were associated with hereditary and sporadic forms of papillary renal cell carcinoma (PRC) (26, 27). Mutations throughout the *MET* coding sequence were later found in lung cancer and in head and neck cancers (28, 29).

The impact of specific *MET* mutations have been studied act at the molecular, cellular and organismal levels. Structural modeling of the Met TK domain indicated that activating PRC mutations interfere with an intrinsic mode of autoinhibition (30, 31). Early cell-based investigations confirmed that kinase activity was deregulated in various mutant forms and revealed that these could have distinct biological effects. For example, the PRC-associated mutations D1228H/N and M1250T showed enhanced kinase activity, Ras pathway activation and focus formation, while L1195V and Y1230C more effectively activated PI3K, promoting cell survival, soft agar colony formation and matrix invasion (32, 33). Although mutations that were reconstituted in HGF-producing cells (such as NIH3T3) could not rigorously address the role of ligand binding in oncogenesis, later studies showed that mutations expressed in epithelial cells required added ligand for soft agar colony formation and that colony formation by NIH3T3 bearing Met M1250T could be blocked by ligand binding antagonists (34). PRC-associated *MET* mutations also have been investigated in mice by engineering changes in the murine *MET* locus (35). Interestingly, mice harboring D1226N, Y1228C, and both M1248T and L1193V mutations developed sarcomas with high frequency and some lymphomas, whereas the M1248T mice developed carcinomas and

lymphomas; no mice developed PRC (35). Furthermore, analogous to the trisomy of chromosome 7 frequently observed in human PRC tumors, trisomy of chromosome 6 (containing the murine *MET* locus) and preferential duplication of the mutant *MET* allele was observed in most tumors. These results independently confirm the oncogenicity of PRC-associated *MET* mutations *in vivo* and suggest that distinct mutations influence the types of cancers that develop in mice (35).

Other alterations in the *MET* coding sequence have been identified in regions encoding the extracellular semaphorin domain (E168D, L229F, S323G, and N375S) and the intracellular juxtamembrane (JM) domain (R988C, T1010I, S1058P, and exon 14 deletions) of non-small cell lung carcinoma (NSCLC)-derived cell lines, in 12.5 % of small lung cell cancer (SCLC) cases, as well as in 8% of samples of lung adenocarcinoma tissues (29, 36–38). Some of these mutations activate proliferation, motility and invasiveness in cultured cells (29). Importantly, the JM domain regulates ligand-dependent Met internalization: Y1003 is phosphorylated in response to HGF binding and recruits c-Cbl, leading to Met ubiquitination and degradation (1). In Met JM domain mutants missing exon 14, the loss of Y1003 results in Met accumulation at the cell surface and persistent HGF-stimulated signaling that leads, in turn, to increased transforming activity and tumorigenic potential (1). Overall, *MET* mutation occurs at a lower frequency than most other mechanisms of pathway activation in tumors; nonetheless, mutations provide strong direct evidence of the pathway's oncogenic potential and may identify patients most likely to benefit from Met-targeted therapeutics.

Consistent with the role of this pathway in organogenesis, oncogenic Met signaling resembles developmental transitions between epithelial and mesenchymal cell types normally regulated by HGF: increased protease production coupled with cell dissociation and motility promotes cellular invasion through extracellular matrices, enabling tumor invasiveness and metastasis. Conversely, silencing the endogenous, overexpressed *MET* gene in tumor cells suppresses tumor growth and metastasis, and induces the regression of established metastases in mouse models (39). In addition, HGF/Met signaling in vascular endothelial cells stimulates tumor angiogenesis, facilitating tumor growth for cancers that are growth-limited by hypoxia, and independently promoting tumor metastasis. Hypoxia alone upregulates *MET* expression and enhances HGF signaling in cultured cells and mouse tumor models (40).

3. The Development of Cancer Drugs Targeting the HGF/Met Pathway

The prevalence of HGF/Met pathway activation in human malignancies has driven rapid growth in drug development programs. Agents currently under development as HGF/Met pathway inhibitors can be broadly subdivided into biologicals and low molecular weight synthetic compounds (Figure 1). Biologicals, or protein-based agents, act through a variety of mechanisms and possess target selectivity and pharmacokinetic (PK) properties that are predictable and often desirable. Nonetheless, their size typically restricts their action to extracellular events and their complexity impacts drug manufacture, routes of administration and shelf-life. Thus it is not surprising that synthetic, low molecular weight TK inhibitors (TKIs) presently outnumber every other class of HGF/Met therapeutic.

3.1. Biological HGF/Met Pathway Antagonists

Biologicals are primarily directed against ligand-receptor binding or related cell-surface events such as receptor clustering, and include [1] truncated HGF isoforms; [2] HGF forms that resist proteolytic activation or its conformational consequences; [3] truncated soluble forms of the Met ectodomain; and [4] neutralizing monoclonal antibodies (mAbs) directed against HGF or Met.

Early studies revealed that NK2, the truncated protein product of a naturally occurring alternative *HGF* mRNA transcript, could competitively antagonize growth stimulated by full-length HGF (41). However, the potential anti-oncogenic efficacy of NK2 was later shown to be compromised by its intrinsic motogenic activity, which enhanced HGF-driven metastasis in mouse models (42–46). A longer truncated isoform of full-length HGF known as NK4 has proven to be a complete competitive antagonist of HGF/Met oncogenic signaling in a variety of preclinical models and is now entering human clinical trials (47–49). The properties of all HGF/Met agents now in human clinical trials are summarized in Table 1 and available trial results in Table 2.

Antagonistic HGF forms that resist proteolytic activation or its conformational consequences exploit the requirement for proteolytic cleavage that converts pro-HGF to a biologically active heterodimer (50–53). Uncleavable forms of HGF have been engineered by substituting single amino acids in the proteolytic site; such agents suppress Met-driven tumor growth, metastasis and angiogenesis in murine tumor models (54). Related antagonists consisting of two-chain HGF mutants exploit the mechanism by which proteolytic conversion allosterically stabilizes HGF-Met binding to promote kinase activation (55). Structure/function analysis of Met extracellular subdomains has also fostered the development of biological HGF/Met pathway antagonists. Soluble Met Sema domain constructs that sequester HGF and interfere with Met homodimerization suppressed HGF-induced tumor cell migration (56), as well as tumor growth and metastasis in mice (57).

Among HGF/Met-targeted biologicals, the most advanced drug candidates are mAbs directed against either HGF or Met. The majority of these block HGF/Met binding, although at least one anti-Met mAb decreases Met activation by inducing ectodomain shedding and degradation (58). Neutralizing mAbs against human HGF, such as L2G7, AMG102 and SCH900105 (formerly AV299) each potently suppressed the growth of tumor xenografts in mice (59–63). AMG102, currently in phase I and II clinical trials (64), binds to the HGF light chain with K_d of 0.22 nM, blocks HGF-Met binding with an IC_{50} of 2.1 nM, and was well tolerated in humans (60, 65). The maximum tolerated dose (MTD) was 20 mg/kg and adverse events (AEs), which included fatigue, constipation, anorexia, nausea and vomiting, were predominantly low grade (66). AMG102 was maintained in the body with a mean half-life of 15.4 hours (66). SCH900105 is currently in phase I trials: this antibody was also very well tolerated in patients at doses up to 20 mg/kg and had a similar 15 h half-life. In its first completed trial, SCH900105 treatment was associated with stable disease (SD) in half of the patients, the longest for 34 weeks (61–63). A humanized, bivalent anti-Met monoclonal antibody, h224G11, inhibits Met phosphorylation and dimerization and blocks proliferation, migration, invasion, morphogenesis and angiogenesis in cell-based studies (63, 67). Another anti-Met mAb that blocks ligand binding, MetMab (formerly OA5D5), is an engineered monovalent antibody that has been shown to inhibit tumor growth in animal models by more than 95 percent (68). MetMab has an IC_{50} of 2.6 to 8.7 nM in intact cells, downregulates constitutively active Met in tumor cell lines (69), and is currently in phase I/II human clinical trials in comparison with erlotinib in patients with NSCLC (64).

3.2. Small Synthetic Met Kinase Inhibitors

Most Met TKIs competitively antagonize occupancy of the intracellular ATP binding site, preventing phosphorylation, TK activation and downstream signaling. ARQ197, in contrast, binds to a region of Met outside of the ATP binding site and impairs kinase activation allosterically (70). Preclinical studies show that Met TKIs potently and selectively suppress growth, migration, and/or survival in a variety of tumor-derived cell lines. These agents are in various stages of development; they are discussed here starting with preclinical candidates and ending with those now entering phase III clinical trials.

Early studies of Met-targeted TKIs, such as SU11274 (IC_{50} of 20 nM) (36, 71, 72) and PHA665752 (IC_{50} of 9 nM) (24, 73), established that Met TKIs could potently suppress oncogenesis and provided a platform for improving potency, selectivity and other drug properties. Agents such as RP1040 (IC_{50} of 1.3 nM) (74) and CEP-A (IC_{50} of 13 nM) (75) are recent preclinical candidates likely to have benefited from those founding reports. RP1040 shows good oral availability and displays a half-life of up to 9 h in intact cells (74). CEP-A shows sustainable pharmacodynamic (PD) effects in mouse studies, resulting in significant tumor growth inhibition, stable disease (SD) and partial regression (75).

Met TKIs now entering phase I clinical trials to establish safety and tolerability include JNJ-38877605 and PF-04217903. The former shows >1000-fold selectivity for the Met kinase relative to >200 related receptor TKs (76), while the latter targets Met as well as anaplastic lymphoma kinase (ALK) (77). Phase I trials with AMG 208 and E7050 are also recruiting patients with advanced solid tumors in which safety, tolerability, PK, and potential PD markers will be evaluated (64). AMG 208 selectively inhibits both ligand-dependent and ligand-independent Met activation (78)}, while E7050 targets both Met and VEGFR2 (79). A phase I study of MK8033, which targets Met with IC_{50} of 1.3 nM and the Met family member Ron, is also underway (64). MP470 inhibits PDGFR, Kit and Met; in preclinical studies, MP470 combined with erlotinib inhibited prostate cancer cell proliferation and tumor xenograft growth (80), and MP470 treatment sensitized glioblastoma cells to radiotherapy in mice (81). A phase I clinical trial of MP470 has shown tolerability of up to 500 mg/day with little toxicity (80). SGX523 showed early promise as a highly selective Met TKI, but phase 1 clinical trials were discontinued after renal toxicity was observed in patients receiving relatively low doses (82). The fact that several other selective Met TKIs do not display this level of renal toxicity suggests that a unique metabolite of SGX523 may have been responsible.

Several Met TKIs are in phase I/II clinical trials that further test safety and efficacy. BMS777607 (IC_{50} of 3.9 nM) has completed a phase I/II study in metastatic cancer patients although results are not yet available (83). MGCD265, targeting Met, VEGFR1–3, Ron, and Tie2 is currently in phase I/II studies in combination with erlotinib or standard of care (SOC) treatments; safety trials have shown a half-life of 20–30 hours with no grade 2 or higher AEs (84, 85). MK2461 has completed phase I/II trials and showed a half-life of approximately 6 hours, few AEs above grade 1 (which included anorexia, fatigue and nausea), and a best response of SD for six treatment cycles (86, 87).

Foretinib (GSK1363089; formerly XL880) and ARQ197 have shown promising results in multiple phase II trials. Foretinib targets Met and VEGFR2; trials have shown a half-life of 60 hours at the maximum dose of 240 mg/day. The most common AEs were grade 1 or 2 fatigue, hypertension, nausea, anorexia and vomiting. Several studies have shown SD for at least 10 months and some patients have experienced >20 percent reduction in tumor size (88–91). ARQ197 is reported to be highly selective for Met and has an IC_{50} of 50 nM *in vitro* (86). Although its mechanism of action is not yet completely defined, this compound may represent a new class of low molecular weight TKI (70). Current phase II clinical trials compare ARQ197 with TKIs against other targets, although results are not yet available (70).

Met TKIs furthest in development include XL184 and PF02341066, both now entering phase III clinical trials. XL184 targets Met, VEGFR2, and Ret and has a half-life of 80–90 hours (92). On average, patients show SD greater than 3 months with several up to 6 months while on treatment (93). A current phase III trial investigates XL184 as a first line treatment, compared to placebo, in patients with medullary thyroid cancer (64). PF-02341066, which has greater Met selectivity relative to PF-04217903 (94), is currently recruiting for phase I,

II and III clinical trials (64). It is well tolerated up to the MTD of 240 mg/day and preclinical studies indicate it is highly effective against the product of the *EML4-ALK* translocation found in a subset of NSCLC patients (95, 96).

4. Advanced Trials and Future Directions: Patient Selection, Pharmacodynamic Markers and Combination Treatments

An important challenge facing the effective use of molecularly targeted therapeutics is identifying those patients most likely to benefit from treatment. Preclinical studies of several Met-targeted agents have included investigating their effectiveness against known Met mutants; for example, PF02341066 is more effective than PF-04217903 against the Y1230C mutation (94). In a current phase II trial of foretinib, PRC patients with germline or somatic MET mutations, MET gene amplification or trisomy of chromosome 7 are being compared to those without these features but otherwise histologically similar tumor phenotype (88–91). Future trials are likely to follow this trend where possible.

Another common patient selection strategy has been the use of immunohistochemical analysis (IHC) of tumor sections, because these specimens are routinely obtained for standard pathological diagnosis. However, few antibodies currently available work well in IHC because recognition is compromised by tissue fixation and paraffin-embedding. Only recently has a mAb targeting the extracellular domain, MET4, shown high sensitivity and low background in IHC (97). Although IHC provides important spatial and morphological information, quantitative comparisons are problematic. As an alternative, immunoassays of tissue extracts can provide precise, absolute measurements of Met content and phosphorylation state, but lack morphological information and typically require frozen tissue samples.

Reliable PD markers have always been important to drug development, and are even more so now that combinations of highly selective targeted drugs are considered. Several ongoing clinical trials of Met-targeted drugs include PD marker studies. Plasma concentrations of soluble Met (sMet), soluble VEGFR2 (sVEGFR2), VEGF, PIGF, and EPO changed significantly during foretinib dosing (89, 90, 98). Plasma HGF, VEGF, sMet, sVEGFR2 were also examined in response to MGCD265 treatment (84, 85); both studies suggest that these may become useful PD markers. In a clinical study of XL184, modulation of plasma VEGFA, sMet, sVEGFR2, sKIT, and PIGF were also consistent with on-target drug effects (99). Studies have also linked PD markers to clinical response, such as plasma HGF levels during XL184 treatment (100), similar to changes in HGF levels reported in a study of RCC patients treated with sorafenib (101) or pazobanib (102).

The emergence of primary and acquired resistance to TKIs from pre-existing or de novo mutations, respectively, must be addressed in the design of future clinical studies. Strategies to overcome this problem include: [1] selecting treatments based on the presence of known susceptibility factors; [2] combining different classes of inhibitors of a single pathway; [3] combining therapeutics against multiple pathways; and [4] combining targeted therapeutics with SOC treatments. An example of the first strategy is the use of MK8033 in patients with *MET* amplification or constitutive Met activation, with the hope of confirming predictive preclinical results (103). Combinations of HGF/Met mAbs and Met TKIs, as in the second strategy, are planned for future trials. The third design is being used in several current trials of Met antagonists: ARQ197, MGCD265, XL184, and PF02341066 are being used in combination with Erlotinib for the treatment of NSCLC and ARQ197 is also being tested in combination with Sorafenib for the treatment of advanced solid tumors (64). Adding Met-targeted therapies to first-line therapies targeting other pathways may be particularly useful for cancers where Met may participate in the acquisition of resistance and thereby

dramatically increase the risk of metastasis. *MET* gene amplification was detected in 22% of lung cancer specimens that had acquired resistance to gefitinib or erlotinib, and treatment of a lung cancer cell line that had acquired gefitinib resistance through *MET* amplification with a Met-targeted TKI restored gefitinib sensitivity (104). Several studies of Met inhibitors in combination with erlotinib for the treatment of NSCLC are now under way with promising results (23). Examples of the fourth strategy are also abundant: trials combining AMG102, ARQ197, MP470, MGCD265, XL184, or PF02341066 with SOC treatments - chemotherapeutic agents or radiotherapy, are also currently underway (64). Again, preclinical studies such as those combining AMG102 with temozolomide or docetaxel for the treatment of gastric, prostate, and colorectal cancers provide a sound rationale and guide initial trial design (59).

In closing, the wealth of basic knowledge about HGF/Met biology has enabled an accurate assessment of the pathway's oncogenic potential and provided the insight needed to develop potent and selective inhibitors and use them with relative safety in humans. Patient selection, of primary importance, will advance as more robust methods are developed to analyze the many known potential diagnostic biomarkers of pathway activity. Methods that rely on DNA or RNA (*e.g.* detecting *MET* gene amplification or mutation) are now faster and more sensitive than those available for quantitating Met protein content and phosphorylation state, but efforts to improve both are underway. Similarly, the need for PD markers that track drug effect and patient response is recognized and clinical PD marker studies currently underway reveal solid candidates. Finally, although the complexity of cancer and the risk of acquired resistance may limit the use of HGF/Met molecular therapeutics as single agents to subgroups of patients, much evidence suggests that pathway involvement is widespread and critical for metastasis. Thus for HGF/Met pathway inhibitors in particular, combinatorial phase II trials with small, carefully selected patient groups may be the most expedient path to more effective cancer treatment.

Acknowledgments

Web site addresses are provided as an informational resource, not as an endorsement of any product or manufacturer. This work was supported by the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research.

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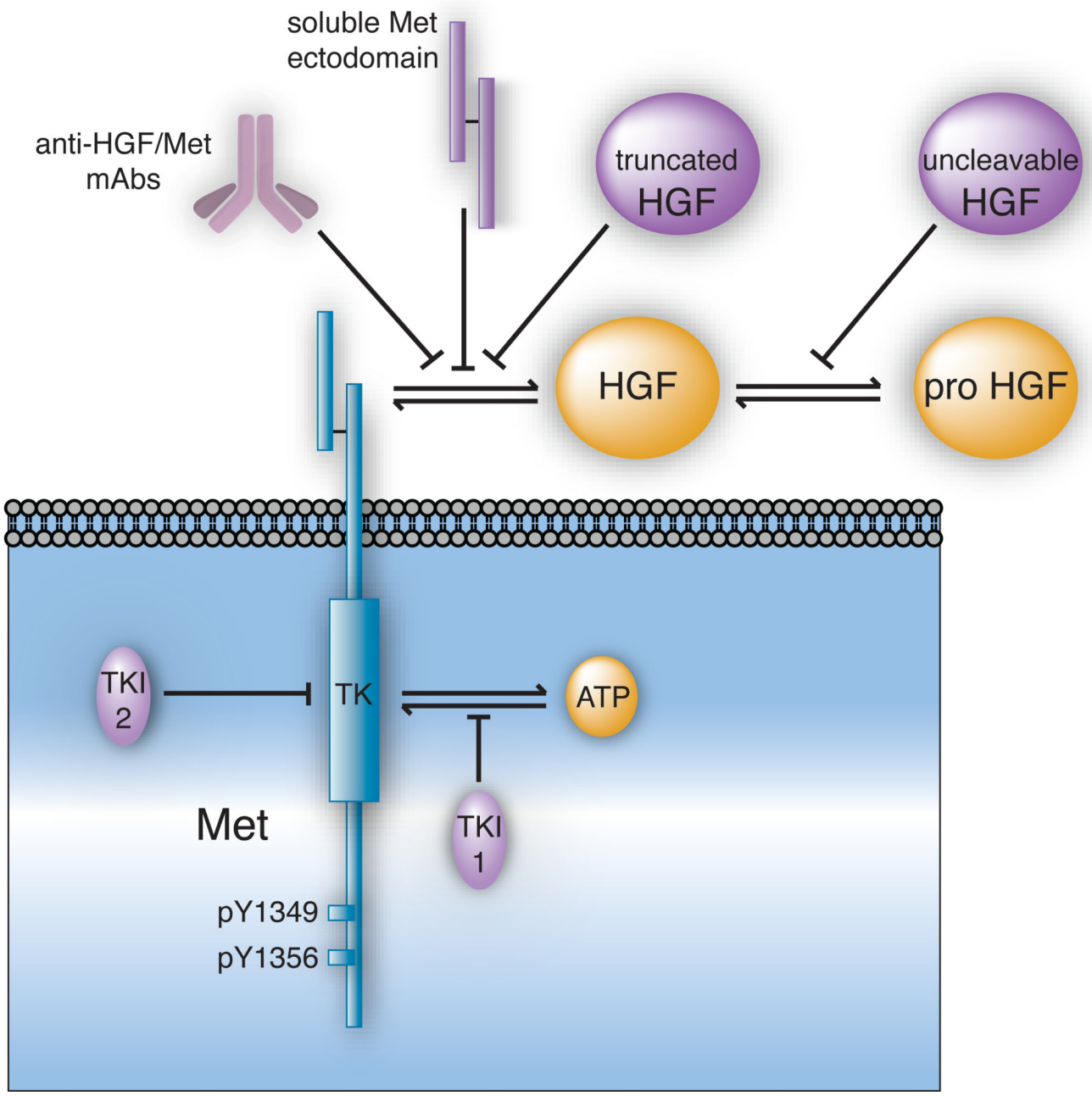

Figure 1. Methods of Blocking the HGF/Met Signaling Pathway

Oncogenic signaling by cellular Met (in blue) and its natural ligands (in yellow) can be antagonized by several distinct inhibitor types (in violet). The intracellular tyrosine kinase (TK) domain and carboxyl terminal docking sites (Y1349 and Y1356) of Met are noted. Pathway inhibitors can be divided broadly into two subtypes (1) biological antagonists of HGF activation and HGF/Met binding, and (2) Met TK inhibitors (TKIs). Biological agents acting outside of the target cell (1) include anti-HGF and anti-Met mAbs, soluble Met ectodomain constructs and truncated HGF isoforms (all of which interfere with HGF/Met binding) and uncleavable forms of HGF (which competitively displace pro-HGF from its activators). Agents acting within the cell (2) include TKIs that competitively displace ATP

from its TK domain binding site (TKI-1) and those which bind outside of the ATP binding pocket and inhibit Met TK activation allosterically (TKI-2).

Table 1

HGF/Met Pathway Inhibitors in Human Clinical Trials (64)

Drug	Design	Phase	Status	Patient Population	Combinations
AMG102	safe dose	Ib/II	Recruiting	wild-type KRAS mCRC	AMG479, platinum chemotherapy
	safety, efficacy	I/II	Recruiting	castrate-resistant prostate cancer	AMG479, mitoxontrone andnprednisone
	dose escalation	I/II	Recruiting	advanced malignant glioma	
	dose escalation	II	Active	advanced malignant glioma	
	dose escalation	II	Active	advanced renal cell carcinoma	
	safety/efficacy	I/II	Recruiting	advanced or metastatic gastric/esophagogastic cancer	Epirubicin, cisplatin and capecitabin
GSK089	safety, efficacy	II	Active	advanced or metastatic gastric cancer, esophageal adenocarcinoma	
	dose escalation	I	Completed	squamous cell cancer of head and neck	
	dose escalation (daily)	I	Completed	solid tumors	
	dose escalation	I	Active	solid tumors	
	bioavailability	I	Recruiting	solid tumors	
	bioavailability	II	Recruiting	papillary renal-cell carcinoma	
	safety study	I	Recruiting	liver cancer	
ARQ197	safety, efficacy	I	Active	advanced solid tumors	
	dose escalation	I	Recruiting	advanced solid tumors	Gemcitabine
	PK, safety	I	Completed	healthy volunteers	
	dose escalation	I	Recruiting	advanced solid tumors	Sorafenib
	Safety efficacy	II	Recruiting	unresectable hepatocellular carcinoma	
	orally administered	I	Active	advanced solid tumors	
	bioequivalence, PK	I	Completed	healthy volunteers	
	open label	I	Completed	metastatic solid tumors	
	safety, PFS	II	Completed	advanced met pancreatic adenocarc.	Gemcitabine (treatment naïve)
	safety study	I	Recruiting	cirrhotic patients with hepatocellular carcinoma	
	double blind	II	Active	NSCLC	Erlotinib with drug or placebo
	open label	I	Recruiting	solid tumors	
	study anti-tumor effect	II	Recruiting	RCC, ASPS, CCS	

Drug	Design	Phase	Status	Patient Population	Combinations
MK2461	safety, efficacy, PK, PD	I/II	Completed	advanced solid tumors	
	safety	I	Completed	advanced cancer	
MP470	safety, open label	I	Recruiting	solid tumors, malignant disease	topotecan, docetaxel, erlotinib, or paclitaxel and carboplatin
	Safety, dose finding	I	Recruiting	adult solid tumors	SOC and multitargeted receptor TKIs
	MTD, PK, PD	I	Recruiting	solid malignancies	
	PD, highest dose		Recruiting	unresolved or metastatic solid tumor or lymphoma	
SGX523	safety, capsules	I	Terminated	solid tumors, advanced cancer	
	safety, capsules	I	Terminated	solid tumors, advanced cancer	
JNJ38877605	safety/dose esc	I	Recruiting	advanced or refractory solid tumors	
MGCD265	safety, efficacy	I/II	Recruiting	advanced malignancies, NSCLC	Erlotinib or docetaxel
	safety (daily dose)	I	Recruiting	advanced malignancies	
	safety, dose escalation	I	Recruiting	advanced malignancies	
XL-184	double blind, safety	II	Recruiting	advanced malignancies, solid tumors	placebo
	safety	I	Recruiting	glioblastoma	temozolomide and radiation
	safety, tolerability	I/II	Recruiting	NSCLC, carcinoma	erlotinib
	efficacy	III	Recruiting	medullary thyroid cancer	placebo
	open label, safety	I	Active	advanced malignancies, lymphoma, thyroid cancer	
	safety, PFS	II	Recruiting	glioblastoma multiforme	
AMG208	safety, PK	I	Recruiting	advanced solid tumors	
PF-04217903	Safety, efficacy	I	Recruiting	advanced cancer, neoplasms	
BMS-777607	Safety, efficacy	I/II	Completed	advanced or metasatic solid tumors	
E7050	open label, safety, efficacy	I	Recruiting	advanced solid tumors	
	does finding, safety, efficacy	I	Recruiting	advanced solid tumors	

Drug	Design	Phase	Status	Patient Population	Combinations
SCH900105	open label, PD	I	Recruiting	neoplasms, met, liver metastases	
	does escalation	I	Recruiting	advanced solid tumors, lymphomas, multiple myeloma	
PF02341066	healthy volunteers, 2 forms	I	Completed	healthy volunteers	
	PG	I/II	Recruiting	young patients with solid tumors	
	orally administered, PK, PD	I	Recruiting	advanced cancer	
	safety, efficacy, PK	II	Not yet Recruiting	NSCLC	erlotinib
	safety, efficacy	III	Recruiting	carcinoma, NSCLC	pemetrexed, docetaxel
	safety, efficacy	II	Recruiting	carcinoma, NSCLC	
MK8033	safety, tolerability, PD	I	Recruiting	advanced solid tumors	omeprazole

Status of clinical trials uses terms as defined at ClinicalTrials.gov.

Abbreviations used: PK, pharmacokinetics; PD, pharmacodynamics; MTD, maximum tolerable dose; PFS, progression free survival; PG, pharmacogenomics; CRC, colorectal cancer; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; ASPS, alveolar soft part sarcoma; CSS, cancer-specific survival

Table 2

Available Results from Human Clinical Trials of HGF/Met Pathway Inhibitors

Drug	Max Tolerable Dose	Half-Life	Adverse Events	IC_{50}	Best Response	References
AMG102	20 mg/kg	15.4 days	Fatigue, constipation, anorexia, nausea, vomiting		60% SD, 48% > 3 months	(65)
SCH900105	20 mg/kg	15 days			50% SD, greatest 34 months	(61–63)
GSK1363089	240 mg	60 hours	Hypertension, nausea, anorexia, fatigue	0.4 – 0.8 nM	33–60% SD > 3 months	(88–91, 105, 106)
MK2461		6.3 hours	Anorexia, fatigue, nausea		9% SD > 6 cycles	(107)
MP470	Not reached, dosed to 500 mg/day		Myelosuppression, diarrhea, constipation, nausea, reflux, fatigue, alopecia, rash, neuropathy, anorexia		12% SD, 23% PR	(108)
SGX523			Kidney toxicity	35 nM		(109,110)
XL-184		80–90 hrs	Palmar/plantar erythema, mucositis at 265 mg/day, diarrhea & hypopigmentation of the hair		40% SD > 3 months	(92,93 ,99 ,111,112)
PF02341066	8 mg QD, 240 mg BID				10% PR	(113,114)