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## Targeting the HGF/MET signalling pathway in cancer therapy

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### Abstract

**Introduction**—Under normal conditions, hepatocyte growth factor (HGF)-induced activation of its cell surface receptor, the Met tyrosine kinase (TK), 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.

**Area covered**—The prevalence of HGF/Met pathway activation in human malignancies has driven rapid growth in cancer drug development programs. The authors review Met structure and function, the basic properties of HGF/Met pathway antagonists now in preclinical and clinical development, as well as the latest clinical trial results.

**Expert opinion**—Clinical trials with HGF/Met pathway antagonists show that as a class these agents are well tolerated. Although widespread efficacy was not seen in several completed phase 2 studies, promising results have been reported in lung, gastric, prostate and papillary renal cancer patients treated with these agents. The main challenges facing the effective use of HGF/Met-targeted antagonists for cancer treatment are 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 and Met

## 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*)<sup>1</sup>. A similar gene rearrangement was later found in patients with gastric carcinoma<sup>1</sup>. Isolation of the full-length *MET* proto-oncogene sequence revealed that it encoded a receptor tyrosine kinase (TK)<sup>1</sup> known as Met (or cellular-Met, c-Met). Hepatocyte growth factor (HGF, also known as scatter factor, SF) was discovered independently of Met<sup>2</sup> and is secreted primarily by mesenchymal cells<sup>1,3</sup>, especially fibroblasts and smooth muscle cells<sup>4,5</sup> and signals through Met in a paracrine manner<sup>6,7,8</sup>.

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#### Declaration of interest

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These and other early studies established that a single receptor transduced multiple biological activities including motility, proliferation, survival and morphogenesis<sup>9–12</sup>.

The HGF and Met proteins are processed proteolytically from single chain precursors into mature disulfide linked heterodimers, both genes are widely expressed during development, and deletion of either gene lethally disrupts embryogenesis<sup>9, 10, 12</sup>. *MET* and *HGF* expression persist throughout adulthood and upregulation of *HGF* after kidney, liver or heart injury suggests that pathway activation protects against tissue damage and promotes repair and regeneration<sup>13–17</sup>.

## 2. Met: Structure and Function

The *MET* gene is located on chromosome 7 band 7q21–q31 and spans more than 120 kb in length, consisting of 21 exons separated by 20 introns<sup>18</sup>. The primary *MET* transcript produces a 150 kDa polypeptide<sup>19</sup> that is partially glycosylated to produce a 170 kDa single chain precursor protein. This 170 kDa precursor is further glycosylated to a mass of approximately 190 kDa and then cleaved into a 50 kDa beta chain and 140 kDa alpha chain which are linked via disulfide bonds<sup>20</sup>.

The Met beta chain has seven conserved subdomains which have functional significance and homology with other cell signaling proteins. The amino-terminal semaphorin (or Sema) domain has a 7-bladed beta-propeller fold<sup>21, 22</sup> that serves as a key element for ligand binding, and is also found in the plexin family of semaphorin receptors<sup>23, 24</sup>. The presence of the semaphorin domain, as well as the more highly conserved tyrosine kinase domain, places Met in a subfamily of tyrosine kinases that includes Ron and the avian Ron ortholog, Sea<sup>19</sup>. Carboxyl-terminal to the Sema domain is the PSI domain, so named because it is found in plexins, semaphorins and integrins<sup>20</sup>. Further downstream are four immunoglobulin domains, also referred to as IPT repeats, because they are found in immunoglobulins, plexins and transcription factors<sup>20</sup>. The PSI domain is thought to function as a linking module to orient the extracellular fragment of Met for proper ligand binding<sup>25</sup>. Although several reports claim that the sema domain is the sole HGF binding domain in Met<sup>21</sup>, one report claims that IPT repeats 3 and 4, located closest to the transmembrane domain, also mediate high affinity HGF binding<sup>26</sup> (Figure 1A).

Like all receptor tyrosine kinases, the Met transmembrane domain is thought to consist of a single alpha helix<sup>6</sup>. The most amino terminal cytoplasmic subdomain, the juxtamembrane (JM) region, contains two protein phosphorylation sites: S985 and Y1003 (numbered per Swissprot P08581). Phosphorylation of S985 negatively regulates kinase activity and phosphorylation of Y1003 recruits c-Cbl, which monoubiquitinates Met and interacts with endophilin, targeting Met for internalization and degradation. A PEST sequence, which may serve as a site for this ubiquitination, is present in the JM domain<sup>27</sup>. A specific protein tyrosine phosphatase (PTP-S) is also reported to bind to this region<sup>28</sup>.

Carboxyl terminal to the JM region is the tyrosine kinase (TK) domain, which shares homology with insulin growth factor I receptors and the Tyro 3 family of immunoregulatory molecules, and lastly, a carboxy-terminal tail region. Upon HGF binding, Met autophosphorylation occurs on tyrosine residues Y1234 and Y1235 within the activation loop of the TK domain, inducing kinase activity, while phosphorylation on Y1349 and Y1356 in the carboxyl terminal region (all numbered per Swissprot P08581) forms a multifunctional docking site for intracellular adaptors that recruit a collection of intracellular signal effectors containing Src homology-2 (SH2) domains and other specific receptor recognition motifs that act as adapters in transmitting signals further downstream<sup>29</sup>. An intact multifunctional docking site is required to mediate transformation and induce a metastatic phenotype<sup>30</sup>.

Among the adaptor proteins and direct kinase substrates thus far implicated in Met signaling are Grb2, Gab1, phosphatidylinositol 3-kinase (PI3K), phospholipase C- $\gamma$  (PLC $\gamma$ ), Shc, Src, Shp2, Ship1, and STAT3<sup>9, 11</sup>. Gab 1 and Grb2 are considered critical effectors and are among those that interact directly with the receptor; through these, a larger network of adaptor proteins are involved in signaling, presumably contributing to the pleiotropic biological effects elicited by HGF stimulation. In particular, the direct binding of Grb2 directly to the Met docking site through Y1356 links the receptor to the Ras/MAPK pathway regulating cell cycle progression<sup>11</sup>. Gab1 is recruited to Met through direct binding and indirectly via Grb2; these interactions initiate branching morphogenesis in several epithelial and vascular endothelial cell types<sup>31</sup>. Gab1 is also highly phosphorylated by the Met kinase, resulting in the additional recruitment of PI3K (which is also recruited to Met directly through its p85 subunit), contributing in turn to cell cycle progression, protection from apoptosis, as well as increased cell motility<sup>10</sup>.

### 3. MET Mutations Associated with Cancer

Under normal conditions, HGF-induced Met 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 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<sup>32</sup>. Indeed, *MET* overexpression is characteristic of several epithelial cell derived cancers and for some is an independent prognostic factor associated with adverse outcome<sup>33</sup>. 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<sup>12, 34, 35</sup>. 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)<sup>36, 37</sup>. Mutations throughout the *MET* coding sequence were later found in lung cancer and in head and neck cancers<sup>6, 38</sup>.

The impact of specific *MET* mutations has been studied at the molecular, cellular and organism levels. Early cell-based investigations indicated 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<sup>39, 40</sup>. 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<sup>41</sup>. PRC-associated *MET* mutations also have been investigated in mice by engineering changes in the murine *MET* locus<sup>42</sup>. 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<sup>42</sup>. 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. Very recently, investigations of two PRC associated Met mutants revealed defect in Met internalization that results in persistent signaling, similar to alterations found in the Met juxtamembrane domain<sup>43</sup>. 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 <sup>42</sup>.

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 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 <sup>38, 44–46</sup>. Some of these mutations activate proliferation, motility and invasiveness in cultured cells<sup>38</sup>. As noted earlier, Y1003 is phosphorylated in response to HGF binding and recruits c-Cbl, leading to Met ubiquitination and degradation <sup>1</sup>. 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 <sup>1</sup>.

The capacity for JM mutations R988C and T1010I to contribute to oncogenesis has been a topic of debate. First identified by Schmidt and colleagues <sup>47</sup>, T1010I was thought to represent a rare polymorphism, owing to lack of disease segregation and failure to induce focus formation or constitutive Met phosphorylation in NIH3T3 cells. Although this potential polymorphism did not stimulate NIH3T3 cell growth in soft agar, it was more active than the wild-type Met in the athymic nude mice tumorigenesis assay, suggesting that it may have effects on tumorigenesis <sup>48</sup> and lead to altered cytoskeletal functions <sup>45</sup>. Recently Tyner and colleagues found these variants in a wide variety of malignancies as well as individuals without cancer, suggesting that R988C and T1010I are indeed rare polymorphisms that may predispose an individual toward cancer when combined with an oncogene that drives cellular proliferation <sup>49</sup>.

Of interest, another novel germ-line missense mutation P1001S (numbered per Swissprot P08581) in exon 14 that encodes the JM domain of Met has been detected in a patient with gastric carcinoma. P1009S caused colony formation in soft agar, was tumorigenic in athymic nude mice, but appears to be oncogenic by a different mechanism: while Met mutations in the tyrosine kinase domain are constitutively activated, the P1009S Met mutant, after HGF/SF treatment, stays phosphorylated for a significantly longer time (24–48 h) than wild-type Met, but it is not constitutively activated. This suggests that the downregulation of Met, which occurs after receptor activation and tyrosine phosphorylation, may be impaired by this mutation <sup>48</sup>. 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 <sup>50</sup>. 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 <sup>51</sup>.

## 4. Pharmacological Inhibitors of 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. Biologicals, or protein-based agents, act through a variety of mechanisms and possess target selectivity and pharmacokinetic 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 (Figure 1B and Table 1).

### 4.1. 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] Competitive molecular analogs of HGF; [2] Decoy Met; and [3] mAbs directed against either HGF or Met.

**4.1.1. Competitive Molecular Analogs of HGF**—Among the competitive HGF analogs NK2, NK4 and uncleavable HGF, anti-tumor efficacy has been demonstrated in preclinical models for the latter two. NK2 is a naturally occurring truncated HGF protein produced by alternative mRNA processing. The potential anti-oncogenic efficacy of NK2 is compromised by its intrinsic motogenic activity, which enhanced HGF-driven metastasis in mouse models<sup>52–56</sup>. NK4 is an engineered HGF fragment that has proven to be a complete competitive antagonist of HGF/Met oncogenic signaling in a variety of preclinical models. Adenovirus-mediated stable induction of NK4 has been shown to significantly inhibit *in vivo* tumor growth and lung metastasis of Lewis lung carcinoma (LLC) and B16F10 melanoma<sup>57</sup> as well as tumor growth in a xenograft model of malignant pleural mesothelioma, without obvious side effects<sup>58</sup>. NK4 gene therapy is thus a safe and promising strategy for the treatment of cancer patients, and further validation in clinical trials is needed. Engineered 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<sup>59–62</sup>.

**4.1.2. Met Decoy Receptor**—Truncated soluble forms of the Met ectodomain, e.g. soluble Met Sema domain constructs that sequester HGF and interfere with Met homodimerization, have been shown to suppress HGF-induced tumor cell migration<sup>63</sup>, as well as tumor growth and metastasis in mice<sup>64</sup>.

**4.1.3. Anti-HGF/Met Monoclonal Antibodies**—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 for one anti-Met mAb, preclinical studies show decreased Met activation by induction of ectodomain shedding and receptor degradation<sup>65</sup>. Neutralizing mAbs against human HGF, such as TAK701, L2G7, AMG102 (rilotumumab) and SCH900105 (also known as AV299) each potently suppressed the growth of tumor xenografts in mice<sup>66–71</sup>.

TAK-701, currently in phase I clinical trials in adult patients with advanced nonhematological malignancies, is a humanized anti-HGF neutralizing antibody. *In vitro*, TAK-701 binds preferably to the mature two-chain form of HGF ( $K_d$  of 13 pM), blocking HGF-Met binding ( $IC_{50}$  of 310 pM). In addition, TAK-701 inhibited the intra cellular phosphorylation of Met ( $IC_{50}$  of 0.45  $\mu$ g/mL)<sup>72</sup> and shows antitumoral activities against



various cancer cells with an autocrine dependence on HGF *in vivo*<sup>73</sup>. The first clinical results for TAK-701 from the phase I dose escalation study, showed that TAK-701 was well tolerated up to 20 mg/kg bi-weekly<sup>74</sup>. The most common adverse events (AEs) were fatigue, constipation and cough; the most serious treatment-related AEs included ileus, muscular weakness, asthenia, urinary tract infection and dehydration. Pharmacodynamic (PD) analysis showed that in five of seven patients free HGF was not detected while being treated with TAK-701<sup>75</sup> and preliminary analysis of all dose groups indicate dose proportional pharmacokinetics (PK).

Rilotumumab (AMG 102) is a fully human monoclonal antibody that binds to the HGF light chain ( $K_d$  of 0.22 nM), also preferably in the context of mature two chain HGF, and blocks HGF-Met binding ( $IC_{50}$  of 2.1 nM). Rilotumumab is under evaluation as monotherapy in phase Ib-II trials respectively in the context of ovarian and renal cancer, as well as in combination with, avastin in glioma, erlotinib in NSCLC, and platinum based chemotherapy in SCLC, mesothelioma, gastric cancer as well as mitoxantrone in prostate cancer. A recent phase Ib trial evaluated AMG102 safety, PK, PD and antitumor activity in combination with bevacizumab at a dose of 3, 10 or 20 mg/kg every two weeks (12 patients) or motesanib (in 2 patients, cohort suspended) in advanced solid tumors. Treatment related AEs among patients receiving rilotumumab plus bevacizumab were generally mild and included fatigue (75%), nausea (58%), constipation (42%), and peripheral edema (42%). PFS ranged from 8 to 122 weeks<sup>76</sup>. Rilotumumab monotherapy was not associated with significant antitumor activity in patients with recurrent glioblastoma (GBM) who had previously received bevacizumab compared with bevacizumab-naïve patients. Rilotumumab PFS was similar among patients (about 4 weeks) at two different dosages of 10 or 20 mg/kg every two weeks or among patients who had previously received bevacizumab compared with bevacizumab-naïve patients. The most common AEs consisted of fatigue (38%), headache (33%), and peripheral edema (23%)<sup>77</sup>. A phase II study of the safety and efficacy of rilotumumab in combination with Epirubicin, Cisplatin and Capecitabine (ECX) as a first line treatment for unresectable locally advanced or metastatic gastric esophagogastric junction adenocarcinoma in a group of 121 patients. Addition of rilotumumab at a dose of 7.5 mg/kg to ECX appeared to improve PFS, the primary endpoint, especially in patients with high Met expression. Although OS was not a primary endpoint, patients with high Met expression in the rilotumumab treatment arms (n = 27) had a median OS of 11.1 months (hazard ratio = 0.29) vs 5.7 months for patients in the ECX + placebo treatment group (n = 11). The rilotumumab + ECX combination arms showed a modestly higher incidence of AEs including peripheral edema, hematologic toxicities and thromboembolic events<sup>78</sup>. A phase II, randomized, double-blinded, placebo-controlled trial compared rilotumumab or ganitumab (AMG 479) with panitumumab (pmab) versus pmab alone in patients with wild-type (WT) *K-RAS* metastatic colorectal cancer (mCRC). While ganitumab failed to generate any signal in this randomized trial, the arm with rilotumumab did show an increased response rate. Seventy nine percent of patients reported AEs as rash, dermatitis, and hypomagnesemia and a PFS of 5.2 months. Results of biomarker analyses, including Met staining, are ongoing<sup>79</sup>. This finding will hopefully lead to further trials investigating the use of HGF/Met inhibitors in colorectal cancer. This is the first study to show promising efficacy of an HGF inhibitor when combined with pmab in pretreated metastatic colorectal cancer patients.

SCH900105 is a humanized anti-HGF IgG1 monoclonal antibody that is now in phase I and II clinical trials. In its first completed trial, SCH900105 treatment was associated with stable disease (SD) in half of the patients, the longest for 34 weeks<sup>68, 69, 71</sup>. Safety and tolerability studies of SCH900105 in combination with erlotinib or gefitinib are ongoing. SCH900105 dosing (20 mg/kg) increased serum HGF and HGF-drug complex, suggesting target engagement, as seen in rilotumumab trials. Early results suggest clinical activity with the combination of SCH900105 and gefitinib in Asian patients with unresectable NSCLC<sup>80</sup>.

h224G11 is a humanized, bivalent anti-Met monoclonal antibody that inhibits Met phosphorylation and dimerization and blocks proliferation, migration, invasion, morphogenesis and angiogenesis in cell-based studies<sup>69, 81, 82</sup>.

Onartuzumab (MetMab, formerly OA5D5), is an engineered anti-Met monovalent antibody that blocks ligand binding ( $IC_{50}$  of 2.6 to 8.7 nM in intact cells) and inhibits tumor growth in animal models by more than 95%<sup>83</sup>. A phase II study evaluating onartuzumab or placebo in combination with erlotinib in advanced NSCLC showed improved outcome in Met positive, previously treated, advanced stage NSCLC. The study showed that patients whose tumors had high levels of Met, as determined by immunohistochemistry (IHC) staining for Met protein, lived twice as long without their disease getting worse when they received onartuzumab plus erlotinib compared to erlotinib alone. The addition of onartuzumab plus erlotinib in these patients significantly improved PFS and OS, resulting in a near 3-fold reduction in the risk of death<sup>84</sup>. A phase III trial restricted to Met positive patients will be activated soon<sup>85</sup>. Onartuzumab is also now under clinical evaluation in randomized double-blinded phase II trials in combination with paclitaxel and bevacizumab in triple negative breast cancer or in combination with Folinic acid Oxaliplatin and Fluorouracil (FOLFOX) and bevacizumab in colorectal carcinoma<sup>86</sup>.

In addition to its development as a therapeutic, preclinical studies indicate that onartuzumab tagged radioisotopically displays several promising features as an immuno-PET reagent to non-invasively image Met in vivo for diagnostic and prognostic endpoints. Imaging and biodistribution studies showed rapid uptake and delayed clearance of the tracer specifically in tumor xenografts. Radiolabeled onartuzumab biodistribution also appeared to be independent of soluble human Met in the plasma of animals bearing human tumor xenografts, suggesting that the normal level of plasma Met in humans may not interfere with tumor-imaging sensitivity<sup>87</sup>. DN30, a murine anti-Met monoclonal antibody that inhibits tumor growth in animal models, also showed promise as an immuno-PET reagent in preclinical studies; a humanized version of DN30 is under development for clinical evaluation<sup>88</sup>.

#### 4.2. Small Synthetic Met Kinase Inhibitors

Most Met TKIs competitively antagonize occupancy of the intracellular ATP binding site, preventing phosphorylation, TK activation and downstream signaling. These inhibitors are known as type I or type II inhibitors depending on whether they bind to the kinase active conformation or an inactive conformation. The majority of inhibitors, Type I, target the ATP binding site in its active conformation, after tyrosyl residues in the activation loop have been phosphorylated. Type II inhibitors include those that use an additional binding site immediately adjacent to the region occupied by ATP, which is made accessible by an activation loop arrangement that is characteristic of inactive kinases<sup>89</sup>. These agents 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)<sup>45, 90</sup> and PHA665752 ( $IC_{50}$  of 9 nM)<sup>34</sup>, established that this class of compounds could potentially suppress oncogenesis and provided a platform for improving potency, selectivity and other drug properties. Recently SU11274 was also successfully used as preclinical molecular imaging probe; tumor uptake of [11C] SU11274 correlated with Met content as measured by IHC in xenograft tumor models, suggesting that [11C] SU11274 PET may have utility for non-invasive quantification of Met expression in vivo<sup>91, 92</sup>

RP1040 ( $IC_{50}$  of 1.3 nM)<sup>93</sup> and CEP-A ( $IC_{50}$  of 13 nM)<sup>69</sup> are recent preclinical candidates; RP1040 shows good oral availability and displays a half-life of up to 9 h in intact cells<sup>93</sup>.

CEP-A shows sustainable PD effects in mouse studies, resulting in significant tumor growth inhibition, SD and partial regression<sup>69</sup>.

S 49076 is a novel, ATP-competitive tyrosine kinase inhibitor of Met, FGFR1/2/3 and AXL. S 49076 blocks autophosphorylation of these RTKs and their downstream signaling in cells with IC<sub>50</sub> values of between 1 and 200 nM depending on the target and cell line. In vivo, oral administration of S 49076 inhibits > 80% tumor growth at 6 mg/kg/day in GTL-16 subcutaneous human gastric carcinoma tumors and in the Met-dependent U87-MG human glioblastoma xenograph model. S 49076 also inhibits FGFR2 autophosphorylation, downstream signaling and tumor growth in FGFR2-dependent SNU-16 gastric tumors, and tumor growth in LS-174T colon carcinoma. Based on these preclinical studies, a phase I study is planned soon to evaluate an oral formulation of S 49076 in patients with advanced solid tumors<sup>94, 95</sup>.

Met TKIs now entering phase I clinical trials to establish safety and tolerability include, AMG 337, AMG 208, INCB28060, LY2801653, EMD1214063 and EMD1204831.

AMG 337 is a selective inhibitor of Met, which inhibits multiple mechanisms of Met activation while AMG 208 selectively inhibits both ligand-dependent and ligand-independent Met activation. Phase I results for INCB28060 show that toxicity was manageable and a favorable PK profile supports exploration of a twice-daily dosing schedule. Dose-dependent decreases in Met phosphorylation, monitored by ELISA, are also promising. AEs included mild tremor, fatigue, nausea, diarrhea, indigestion, headache, and agitation<sup>96</sup>.

LY2801653 demonstrated dose dependent inhibition of Met phosphorylation in xenograft tumors by IHC, with a long lasting PD effect. LY2801653 displayed potent anti-tumor efficacy in NSCLC, pancreatic, and breast tumor models. Enhanced anti-tumor efficacy was achieved when erlotinib was combined with LY2801653 in NSCLC resistant to EGFR inhibitors<sup>97</sup>.

EMD1214063 (IC<sub>50</sub> of 1 to 6nM) and EMD1204831 (IC<sub>50</sub> of 15nM) are highly selective Met inhibitors when tested in vitro against a large panel of different kinases. In vivo, oral administration of EMD1214063 and EMD1204831 result in a potent inhibition of HGF dependent and independent Met driven tumor xenografts. PK/PD analysis reveal efficient, dose and time dependent inhibition of Met phosphorylation and reduction of tumor derived IL-8<sup>98, 99</sup>. Dose-escalation studies designed to explore the safety, tolerability, PK and clinical activity of EMD1214063 and EMD1204831 are now recruiting patients with advanced solid tumors.

JNJ-38877605, a highly Met-selective TKI as determined by comprehensive kinase profiling in vitro, entered phase I in 2008 but the study was terminated early due to increase in serum creatinine levels suggestive of renal toxicity and minimal PD activity. Phase I clinical trials for SGX523, another highly selective Met TKI with structural similarity to JNJ-38877605, were also discontinued after renal toxicity was observed in patients receiving relatively low doses<sup>100</sup>.

PF-042793 is a highly selective Met inhibitor with high potency against wild type Met (K<sub>i</sub> = 6–7 nM), but was found to be less effective against clinically relevant *MET* mutations evaluated in cultured cells. Results are awaited for a phase I study testing safety, dose and blood concentration of PF-042793.

A phase I study of MK8033 (IC<sub>50</sub> of 1.3 nM), which targets Met and the Met family member Ron, is completed but results are not yet available. Future plans include a trial of



this agent in refractory colorectal cancer, with pre- and post-treatment biopsies to evaluate for relevant molecular signatures <sup>101</sup>.

Several Met TKIs are in phase I/II clinical trials that further test safety and efficacy. Golvatinib (E7050) targets both Met (IC<sub>50</sub> of 6–37nM) and VEGFR2 <sup>102</sup>. A phase I clinical study will determine the maximum tolerated dose (MTD) of golvatinib given orally in patients with advanced solid tumors. Three phase Ib/II studies will determine the benefit observed in subjects receiving golvatinib in combination with either sorafenib (hepatocellular carcinoma, HCC), E7080 (recurrent glioblastoma or unresectable stage III/IV melanoma) or cetuximab (platinum-resistant squamous cell carcinoma of the head and neck). Phase Ib/II studies will be conducted in two parts: a phase Ib part comprising a dose escalation and an expansion cohort; and a phase II part, which will comprise two cohorts. Approximately 95 patients will be enrolled in each study (10–15 patients in the phase Ib portion and 80 patients in the phase II portion). Patients who experience evidence of clinical benefit may continue golvatinib in combination with the other drug for as long as clinical benefit is sustained and the treatment is well tolerated.

Amuvatinib (MP470) an oral multi-targeted tyrosine kinase inhibitor which inhibits the mutant forms of c-Kit, PDGFR alpha and Met, sensitized glioblastoma cells to radiotherapy in mice <sup>103</sup>. When combined with erlotinib, amuvatinib inhibits prostate cancer cell proliferation and tumor xenograft growth. Amuvatinib also disrupts DNA repair, likely through suppression of the homologous recombination protein Rad51 <sup>104</sup>. Tumor responses in SCLC were observed in a phase Ib clinical study in combination with VP-16 and carboplatin. PK data suggests that co-administration of amuvatinib did not alter exposures of standard of care (SOC) agents VP-16 or carboplatin as measured by overall exposure <sup>105</sup>. A phase II clinical trial is recruiting SCLC subjects who have not responded to standard treatment or relapsed after standard treatment. The outcome will measure overall objective response rate (CR or PR), PFS and OS, duration of response, safety and tolerability and metabolites PK and other biomarkers <sup>106</sup>.

A phase I/II study of BMS777607 (IC<sub>50</sub> of 3.9 nM) in metastatic cancer patients has been completed but results are not yet available <sup>107</sup>. BMS-777607 inhibited both ligand stimulated and constitutive Met phosphorylation in preclinical studies with an IC<sub>50</sub> of 20 nmol/L and impaired xenograft growth <sup>107</sup>. A recent study also found BMS-777607 to be capable of inhibiting Met signaling and suppressing HGF-stimulated prostate cancer cell scattering, migration, invasion, and proliferation <sup>108</sup>.

MGCD265, targeting Met, VEGFR1-3, Ron and Tie2, is currently in phase I/II studies in combination with erlotinib or SOC treatments; safety trials have shown a half-life of 20–30 hours with no grade 2 or higher AEs <sup>109</sup>. In vivo anti-tumor activity of MGCD265 has been reported in combination with either docetaxel, paclitaxel, or erlotinib in multiple xenograft models including NSCLC models that express an *EGFR* mutant resistant to erlotinib (T790M). The combination of MGCD265 with either a taxane or erlotinib resulted in improved antitumor activities when compared to treatments with either agent alone. In addition, these combinations were well tolerated in xenograft models and do not show drug-drug interactions, supporting the clinical development of MGCD265 in combination with docetaxel or erlotinib in patients with NSCLC <sup>110</sup>.

MK-2461 is a Type 1 inhibitor with similar potency (2.5 – 10 nM) for Met, Flt1 and Ron <sup>111</sup>. Nine other kinases, including FGFR1, FGFR2, FGFR3, PDGFR $\beta$ , KDR, Flt3, Flt4, TrkA, and TrkB, were found to be 8- to 30-fold less sensitive to MK-2461 than Met <sup>111</sup>. MK-2461 has completed phase I/II trials and showed a half-life of approximately 6 hours,

few AEs above grade 1 (anorexia, fatigue and nausea), and a best response of SD for six treatment cycles <sup>112</sup>.

Foretinib (GSK1363089; formerly XL880) has shown promising results in phase II trials. Foretinib targets Met VEGFR2, Ron and Tie-2. Phase I trials showed a half-life of 60 hours and generally good drug tolerance with the most common AEs of grade 1 or 2 (fatigue, hypertension, nausea, anorexia and vomiting) <sup>113</sup>. Foretinib did not show efficacy in a phase II study for advanced or metastatic gastric cancer <sup>114</sup>. In a phase II trial of foretinib in PRC, several patients showed SD for at least 10 months; several patients with germline *MET* mutations experienced PRs by RECIST criteria while others showed 10–30% percent reduction in tumor size <sup>115, 116</sup>. Recent preclinical results indicate that foretinib and human EGFR (HER) targeted agents synergistically suppressed the growth of tumor cells with Met and HER1/2 amplification or overexpression <sup>117</sup>. A phase I/II study of foretinib in combination with lapatinib in patients with HER 2 over-expressing metastatic breast cancer is now recruiting patients.

Tivantinib (ARQ197) may represent a distinct type of low molecular weight TKI (neither Type I or II; tentatively identified as Type III), as it apparently binds to a region of Met outside of the ATP binding site and impairs kinase activation allosterically. Based on kinase profiling studies *in vitro*, it is reported to be highly selective for Met (IC<sub>50</sub> of 50 nM *in vitro*), but it binds only to the inactive form <sup>118</sup>. It is further noted that *in vivo* a relatively high dose of tivantinib inhibited tumor growth in the MDA-MB-231 human breast cancer cell-derived mouse tumor model <sup>119</sup>, whereas another potent Met inhibitor showed little antitumor activity in this model <sup>120</sup>. Although MDA-MB-231 cells express Met <sup>121</sup>, it is unclear if the growth of the implanted cells in mice is primarily driven by Met activity. Therefore, it is possible that antitumor activity observed using relatively high doses of tivantinib might be due to unidentified off-target effects and attributing tivantinib clinical activity solely to Met inhibition should be done cautiously. Phase I/II clinical trials demonstrated promise in terms of both tolerability and tumor response. A phase II study of tivantinib enrolled 167 patients with advanced NSCLC of any histology who were previously treated with a single line of chemotherapy; patients were randomized to receive either erlotinib alone or as erlotinib combined with tivantinib. The trial did require availability of tumor tissue for analysis of *EGFR*, *K-RAS*, and *MET* mutations status. PFS improvement was particularly prominent among patients with nonsquamous histology, *EGFR* wild-type status, and *K-RAS* mutations treated with tivantinib plus erlotinib; no significant differences in side effects were observed (rash, diarrhea, and some fatigue) between the groups <sup>122</sup>. In January 2011, the first patient was enrolled in the phase III trial of tivantinib in combination with erlotinib for patients diagnosed NSCLC who have received one or two prior systemic anti-cancer therapies. The phase III trial is a randomized, double-blinded, controlled study of previously treated patients with locally advanced or metastatic, non-squamous NSCLC who will receive tivantinib plus erlotinib or placebo plus erlotinib. The primary objective is to evaluate OS in the intent-to-treat population (ITT). Secondary endpoints include OS in the subpopulation of *EGFR* wild type patients, PFS in the ITT population, and further assessment of the safety of tivantinib in combination with erlotinib <sup>123</sup>.

Met TKIs furthest in development include Cabozantinib (XL184) and Crizotinib (PF-02341066), both now in phase III clinical trials. Cabozantinib (XL184) is a multikinase inhibitor that potently targets Met, VEGFR2, and Ret and has a half-life of 80–90 hours <sup>124</sup>. On average, patients show SD greater than 3 months with several up to 6 months while on treatment <sup>125</sup>. In January 2011, cabozantinib was granted orphan drug status by the U.S. FDA for treatment of follicular, medullary, and anaplastic thyroid carcinoma, and metastatic or locally advanced papillary thyroid cancer. Cabozantinib is being evaluated in phase II in

solid tumors including metastatic castration-resistant prostate cancer (mCRPC), ovarian cancer<sup>126</sup>, melanoma<sup>127</sup>, breast cancer, NSCLC<sup>128</sup> and hepatocellular cancer<sup>129</sup>, and in a phase I trial in renal cell carcinoma and differentiated thyroid cancer. Remarkable interim data from the phase II study on mCRPC were presented in an oral abstract session in 2011 ASCO Annual Meeting<sup>130, 131</sup>. Cabozantinib, at a dose of 40 mg daily, reduced measurable soft-tissue lesions, showed resolution (complete or partial) or stabilization of bone metastases, decreased bone pain, and reduced narcotic use<sup>132–134</sup>. Because of the relatively broad target spectrum of this TKI, it is unclear whether these results are attributable to Met inhibition.

Crizotinib (PF-02341066), is a dual Met and Anaplastic Lymphoma Kinase (ALK) inhibitor. In August 2011, the U.S. FDA approved crizotinib for lung cancer patients with *ALK* gene rearrangements<sup>135</sup>. Currently, clinical development of crizotinib is focused primarily on *ALK* rearrangements in NSCLC. However a recent report describes rapid and durable clinical response to crizotinib in a NSCLC patient with *de novo MET* amplification and no *ALK* rearrangement, suggesting that *de novo MET* amplification may be a primary oncogenic driver in some NSCLC and thus a valid clinical target<sup>136</sup>.

## 5. Conclusion

Preclinical evidence supports the involvement of dysregulated Met signaling in a variety of human cancers. As anti-cancer therapeutics, HGF/Met 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. The clinical assessment of these agents is complicated by several factors, ranging from specific biological and pharmacological properties of the investigational agent to the molecular and genetic characteristics of the patients studied in clinical trials. However, substantial progress has been made, and additional trials with adequate control arms in carefully selected patient populations are required to further confirm clinical benefits and assess the potential long-term benefit and the safety of agents that have shown early promising results.

## 6. Expert Opinion

Clinical trials with HGF/Met pathway antagonists show that as a class these agents are well tolerated. Although widespread efficacy was not seen in several completed phase 2 studies, promising results have been reported in lung, gastric, prostate and PRC patients treated with these agents. An important challenge facing the effective development of targeted agents such as Met pathway inhibitors is identifying those patients most likely to achieve maximal benefit and minimal toxicity from treatment. Success will be dependent on the accurate and timely assessment of the molecular and genetic background in the patients, which include various molecular changes (e.g., *MET* overexpression, amplification and mutation, and HGF elevation) leading to Met pathway activation and genetic alterations resulting in the activation of other cancer-promoting pathways. Preclinical studies of several Met-targeted agents have included investigating their effectiveness against known *MET* mutants. For example, selective inhibitors such as PF-2341066/4217903 are active against some *MET* mutations surrounding the ATP binding site but less active against mutations in the activation loop of the Met kinase domain<sup>89</sup>. It is important that clinical trials are designed with this information in mind. An interim report of phase II clinical findings showed that foretinib is active against PRC patients with germline *MET* mutations compared to those without but with otherwise histologically similar tumor phenotype<sup>116</sup>. These results underscore the importance of assessing *MET* sequence status in patient selection and/or stratification; since it is not yet clear whether the presence of other *MET* gene abnormalities,

such as amplification or chromosome 7 polysomy, indicate sensitivity to Met targeted agents, patients with these features should also be identified.

The use of IHC to assess Met protein abundance in tumor sections also offers promise as an effective patient selection strategy. These specimens are routinely obtained for standard pathological diagnosis and provide important spatial and morphological information. Early findings indicated that great care must be taken in qualifying antibodies for target affinity and selectivity. Phase II clinical trials of the highly selective Met antagonists onartuzumab and rilotumumab, for the treatment of NSCLC and gastroesophageal cancer, respectively, afforded retrospective assessments of outcome stratified on the basis of tumor Met content as determined by IHC where efficacy appeared to correlate with high Met abundance. Accordingly, a phase III clinical trial of onartuzumab restricted to NSCLC patients with a Met diagnostic-positive status will be activated soon. All patients have to provide tissue specimens or other material to be analyzed for Met expression as a requirement for entry. Patients will be stratified by tumor Met abundance as Met-high or Met-low using a commercially available IHC kit according to a pre-defined scoring system.

As for other tyrosine kinases thought to be valid cancer drug targets, the use of antibodies against sites of Met tyrosyl phosphorylation implicated in kinase activation and effector binding have the potential to be powerful tools for patient selection. However, results of their use in IHC have been mixed. Challenges to developing robust diagnostic assays of this class include [1] the inherent instability of protein phosphorylation during sample procurement and processing, [2] the limited antigenic features that distinguish a phosphorylated site from its unmodified counterpart, [3] the inherent similarity of tyrosyl phosphorylation sites among different receptor TKs that are co-expressed in many cancers, and [4] the general decline of IHC staining quality with storage for fixed/paraffin embedded as well as frozen tissue. An important alternative to IHC are two-site immunoassays of tissue extracts that can provide precise, absolute measurements of Met content and phosphorylation state. These assays lack the morphological information provided by IHC and usually require flash frozen tissue samples procured and processed according to protocols optimized for this purpose. Assays of this type for Met are in development and should complement IHC assessment of Met content with absolute measurements of content and activation state in the near future <sup>137</sup>.

PD studies have the potential to dramatically impact the drug development process, even more so now that combinations of highly selective targeted drugs are considered. When used in conjunction with patient selection, proven PD markers can provide a rational basis for clinical study design and interpretation. Several ongoing clinical trials of Met-targeted drugs include ancillary PD marker studies. Some completed studies have linked PD markers to clinical response, such as plasma HGF levels during XL184 treatment <sup>138</sup>, similar to changes in HGF levels reported in a study of RCC patients treated with sorafenib <sup>139</sup> or pazopanib <sup>140</sup>. Abnormally high plasma HGF concentrations have been associated with advanced disease and poor outcome for several cancers, notably breast and gastric cancer; in a more recent study of RCC patients, serum HGF values correlated directly with clinical stage and tumor grade, and inversely with patient survival <sup>141</sup>. Thus circulating HGF levels may be relevant to prognosis in several cancers, suggesting that monitoring plasma HGF levels during treatment may help predict response.

Plasma concentrations of soluble Met (sMet), soluble VEGFR2 (sVEGFR2), VEGF, PIGF, and EPO changed significantly during foretinib dosing <sup>115, 116, 142</sup>. Plasma HGF, VEGF, sMet, sVEGFR2 were also examined in response to MGCD265 treatment <sup>109, 143</sup>; 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<sup>144</sup>. A phase Ib, open-label, dose escalation study to evaluate PD markers of crizotanib in combination with VEGF inhibitors in patients with advanced solid tumors will start recruiting patients soon. Detailed analyses of these PD results may help refine the rationale for targeting several kinases implicated in various human cancers.

The emergence of primary and acquired resistance to TKIs from pre-existing or de novo mutations, respectively, should 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 targeted therapeutics with SOC treatments; and [4] combining therapeutics against multiple pathways. An example of the first strategy is the use of MetMab in NSCLC patients with a Met diagnostic-positive status, with the hope of confirming previous clinical results. Combinations of HGF/Met mAbs and Met TKIs, as in the second strategy, are planned for future trials. A combination of agents with distinct activity profiles might also prevent the development of resistant mutations within the Met pathway and thereby improve clinical benefit. The third design is being used in several current trials of Met antagonists: trials combining AMG102, MetMab, ARQ197, MK8033, MP470, MGCD265, XL184, or PF02341066 with SOC treatments -chemotherapeutic agents or radiotherapy, are also currently underway. Again, preclinical studies such as those combining AMG102 with temozolomide or docetaxel for the treatment of gastric, prostate, and colorectal cancers provided a sound rationale and guided initial trial design<sup>67</sup>.

Examples of the fourth strategy are also abundant and supported by preclinical data<sup>145</sup>. Many Met inhibitors are currently tested for safety/efficacy combined with various targeted agents that block other important pathways in cancer. Met-targeted therapies are being evaluated clinically with VEGF or EGFR inhibitors, and early results are promising. AMG102, MetMab, ARQ197, MGCD265, XL184, and PF02341066 are being used in combination with Erlotinib for the treatment of NSCLC. MK8033, PF02341066 and ARQ197 are also being tested in combination with sorafenib for the treatment of advanced solid tumors. 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<sup>146</sup>. Following these results in NSCLC, MetMab and ARQ197 progressed into phase III clinical testing in combination with erlotinib.

In closing, the key to successful development of targeted therapies will be dependent on accurate and timely identification of the critical, dysfunctional nodes in the oncogenic pathways of the individual patient, whose effective inhibition will hopefully result in reversal of the malignant state. 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. Periodic monitoring of molecular changes in patients may be necessary to benefit from a treatment regimen with targeted therapy since patient genotype and phenotype may evolve dynamically under the selective pressure of targeted therapies<sup>147</sup>. 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, 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 with endpoints that include time-to-first metastasis may be the most expedient path to more effective management of disease progression.

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Web site addresses are provided as an informational resource, not as an endorsement of any product or manufacturer.

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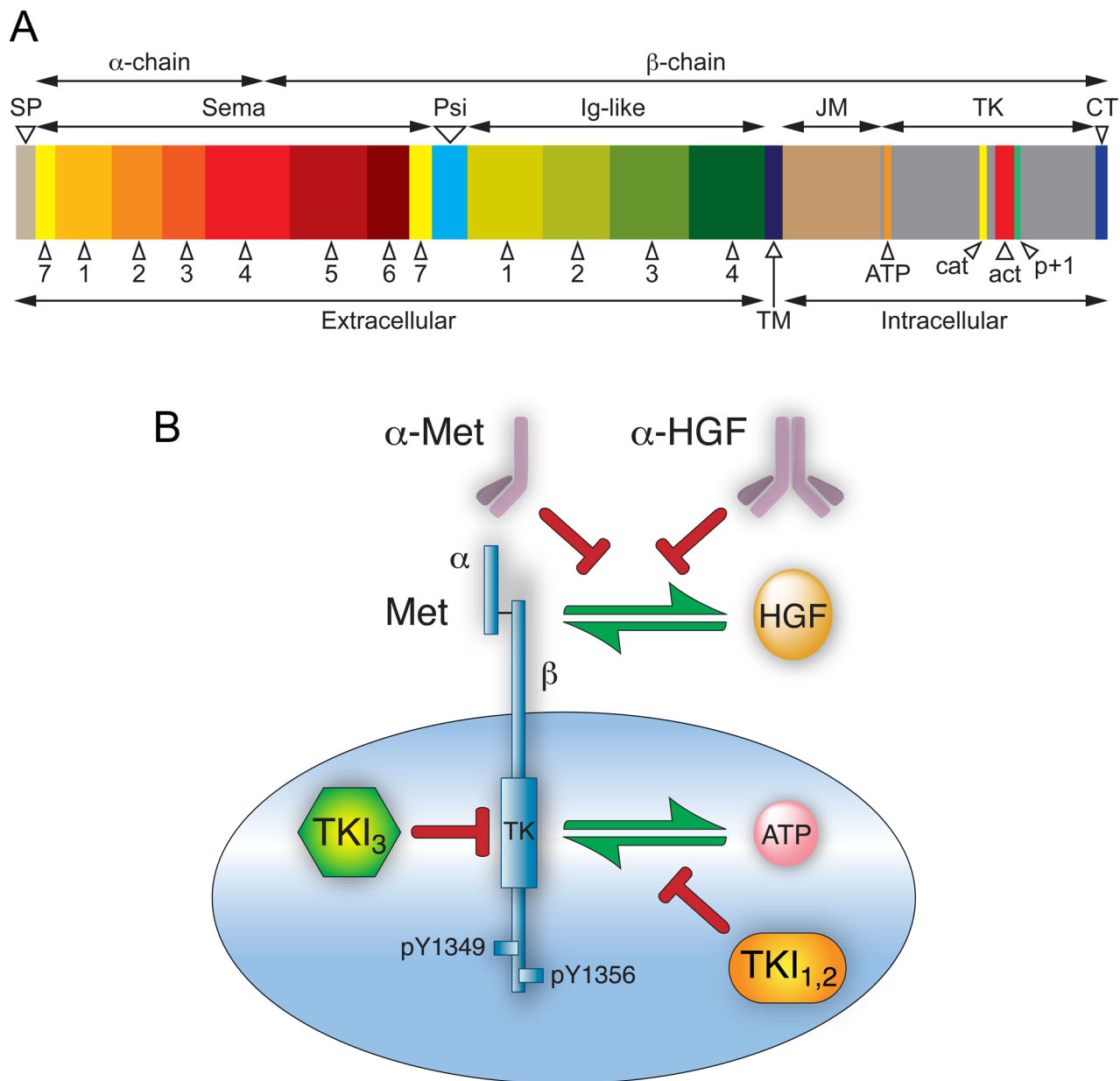
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### Highlights

- Despite regulation at multiple levels, HGF/Met signaling frequently contributes to oncogenesis, tumor progression and metastasis in a variety of human cancers.
- Cancer drug development programs targeting HGF or Met have grown significantly, with > 100 human clinical trials in progress or completed.
- HGF/Met pathway antagonists are generally well tolerated; promising results have been reported in lung, gastric, prostate and papillary renal cancer patients.
- Challenges facing the effective use of HGF/Met-targeted treatments include patient selection, biomarker development and identifying therapy combinations.
- Basic information, reagents and model systems for HGF/Met signaling will be invaluable in meeting these challenges and achieving effective disease control.





**Figure 1. Met domain structure and routes to antagonize the HGF/Met pathway**

**A.** Schematic of Met domain structure; domain lengths are proportional to number of constituent amino acid residues. Mature Met is a disulfide-linked two chain heterodimer with an extracellular amino terminal α-chain (45 kDa) and a carboxyl terminal β-chain (145 kDa) containing extracellular, transmembrane and intracellular domains. The signal peptide (SP) is not present in mature protein. The extracellular domain contains a sema homology region (Sema) organized in 7 blades; a cysteine-rich region (Psi); and four immunoglobulin-like repeats (Ig-like). The intracellular domain contains juxtamembrane (JM), tyrosine kinase (TK) and carboxyl terminal (CT) domains. Within the TK domain are the ATP binding site (orange), catalytic loop (cat, yellow), activation loop (act, red) and p+1 loop (p+1, green). **B.** At least three routes of pathway intervention have been followed as selective Met anticancer drug development strategies: 1) fully human monoclonal antibodies that

neutralize HGF by binding to one of its two Met binding sites; 2) monovalent (one-armed), monoclonal antibodies designed to bind to Met and inhibit HGF binding; and 3) tyrosine kinase inhibitors classified as type I, type II (TKI<sub>1,2</sub>) and type III (TKI<sub>3</sub>) as described in text.

Table 1

**HGF/Met pathway inhibitors in human clinical trials**

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

Drug	Design	Phase	Status	Patient population	Combinations	ClinicalTrials.gov Identifier
<b>Rilotumumab (AMG 102)</b>	Safety	Ib/II	Active	NSCLC <sup>1</sup>	Cisplatin/Etoposide	NCT00791154
	Safety/Efficacy	I/II	Active	mCRC <sup>2</sup> , wt KRAS	Panitumumab	NCT00788957
	Safety/Efficacy	I/II	Active	CRPC <sup>3</sup>	Mitoxantrone/Prednisone	NCT00770848
	Safety/Efficacy	II	Active	RCC <sup>4</sup>		NCT00422019
	Safety/Efficacy	II	Active	Advanced Malignant Glioma		NCT00427440
	Safety/Efficacy	I/II	Active	Locally Advanced/Metastatic EGI Adenocarcinoma <sup>5</sup>	ECX <sup>x</sup>	NCT00719550
	Safety	I/II	Recruiting	NSCLC	Erlotinib	NCT01233687
	Efficacy/Safety	II	Recruiting	Recurrent Malignant Glioma	Avastin	NCT01113398
	Efficacy	II	Recruiting	Advanced Gastroesophageal Adenocarcinoma	FOLFOX <sup>xx</sup>	NCT01443065
	Safety	II	Recruiting	Persistent/Recurrent Ovarian Epithelial Cancer, Fallopian Tube Cancer, Primary Peritoneal Cancer		NCT01039207
<b>Onartuzumab (MetMab)</b>	Safety	I	Completed	Advanced Solid Malignancies	Avastin	NCT01068977
	Efficacy	II	Active	NSCLC	Erlotinib	NCT00854308
	Efficacy	II	Recruiting	Metastatic/Recurrent, triple-negative Breast Cancer	Bevacizumab and Paclitaxel	NCT01186991
	Efficacy	II	Recruiting	mCRC	FOLFOX/Bevacizumab	NCT01418222
	Safety/Efficacy	III	Not yet recruiting	NSCLC (Met diagnostic-positive)	Erlotinib	NCT01456325
<b>Ficlatuzumab (AV-299)</b>	Safety/Efficacy	I	Terminated	Glioblastoma		NCT01189513
	Safety/Tolerability	I	Active	Advanced/Metastatic Solid Malignancies		NCT00969410
	Safety/Efficacy	I/II	Active	NSCLC	Gefitinib	NCT01039948
	Safety	I	Active	Relapsed/Refractory Solid Malignancies	Erlotinib	NCT00725634
<b>TAK-701</b>	Safety/Tolerability/PK	I	Active	Non-Hematologic Malignancies		NCT00831896
<b>AMG 337</b>	Safety	I	Recruiting	Advanced Solid Malignancies		NCT01253707
<b>AMG 208</b>	Safety	I	Recruiting	Advanced Solid Malignancies		NCT00813384
<b>Tivatimib (ARQ 197)</b>	Safety/Efficacy	I	Completed	Advanced Solid Malignancies		NCT00612209
	Bio-availability	I	Completed	Advanced Solid Malignancies		NCT01149720
	Safety/Efficacy	II	Active	GC <sup>6</sup>		NCT01152645
	Safety/Efficacy	I/II	Recruiting	CRC, wt KRAS	Irinotecan/Cetuximab	NCT01075048

Drug	Design	Phase	Status	Patient population	Combinations	ClinicalTrials.gov Identifier
	Safety/Efficacy	II	Recruiting	Advanced/Metastatic NSCLC, KRAS mutation +	Erlotinib	NCT01395758
	Safety	I	Completed	Advanced Solid Malignancies	Gencitabine	NCT00874042
	Safety/Efficacy	II	Active	HCC <sup>7</sup>		NCT00988741
	Safety	I	Recruiting	Advanced Solid Malignancies	Sorafenib	NCT00827177
	PK#	I	Completed	Healthy volunteer		NCT00651638
	Safety	I	Active	NSCLC	Erlotinib	NCT01251796
	Safety	I	Active	Advanced/Recurrent NSCLC	Erlotinib	NCT01069757
	Safety/Efficacy	III	Recruiting	Non Squamous NSCLC	Erlotinib	NCT01244191
	Safety/Tolerability	I	Completed	Metastatic Solid Malignancies		NCT00302172
	Efficacy	II	Completed	Unresectable Locally Advanced/Metastatic Pancreatic Adenocarcinoma	Gemcitabine	NCT00558207
	Safety/Efficacy	I	Completed	Advanced Solid Malignancies	Erlotinib	NCT00612703
	Efficacy	II	Withdrawn	Locally Advanced/Metastatic GC	Oxaliplatin/Capecitabine/Irinotecan	NCT01070290
	Safety	I	Recruiting	Advanced Solid Malignancies	Pazopanib	NCT01468922
	Safety	I	Active	HCC (Cirrhotic patients)	Erlotinib	NCT00802555
	Efficacy	II	Completed	Advanced/Metastatic NSCLC	Erlotinib	NCT00777309
	PK	I	Completed	Healthy Volunteer		NCT00658554
	Safety/Tolerability	I	Active	Advanced Solid/Recurrent Malignancies		NCT00609921
	Efficacy	III	Recruiting	Advanced/Metastatic Non Squamous NSCLC wt EGFR	Erlotinib	NCT01377376
	Safety/Efficacy	II	Active	Refractory Germ Cell Tumors		NCT01055067
	Safety/Efficacy	I/II	Recruiting	Subjects previously enrolled in other ARQ 197 study		NCT01178411
	Safety/Efficacy	II	Completed	MIT <sup>δ</sup> associated with RCC <sup>9</sup> /ASPS <sup>10</sup> /CCS <sup>11</sup>		NCT00557609
	Safety/Efficacy	II	Not yet recruiting	Relapsed Multiple Myeloma		NCT01447914
<b>BMS777607</b>	Safety/Efficacy	I/II	Completed	Advanced/Metastatic Solid SCCHN <sup>12</sup> , PRCC <sup>13</sup> Malignancies, CRPC,		NCT00605618
<b>E7050</b>	Efficacy	I/II	Recruiting	Advanced Solid Malignancies, Glioblastoma, Unresectable Stage III/IV Melanoma	E7080	NCT01433991
<b>EMD 1214063</b>	Safety	I	Recruiting	Advanced Solid Malignancies		NCT01014936
<b>EMD1204831</b>	Safety	I	Recruiting	Advanced Solid Malignancies		NCT01110083
<b>Foretinib (GSK1363089)</b>	Safety/Efficacy	II	Completed	Recurrent/Metastatic SCCHN		NCT00725764
	Safety	I	Completed	Advanced Solid Malignancies		NCT00743067
	Safety/Efficacy	II	Completed	mGC		NCT00725712
	Bio-availability	I	Completed	Advanced Solid Malignancies		NCT00742261

Drug	Design	Phase	Status	Patient population	Combinations	ClinicalTrials.gov Identifier
<b>INCB28060</b> <b>LY2801653</b> <b>MK8033</b>	Safety/Efficacy	I	Active	HCC		NCT00920192
	Safety/Efficacy	II	Active	PRCC		NCT00726323
	Safety/Efficacy	I/II	Recruiting	Locally Advanced/Metastatic NSCLC	Erlotinib	NCT01068587
	Safety/Efficacy	I/II	Recruiting	HER2 Over-Expressing Metastatic Breast Cancer	Lapatinib	NCT01138384
	Safety/Efficacy	II	Recruiting	ER+/PR+and HER2-Brest Cancer /4		NCT01147484
	Safety/Tolerability	I	Recruiting	Advanced Solid Malignancies		NCT01072266
	Safety/Tolerability	I	Recruiting	Advanced and/or Metastatic Cancer		NCT01285037
	Safety	I	Completed	Advanced Solid Malignancies	Omeprazole	NCT00559182
	Safety/Efficacy	I/II	Not yet recruiting	Locally Advanced/Metastatic Solid Malignancies, GC	Ciplastin/Capecitabine	NCT01355302
	Safety/Efficacy	I	Completed	Advanced Solid Malignancies		NCT00921869
<b>Amuvatinib (MP470)</b>	Safety/Efficacy	I/II	Recruiting	Platinum Resistant, Recurrent/Metastatic SCCHN	Cetuximab	NCT01332266
	Safety/Efficacy	I/II	Recruiting	Locally Advanced/Metastatic HCC	Sorafenib	NCT01271504
	Safety/Efficacy	I	Not yet recruiting	Advanced Solid Malignancies		NCT01428141
	Safety	I	Recruiting	Advanced Solid Malignancies		NCT00869895
	Safety	I	Completed	Advanced Solid Malignancies		NCT00894894
	Safety/Efficacy	I	Completed	Advanced Solid Malignancies	Topotecan/Docetaxel/Erlotinib/Paclitaxel/Carboplatin/Etoposide	NCT00881166
	Efficacy	II	Recruiting	SCLC	Platinum/Etoposide	NCT01357395
	Safety/PK/PD *	NA	Terminated	Metastatic Solid Malignancies/Lymphoma		NCT00504205
	Safety/Efficacy	I/II	Recruiting	Advanced Malignancies/NSCLC	Erlotinib/Docetaxel	NCT00975767
	Safety	I	Recruiting	Advanced Solid Malignancies		NCT00697632
<b>MGCD265</b>	Safety	I	Completed	Advanced Solid Malignancies		NCT00679133
	Safety/Efficacy	I/II	Completed	Advanced Solid Malignancies		NCT00496353
	Safety	I	Completed	Advanced Solid Malignancies		NCT00518739
	PK	I	Not yet recruiting	Subjects With Impaired Renal Function		NCT01419041
	Safety/PK/PD	I	Not yet recruiting	Advanced Solid Malignancies		NCT01441388
	Safety/Efficacy	I	Recruiting	ALK+ Tumors /5	Axitinib/Sunitinib/Bevacizumab/Sorafenib	NCT01121588
	PK	I	Completed	Japanese Healthy Male Volunteers		NCT01250730
	PK	I	Completed	Healthy Volunteer		NCT01297595
	Safety/Efficacy	I/II	Recruiting	NSCLC	Erlotinib	NCT00965731
	PK	I	Completed	Healthy Volunteer		NCT01168934
<b>Crizotinib</b> <b>PF02341066</b>	Safety/Efficacy	I	Recruiting	NSCLC		NCT01121575
	Safety/Efficacy	I	Recruiting	NSCLC		
	Safety/Efficacy	I	Recruiting	NSCLC		
	Safety/Efficacy	I	Recruiting	NSCLC		
	Safety/Efficacy	I	Recruiting	NSCLC		
	Safety/Efficacy	I	Recruiting	NSCLC		
	Safety/Efficacy	I	Recruiting	NSCLC		
	Safety/Efficacy	I	Recruiting	NSCLC		
	Safety/Efficacy	I	Recruiting	NSCLC		
	Safety/Efficacy	I	Recruiting	NSCLC		



Drug	Design	Phase	Status	Patient population	Combinations	ClinicalTrials.gov Identifier
<b>PF02341066</b>	PK <sup>^</sup>	I	Completed	Healthy Male Volunteer		NCT01082380
	PK	I	Completed	Healthy Volunteer	Ketoconazole	NCT01149785
	PK	I	Completed	Healthy Volunteer	Rifampin	NCT01147055
	PK	I	Completed	Healthy Volunteer		NCT01154218
	Safety	I	Recruiting	Advanced Solid Malignancies		NCT00585195
	Safety/Efficacy	III	Recruiting	NSCLC, ALK+	Pemetrexed/Docetaxel	NCT00932893
	Safety/PK	I/II	Recruiting	Relapsed/Refractory Solid Malignancies or Anaplastic Large Cell Lymphoma (Young Population)		NCT00939770
	Safety/Efficacy	II	Recruiting	NSCLC, ALK+		NCT00932451
	Bio availability	I	Completed	Healthy Volunteer		NCT00939731
	Taste Assessment	I	Completed	Healthy Volunteer		NCT01125904
<b>PF04217903</b>	Safety	I	Recruiting	NSCLC	PF 00299804	NCT01441128
	Obtain tissue	I	Recruiting	NSCLC, ALK+		NCT01300429
	Safety/Efficacy	III	Recruiting	Recurrent/Metastatic Non Squamous Cell Carcinoma of the Lung ALK +		NCT01154140
	Safety/Efficacy	I	Completed	Advanced Solid Malignancies		NCT00706355
	Safety/Efficacy	II	Not yet recruiting	mCRPC		NCT01428219
	Safety/Efficacy	II	Not yet recruiting	Carcinoid/Pancreatic Neuroendocrine Tumor		NCT01466036
	Efficacy	II	Recruiting	Breast Cancer, ER+/PR+ and HER2-		NCT01441947
	Safety/Efficacy	I	Recruiting	mCRPC		NCT01347788
	Safety	I	Active	Advanced Solid Malignancies		NCT00215605
	Safety/Efficacy	II	Recruiting	Advanced Solid Malignancies		NCT00940225
<b>Cabozantinib (XL184)</b>	Efficacy	III	Active	MTC / $\delta$		NCT00704730
	Safety/Efficacy	II	Active	Glioblastoma Multiforme	Erlotinib	NCT00704288
	Safety/Efficacy	I/II	Active	NSCLC	Rosiglitazone	NCT00596648
	PK	I	Active	Advanced Solid Malignancies	Temozolomide/Radiation Therapy	NCT01100619
	Safety	I	Active	Glioblastoma		NCT00960492
	Safety/Efficacy	II	Active	Grade IV Astrocytic Tumor		NCT01068782
	Safety	I	Completed	Advanced/Metastatic Solid Malignancies (Japanese)		NCT01018745

#PK: Pharmacokinetics

\*PD: Pharmacodynamics

<sup>1</sup> [14C]PF 02341066

<sup>1</sup> NSCLC: Non Small Cell Lung Cancer

<sup>2</sup> CRC: Colorectal Cancer

<sup>3</sup> CRPC: Castrate Resistant Prostate Cancer

<sup>4</sup> RCC: Renal Cell Carcinoma

<sup>5</sup> EGI: Gastric or Esophagogastric Junction adenocarcinoma

<sup>6</sup> GC: Gastric Cancer

<sup>7</sup> HCC: Hepatocellular Carcinoma

<sup>8</sup> MIT: Microphthalmia transcription factor associated Tumors

<sup>9</sup> RCC: Renal Cell Carcinoma

<sup>10</sup> ASPS: Alveolar Soft Part Sarcoma

<sup>11</sup> CCS: Clear Cell Sarcoma

<sup>12</sup> PRCC: Papillary Renal-Cell Carcinoma

<sup>13</sup> SCCN: Squamous Cell Carcinoma for the Head and Neck 14

<sup>14</sup> ER+/PR+and HER2- Breast Cancer: Estrogen-receptor- positive/Progesterone-recepto r-positive and Human Epidermal Growth Factor Receptor 2 negative Breast Cancer

<sup>15</sup> ALK: Anaplastic Lymphoma Kinase

<sup>16</sup> MTC: Metastatic Medullary Thyroid Cancer

<sup>x</sup> ECX: Capecitabine/Epirubicin/Cisplatin

<sup>xx</sup> FOLFOX: Oxaliplatin/Folic Acid/5-fluoro-uracil