Hepatocyte growth factor/MET in cancer progression and biomarker discovery

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Signaling driven by hepatocyte growth factor (HGF) and MET receptor facilitates conspicuous biological responses such as epithelial cell migration, 3-D morphogenesis, and survival. The dynamic migration and promotion of cell survival induced by MET activation are bases for invasion–metastasis and resistance, respectively, against targeted drugs in cancers. Recent studies indicated that MET in tumor-derived exosomes facilitates metastatic niche formation and metastasis in malignant melanoma. In lung cancer, gene amplification-induced MET activation and ligand-dependent MET activation in an autocrine/paracrine manner are causes for resistance to epidermal growth factor receptor tyrosine kinase inhibitors and anaplastic lymphoma kinase inhibitors. Hepatocyte growth factor secreted in the tumor microenvironment contributes to the innate and acquired resistance to RAF inhibitors. Changes in serum/plasma HGF, soluble MET (sMET), and phospho-MET have been confirmed to be associated with disease progression, metastasis, therapy response, and survival. Higher serum/plasma HGF levels are associated with therapy resistance and/or metastasis, while lower HGF levels are associated with progression-free survival and overall survival after treatment with targeted drugs in lung cancer, gastric cancer, colon cancer, and malignant melanoma. Urinary sMET levels in patients with bladder cancer are higher than those in patients without bladder cancer and associated with disease progression. Some of the multi-kinase inhibitors that target MET have received regulatory approval, whereas none of the selective HGF-MET inhibitors have shown efficacy in phase III clinical trials. Validation of the HGF-MET pathway as a critical driver in cancer development/progression and utilization of appropriate biomarkers are key to development and approval of HGF-MET inhibitors for clinical use.

The MET oncogene was first isolated on the basis of its transforming activity, caused by a fusion of genes composed of the translocated promoter region (TPR) locus on chromosome 1 and MET sequence on chromosome 7 (TPR-MET).1) Isolation of the full-length MET proto-oncogene sequence revealed that it encoded a transmembrane receptor tyrosine kinase (TK).2) MET was thereafter identified as the receptor for hepatocyte growth factor (HGF).3) Hepatocyte growth factor was identified and cloned as a mitogenic protein for hepatocytes,4,5) while subsequent studies indicated that it was the same as scatter factor, an epithelial cell motility factor derived from fibroblasts and mesenchymal cells.6–8)

Conspicuous responses that are driven by the HGF-MET receptor pathway are dynamic 3-D morphogenesis and survival of cells. The induction of epithelial branching tubulogenesis in a 3-D collagen matrix by HGF had particular impact, because HGF was the first bioactive molecule to induce epithelial tubulogenesis.9) Impairment in the hepatic progenitor cell survival and the migration of myogenic precursor cells seen in MET knockout mice indicate potent actions of HGF in dynamic migration and promotion of cell survival.10) It was easy to speculate that the dynamic migration induced by HGF could also contribute critically to the biological basis of invasion and metastasis in tumor tissues. Meanwhile, involvement of the HGF-MET pathway in acquisition of a resistant phenotype against molecular targeted drugs was elucidated.11,12) The potent action of HGF to promote cell survival is a prevalent biological basis for drug resistance in cancers.

Both HGF and MET are targets in anticancer drug discovery.13) More than 10 different HGF-MET inhibitors entered into clinical trials, many of which were completed with unsatisfactory results. Recently, previously overlooked mutations in MET, resulting in deletions in the cytoplasmic juxtamembrane (JM) domain, have been found to be potential oncoprotein in non-small-cell lung cancer (NSCLC). Clinical studies have indicated favorable responses to MET inhibitors in patients...
with this variant MET.\(^\text{(14,15)}\) We describe here recent progress in HGF-MET research on tumor biology and biomarker discovery.

**Structures and Regulation of HGF-MET**

The mature form of MET is composed of a 50-kDa \(\beta\)-chain and 145-kDa \(\alpha\)-chain (Fig. 1a). The extracellular region is composed of SEMA, plexin–semaphorin–integrin (PSI), and immunoglobulin-like fold–plexin–transcription factor (IPT) 1–IPT4 domains. The intracellular region contains JM and TK domains. The binding of HGF to MET induces MET clustering and phosphorylation of Y1234 and Y1235, followed by phosphorylation of Y1349 and Y1356 in the carboxyl terminal region, to which adaptor molecules associate and transmit signals downstream.\(^\text{(7,8,13)}\) Hepatocyte growth factor is secreted as a single-chain precursor (pro-HGF) and extracellular processing into a two-chain mature HGF is coupled to the activation of HGF (Fig. 1b). Hepatocyte growth factor-activator and matriptase are the main proteases responsible for the processing of HGF.\(^\text{(16)}\) Hepatocyte growth factor binds to MET through two interfaces: the NK1 (N-terminal and first kringle domains) binds with high affinity whereas the \(\beta\)-chain binds with low affinity. The structure of the complex between the \(\beta\)-chain of HGF and the SEMA-PSI domains of MET were revealed by crystallographic analysis (Fig. 1c).\(^\text{(17)}\) The activation of MET receptor by bivalent MET-binding macrocyclic peptides indicate that stable dimerization of MET with ligands of appropriate length provides a fundamental structural basis for activation of MET.\(^\text{(18)}\)

The JM domain, which is composed of 47 highly conserved amino acids, contains two protein phosphorylation sites and acts as a negative regulator in terms of MET-dependent signal transduction. One is Y1003 phosphorylation and the other is S985 phosphorylation. The CBL ubiquitin ligase binds phosphorylated Y1003, and this CBL binding results in MET ubiquitination, endocytosis, and degradation.\(^\text{(19)}\) The CBL-mediated degradation of activated MET provides a mechanism that either attenuates or terminates MET-mediated signaling. Ser985 is phosphorylated by protein kinase-C and is dephosphorylated by protein phosphatase-2A.\(^\text{(20)}\) When MET-S985 is phosphorylated, HGF-induced MET activation and subsequent biological responses are suppressed.\(^\text{(20)}\)

**Metastasis and Tumor Microenvironment**

A definitive role of stromal fibroblasts in invasion of cancer cells into 3-D collagen was first noted using human oral squamous cell carcinoma cells,\(^\text{(21)}\) and subsequent study indicated neutralization of HGF inhibited 3-D invasion induced by stromal fibroblasts. Independently, induction of invasiveness into collagen by HGF/scatter factor was noted during characterization of scatter factor.\(^\text{(6)}\) These early studies showed the importance of HGF as a fibroblast-derived factor that facilitates the aggressive invasion of cancer cells.

The metastatic tumor microenvironment (premetastatic/metastatic niche) emerged as an important player in metastatic colonization and growth. A variety of stromal cells, such as macrophages, inflammatory cells, endothelial cells, and cancer-associated fibroblasts contribute to the formation of the metastatic microenvironment.\(^\text{(22)}\) Growth factors play promoting roles in forming the metastatic microenvironment. Hepatocyte growth factor functions as a stromal cell-derived factor that strongly influences cancer cell invasiveness in the tumor.
microenvironment. Selective inhibition of the HGF-MET pathway suppressed metastasis in experimental models. A recent topic in cancer metastasis is the involvement of exosomes in metastasis. MET in exosomes promotes metastatic microenvironment formation in metastatic melanoma (Fig. 2). The exosomes from highly metastatic mouse and human melanoma cells contained high levels of MET, and exosomes in circulation localized to sites of metastatic tissues and increased vascular permeability, which promotes the migration of tumor cells. The exosomes also increased activated MET in bone marrow-derived cells, thereby being reprogrammed to a proangiogenic phenotype, and the bone marrow-derived cells mobilized to lungs where they could aid angiogenesis, invasion, and metastasis. Administration of exosomes that contained high levels of MET facilitated metastasis of melanoma cells with lower metastatic ability and 29% of patients with acquired and intrinsic resistance, respectively.

After the discovery of EML4-ALK as a driver oncogene in patients with NSCLC, alectinib was developed as a selective anaplastic lymphoma kinase (ALK) TKI. Based on its high objective response rate, long median progression-free survival, and favorable toxicity profile, alectinib has been approved in Japan and the USA. However, patients eventually acquire resistance to alectinib. Among several different mechanisms, alectinib-resistant EML4-ALK-positive NSCLC cells can acquire the ability to express HGF and the ensuing autocrine activation of MET caused by cancer cell-derived HGF confers acquired resistance to alectinib. Collectively, the expression of HGF in cancer cells and/or stromal cells in the tumor microenvironment participates in the resistance to EGFR and ALK TKIs.

**Drug Resistance**

The tumor microenvironment participates not only in cancer metastasis but also resistance to molecular-targeted drugs. Stromal cells influenced the sensitivity to anticancer drugs, and proteomic analysis revealed that stromal cell-derived HGF is a predominant factor that confers resistance to molecular-targeted drugs such as RAF inhibitor. The biochemical basis to how HGF so potently promotes survival as well as cell motility might relate to the adaptor protein GRB2-associated binding protein 1 (GAB1). The GAB1 protein has a unique recognition structure “MET-binding domain” that mediates its binding to phosphorylated MET. Indeed, phenotypes in MET- and GAB1- mice showed extensive similarities.

Non-small-cell lung cancer patients developed acquired resistance to epidermal growth factor receptor (EGFR) TK inhibitors (TKIs) within a few years, and 20–25% of the patients showed intrinsic resistance to EGFR-TKIs. As an acquired resistance mechanism, the T790M second mutation in MET is found in approximately 40% of patients with acquired resistance to EGFR-TKIs, and overexpression of HGF was seen in approximately 61% of patients with acquired resistance to EGFR-TKIs. MET activation is associated with tumor progression and high-grade gliomas.

**MET Mutations**

The tight association between MET mutation and cancer development was first reported in hereditary and sporadic forms of papillary renal cell carcinoma. Germline and somatic missense mutations (M1131T, V1188L, L1195V, V1220L, D1228N/H, Y1230C/H, M1250T/I) located in the TK domain of MET are found in papillary renal carcinomas (Fig. 3), and these are likely to be gain-of-function mutations. Missense mutations have been found in childhood hepatocellular carcinoma, head and neck squamous cell carcinoma, ovarian cancer, and small-cell lung cancer.

The JM-deleted MET generated by exon 14 skipping (MET-Aexon14) due to intronic mutations was noted in NSCLC cancer tissues and cells. The expression of MET-Aexon14 in cells resulted in the loss of association with the CBL E3 ubiquitin ligase, decreased ubiquitination and prolonged activation of signaling molecules. Considering the notion that MET-Y1003 phosphorylation in the JM domain provides CBL-binding for ubiquitination, MET-Aexon14 variant may have a longer lifespan in terms of protein stability and signaling.

Another mutant variant of MET with deleted extracellular IPT domains was found in approximately 6% of high-grade gliomas. The mutation is caused by intronic mutations and the skipping of exon 7 (encoding a part of IPT1) and exon 8 (encoding a part of IPT2) generates a single pseudo-IPT domain. This MET exon 7–8 skipping variant is mainly
present as an unprocessed single chain form and located in the cytoplasm, suggesting an impairment in biosynthetic processing and subsequent translocation to the cell membrane. Missense mutations in MET have been found in a variety of cancers, and the positions of mutational changes are located not only in the intracellular domains, but also extracellular regions (Figs 1C, 3A). The significance of these extracellular mutations is unknown.

**Discovery of HGF/MET as Biomarkers**

Collectively, HGF and sMET in blood, tissues, and/or urine are associated with changes in tumor characteristics and therapeutic responses in several types of tumors, indicating the significance of HGF, sMET, and related molecules as possible biomarkers for evaluation of tumor characteristics and therapeutic responses (Table 1). A substantial number of reports have documented increased circulating levels of HGF in a wide spectrum of cancers, and robust and sensitive immunoassays of soluble HGF protein have become widely available. Inflammatory mediators, including interleukin-1α (IL-1α), IL-1β, tumor necrosis factor-α, and prostaglandin E2 increase gene expression of HGF in stromal cells. Because these inflammatory mediators are increased in the tumor microenvironment and contribute to a drug-resistant and/or metastatic tumor microenvironment, it is likely that these inflammatory mediators participate in upregulation of HGF in tumors.

**MET gene amplification and/or protein overexpression also frequently occur in cancer, which has accelerated investigations into MET gene copy number in tumors or by circulating soluble DNA, as well as MET protein content and phosphorylation (activation) state in tumor samples using a variety of approaches. Technical difficulties associated with the lability of MET and phospho-MET in formalin-fixed, paraffin-embedded samples have hindered the development of clinically validated assays for use with archival tumor specimens, but recently reported assays for use with flash-frozen biopsy samples have provided reliable alternatives.**

**Fig. 3.** MET mutations found in cancer patients. (a) Positions of missense and deletion mutations in each domain of MET. The deletion mutations in extracellular immunoglobulin-like fold–plexin–transcription factor (IPT) domains and the intracellular juxtamembrane (JM) domain are caused by exon skipping. (b) Crystal structures of MET tyrosine kinase (TK) domain and positions of missense activating mutations found in patients with papillary renal cell carcinoma. Amino acids changed by missense mutations are indicated by red balls. The autoinhibited form (left panel, PDB ID 2G15) and crizotinib (a dual inhibitor for anaplastic lymphoma kinase and MET) bound form (right panel, PDB 2WGI) are shown. The structural change of the activation loop (A1221–K1248, colored red) occurs following Y1234/Y1235 phosphorylation and upregulates enzymatic activity. The images of PDB ID 2G15 (left) (Wang W, Marimuthu A, Tsai J, Kumar A, Kruptka HI, Zhang C, Powell B, Suzuki Y, Nguyen H, Tabrizizad M, Luu C, West BL. Structural characterization of autoinhibited c-Met kinase produced by coexpression in bacteria with phosphatase. Proc Natl Acad Sci USA. 103: 3563-3568, 2006) and PDB ID 2WGJ (right) (Cui JJ, Tran-Dubé M, Shen H, Nambu M, Kung PP, Pairish M, Jia L, Meng J, Funk L, Botrous I, McGuck M, Grodsky N, Ryan K, Padrique E, Alton G, Timofeevski S, Yamazaki S, Li Q, Zou H, Christensen J, Mroczkowski B, Bender S, Kania RS, Edwards MP. Structure based drug design of crizotinib (PF-02341066), a potent and selective dual inhibitor of mesenchymal-epithelial transition factor (c-MET) kinase and anaplastic lymphoma kinase (ALK). J Med Chem. 54: 6342-6363, 2011) were created with PyMOL.
| Tumor type       | Subtype, specification | Marker type | Changes and significance as biomarkers                                                                 | References |
|------------------|------------------------|-------------|--------------------------------------------------------------------------------------------------------|------------|
| Gastric cancer   | Resection             | Serum HGF  | Higher preoperative HGF levels than the control group (391 vs 193 pg/mL)                              | 41         |
|                  | Response to trastuzumab | Serum HGF  | Lower HGF levels in the responsive group (PR+SD) than in those with PD. Association between high HGF levels with worse OS | 42         |
|                   |                        | Plasma sMET | Lower sMET levels compared to matched controls (1.390 vs 1.610 ng/mL)                                | 43         |
| Helicobacter pylori-infected | Resection         | Serum sMET, tissue MET, serum and tissue HGF | Association between advanced progression and preoperative serum HGF. Correlation of tissue MET with lymphatic vessel invasion, lymph node metastasis, maximum tumor diameter, and OS. No correlation between serum HGF and tissue HGF or MET content | 42         |
| Lung cancer      | Small-cell lung cancer | Serum HGF  | Higher HGF levels compared to healthy individuals (1886 pg/mL vs 1131 pg/mL). Association between higher HGF levels and worse PFS and liver metastases. Increased HGF levels at progression after two to three cycles of chemotherapy. Longer OS in patients with decreased HGF levels at response time from baseline levels than patients with increased levels. Shorter OS in patients with higher HGF levels than those with lower HGF levels. Association with tumor epithelial-mesenchymal transition markers in patients with high HGF levels (>median) | 44         |
|                  |                        | Serum HGF  | Higher HGF levels compared to and healthy subjects.                                                 | 45         |
|                  |                        | Tissue MET, tissue pMET | MET overexpression and increased pMET in 54% and 43% patients, respectively. Correlation between pMET status and OS | 46         |
|                  |                        | Tissue HGF | High HGF immunoreactivity in patients with acquired gefitinib resistance in the absence of T790M EGFR mutation and MET gene amplification. Low HGF immunoreactivity in majority of responders to gefitinib | 12         |
|                  |                        | Plasma HGF | High HGF levels in 13% of patients resistant to EGFR-TKI without detectable T790M circulating DNA. High HGF levels in 25% of patients resistant to EGFR-TKI with detectable T790M circulating DNA. Increase after administration of EGFR-TKI. Higher HGF levels in patients with PD compared to PR and SD (724.1 ± 216.4 pg/mL vs 381.7 ± 179.0 pg/mL and 396.5 ± 148.3 pg/mL, respectively) | 47         |
|                  |                        | Plasma HGF | Higher HGF levels than normal and pretreatment with EGFR-TKI. Increase after administration of EGFR-TKI. Higher HGF levels in patients with PD compared to PR and SD (724.1 ± 216.4 pg/mL vs 381.7 ± 179.0 pg/mL and 396.5 ± 148.3 pg/mL, respectively) | 48         |
|                  |                        | Plasma HGF | Higher HGF levels in gefitinib non-responders than in responders. Association between low HGF levels and longer RFS and OS independent of EGFR mutation status | 49         |
|                  |                        | Plasma sMET, tissue MET | Association between sMET and tissue MET expression level. Decrease in sMET levels after surgical resection to levels close to those in disease-free volunteers | 50         |
|                  |                        | Plasma sMET, tissue MET | Association between high sMET levels and poor OS (9.5 vs 22.2 months) | 51         |
| Tumor type          | Subtype, specification | Marker type          | Changes and significance as biomarkers                                                                                                                                                                                                 | References |
|---------------------|------------------------|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Breast cancer       | Stage II/III           | Serum HGF            | Higher HGF levels in CR or PR in patients treated with neoadjuvant chemotherapy doxorubicin and docetaxel. Longer RFS in patients with highest HGF levels when HGF levels were divided into four groups                                                                 | 52         |
|                     |                        | Tissue HGF          | Association between high tissue HGF levels and lymph node metastasis. Higher sensitivity to chemotherapy (CR, PR, and SD) in HGF-low patients than in HGF-high patients                                                                 | 53         |
| Meta-analysis       | MET levels             |                      | Association between MET overexpression and worse PFS compared to normal expression                                                                                                                                                    | 54         |
| Breast cancer cell  | Reverse phase protein  | Higher pMET (Y1234/35) levels in triple-negative (negative for estrogen receptor, progesterone receptor, and ERBB2/HER2) cases                                                                                                               | 55         |
| lines               |                        | Tissue MET and pMET by reverse phase protein array | Determination of dichotomized values of MET and pMET as significant prognostic factors for RFS and OS. Association between high MET levels and worse RFS and OS in hormone receptor-positive cases. Association between high pMET levels and worse RFS and OS in HER2-positive cases. Higher risk of recurrence and death in patients with high MET. Higher risk of recurrence in patients with high pMET | 56         |
| Prostate cancer     | Plasma HGF             | Higher median HGF level in prostate cancer patients compared to control group (505 vs 397 pg/mL). Higher HGF levels in subset of patients with lymph node and/or seminal invasion                                                                 | 57         |
|                     | Urinary sMET           | Higher sMET levels in patients with metastatic cancer than in localized cancer                                                                                                                                                    | 58         |
|                     | Plasma sMET            | Higher sMET levels in patients than those in healthy group                                                                                                                                                                | 40         |
| Renal cell carcinoma| Clear cell type        | Serum HGF            | Higher HGF levels in patients than healthy individuals. Higher median HGF level in stage 3-4 than stage 1-2 (1252.9 vs 948.7 pg/mL). Higher HGF levels in patients with distant metastasis than those without metastasis (1375 vs 836.6 pg/mL) | 59         |
|                     | Clinical trial with    | Plasma HGF           | Correlation between low HGF baseline level and larger decrease in tumor burden after pazopanib treatment. Correlation between low baseline HGF levels and PFS (48.1 vs 32.1 weeks)                                                                 | 60         |
|                     | pazopanib              |                      |                                                                                                                                                                                                                                |            |
|                     | Clinical trial with    | Plasma HGF and sMET, tissue MET | No correlation of these values with treatment efficacy                                                                                                                                                                                                                                         | 61         |
|                     | rilotumumab            |                      |                                                                                                                                                                                                                                |            |
| Malignant melanoma  | Serum HGF              | Higher HGF levels in advanced disease. Higher HGF levels in patients with progressive disease. Correlation of baseline high level (above median) with lower PFS and OS                                                                 | 62         |
|                     | Serum sMET             | Lower sMET levels in metastasis-free patients and healthy donors than those with metastatic disease. Superior changes in sMET than those in lactate hydrogenase and S100 for liver function                                   | 63         |
Table 1 (Continued)

| Tumor type                     | Subtype, specification               | Marker type       | Changes and significance as biomarkers                                                                                                                                                                                                 | References |
|--------------------------------|--------------------------------------|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Multiple myeloma               | HGF mRNA in bone marrow              | Higher HGF mRNA expression levels in patients than those of healthy individuals. No relation to the number of myeloma cells                                                                                                               | 64         |
|                                | Serum HGF                            | Higher median HGF levels at diagnosis vs in remission (2001 vs 1049 pg/mL); Higher median HGF levels in relapsed vs in remission patients (1370 vs 1049 pg/mL)                                                                              | 65         |
|                                | Serum sMET                           | No significant difference in sMET between patients and healthy individuals; Negative correlations of sMET with disease stage and bone marrow plasma cell percentage                                                                 | 66         |
| Colon cancer                   | Patients underwent carcinoma resection | Serum HGF        | Correlation of higher HGF levels with advanced stage (stage III/IV), tumor size, lymph node metastasis, and distant metastasis. Poor prognosis in patients with elevated HGF                                                                  | 67         |
|                                | Metastatic cancer, treated with anti-EGFR antibody KRAS wild-type | Serum HGF        | Correlation between low HGF levels and longer PFS and OS                                                                                                                                                                                                 | 68         |
| Hepatocellular carcinoma       | Serum HGF                            | Correlation between higher HGF levels post-hepatectomy with metastasis. Higher HGF levels in patients with hepatocellular carcinoma than those with C-viral chronic hepatitis or liver cirrhosis | 69–71      |
|                                | Serum HGF                            | Higher pre-hepatectomy portal HGF levels than peripheral HGF levels. Higher post-hepatectomy portal HGF levels compared to pre-hepatectomy portal levels                                                                                              | 69         |
|                                | Metastatic patients treated with sotravenib ± erlotinib Clinical trial of tivantinib | Plasma HGF       | Correlation of higher baseline HGF levels with poor OS regardless of treatment compared to those with lower HGF levels                                                                                                                                 | 72         |
|                                | Serum HGF                            | Correlation of low baseline HGF with longer OS. Longer OS in patients treated with tivantinib with low HGF than in those with high HGF                                                                                                               | 73         |
| Ovarian cancer                 | Serum HGF                            | Higher preoperative HGF levels than those with benign tumors or borderline tumors. Higher HGF levels in advanced-stage (III/IV) patients than those in early stage (I/II). Correlation of higher preoperative HGF levels with lower OS (23 vs 41 months). Longer disease-free survival in patients with low preoperative HGF | 74         |
| Bladder cancer                 | Urinary sMET                          | Higher sMET levels in bladder cancer patients compared to individuals in the same urology clinic but negative for any genitourinary malignancy. Distinguishable by urinary sMET between bladder cancer patients with muscle-invasive disease from those with non-muscle-invasive disease | 75         |
| Glioma                         | Treated by radiotherapy               | Serum HGF        | Lower median serum HGF in patients with high and moderately differentiated tumors than those with poorly differentiated tumors (964.8 pg/mL vs 1576.1 pg/mL). Different median time to progression (6 vs 17 months) for patients with HGF levels below vs above value of overall median serum HGF level (1219.5 pg/mL) | 76         |

CR, complete response; EGFR, epidermal growth factor receptor; ERBB2, Erb-B2 receptor tyrosine kinase 2; HER2, human epidermal growth factor receptor 2; OS, overall survival; PD, progressive disease; PFS, progression-free survival; pMET, phosphorylated MET; PR, partial response; RFS, relapse-free survival; SD, stable disease; sMET, soluble MET; TKI, tyrosine kinase inhibitor.
| Drug | Design            | Phase | Patient population                                                                 | Combinations                                                                                          |
|------|------------------|-------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| INCB28060/(INC280) | Safety/tolerability | I     | c-MET-dependent advanced solid tumors                                              | Bevacizumab/platinum/paclitaxel and pemetrexed/platinum                                              |
| Cabozantinib (XL184) | Safety/PK | I     | Hepatic impaired adult subjects                                                    | Bevacizumab/platinum/paclitaxel and pemetrexed/platinum                                              |
| Onartuzumab (MetMAb) | Safety/efficacy | II    | NSCLC                                                                              | Paclitaxel/platinum                                                                                   |
| Cabozantinib (XL184) | Safety/efficacy | II    | Previously treated, symptomatic castration-resistant prostate cancer               | Mitoxantrone/prednisone                                                                              |
| Crizotinib (PF02341066) | Safety/efficacy | II    | Altered ALK and/or MET in locally advanced and/or metastatic anaplastic            | Vemurafenib, sorafenib                                                                               |
| Crizotinib (PF02341066) | Safety/efficacy | I     | Advanced malignancies                                                              | Pemetrexed or pazopanib                                                                               |
| Cabozantinib (XL184) | Safety/efficacy | I     | Multiple myeloma with bone disease                                                | Pemetrexed or pazopanib                                                                               |
| Cabozantinib (XL184) | Safety/efficacy | I     | Solid tumors                                                                       | Vemurafenib, sorafenib                                                                               |
| Onartuzumab (MetMAb) | Safety/efficacy | II    | Gastric cancer                                                                     | mFOLFOX6                                                                                              |
| Cabozantinib (XL184) | Efficacy        | II    | Castration-resistant prostate cancer with bone metastases                          | Erlotinib or gefitinib                                                                               |
| LY2875358            | Safety           | I     | Japanese participants with advanced malignancies                                   | Erlotinib or gefitinib                                                                               |
| Cabozantinib (XL184) | Safety/efficacy | III   | Metastatic castration-resistant prostate cancer previously treated with docetaxel| Prednisone                                                                                           |
| Crizotinib (PF02341066) | Safety           | I     | Younger patients with relapsed or refractory solid tumors or anaplastic           | Cyclophosphamide, dextrazoxane, doxorubicin, topotecan, vincristine                                   |
| INCB28060/(INC280)   | Safety/efficacy | lb/II | NSCLC, EGFR-mutated, c-MET-amplified, EGFR-inhibitor insensitive                  | Gefitinib                                                                                             |
| Cabozantinib (XL184) | Safety/efficacy | II    | Advanced NSCLC, KIF5B/RET-positive                                                 | Dasatinib                                                                                             |
| Crizotinib (PF02341066) | Safety/efficacy | I     | Diffuse intrinsic pontine glioma, high grade glioma, pediatric                     | Dasatinib                                                                                             |
| SAR125844            | Safety/efficacy/PD | I     | Asian advanced malignant solid tumor patients                                      | Dasatinib                                                                                             |
| Onartuzumab (MetMAb) | Safety/efficacy | III   | Metastatic gastric cancer, HER2–, Met-positive                                      | mFOLFOX6                                                                                              |
| Cabozantinib (XL184) | Expended access  |       | Medullary thyroid cancer                                                            | Docetaxel, prednisone                                                                                 |
| Cabozantinib (XL184) | Safety           | I     | Advanced prostate cancer                                                           | Docetaxel, prednisone                                                                                 |
| Cabozantinib (XL184) | Efficacy         | II    | Advanced urothelial cancer                                                         | Docetaxel, prednisone                                                                                 |
| Rilotumumab (AMG 102) | Efficacy         | III   | Locally advanced/metastatic gastric or esophagogastric junction adenocarcinoma      | Docetaxel, prednisone                                                                                 |
| Cabozantinib (XL184) | Efficacy         | III   | Castration-resistant prostate cancer                                               | Erlotinib                                                                                             |
| Cabozantinib (XL184) | Efficacy         | II    | Stage IV NSCLC, EGFR wild-type                                                    | Erlotinib                                                                                             |
| Crizotinib (PF02341066) | Safety/efficacy | II    | Persistent or recurrent ovarian epithelial cancer, fallopial tube, or peritoneal   | Randomized vs paclitaxel                                                                             |
| Cabozantinib (XL184) | Efficacy         | II    | Adults with advanced soft tissue sarcoma                                           | Randomized vs paclitaxel                                                                             |

**Table 2. Clinical trials of hepatocyte growth factor (HGF)-MET inhibitors**
Table 2 (Continued)

| Drug                                      | Design     | Phase | Patient population                                                                 | Combinations                        |
|-------------------------------------------|------------|-------|------------------------------------------------------------------------------------|--------------------------------------|
| Volitinib savolitinib/AZD6094/HMPL-50     | Safety/PK  | I     | Advanced solid tumors                                                               |                                      |
| Rilotumumab (AMG 102)                     | Safety/efficacy | II/IIb | Japanese subjects with advanced solid tumors or advanced or metastatic gastric or esophagogastric junction adenocarcinoma |                                      |
| MSC2156119I/EMD1214063                    | Safety/efficacy | I     | Solid tumors                                                                       |                                      |
| Cabozantinib (XL184)                      | Efficacy   | II    | Castration-resistant prostate cancer with visceral metastases                       |                                      |
| Met RNA CAR T cells                       | Safety/efficacy | I     | Metastatic breast cancer, triple-negative breast cancer                              |                                      |
| Cabozantinib (XL184)                      | Safety/efficacy | III   | Subjects with metastatic renal cell carcinoma                                       | Randomized vs everolimus             |
| INCB28060 (INC280)                        | Safety/efficacy | Ib/II | Recurrent glioblastoma                                                              | Buparlisib                           |
| LY2875358                                 | Efficacy   | II    | Gastric cancer                                                                     | Erlotinib                            |
| Onartuzumab (MetMAb)                      | Safety/efficacy | III   | Met-positive, stage IIIb or IV NSCLC with activating EGFR mutation                  | Erlotinib                            |
| Onartuzumab (MetMAb)                      | Safety/PK  | Ib    | Advanced hepatocellular carcinoma                                                   | Alone or sorafenib                   |
| LY2875358                                 | Efficacy   | II    | NSCLC with activating EGFR mutations                                                | Erlotinib                            |
| LY2875358                                 | Efficacy   | II    | NSCLC                                                                              | Erlotinib                            |
| Cabozantinib (XL184)                      | Safety/efficacy | III   | Subjects with hepatocellular carcinoma who have received prior sorafenib treatment  | Randomized vs placebo                |
| INCB28060 (INC280)                        | Safety     | I     | Met-positive NSCLC                                                                  | Erlotinib                            |
| MGCD265                                   | Safety     | I     | Healthy subjects in fasting state                                                   |                                      |
| INCB28060 (INC280)                        | Safety/efficacy | II    | Advanced hepatocellular carcinoma after progression or sorafenib intolerance         |                                      |
| Onartuzumab (MetMAb)                      | Safety/PK  | Ib    | Advanced solid malignancies                                                         | Vemurafenib, and/or cobimetinib      |
| LY2801653                                 | PK/radiolabeled | I     | Healthy participants                                                               | Gefitinib                            |
| MSC2156119I                               | Safety/efficacy | I/Ii  | Advanced NSCLC                                                                     |                                      |
| MSC2156119I                               | Safety/efficacy | I/Ii  | Asian subjects with hepatocellular carcinoma                                       |                                      |
| Crizotinib (PF02341066)                   | Safety     | I     | Advanced solid tumors                                                               | Axitinib                             |
| AMG 337                                   | Efficacy   | II    | MET-amplified gastric/esophageal adenocarcinoma or other solid tumors               |                                      |
| INCB28060 (INC280)                        | Efficacy   | II    | Papillary renal cell carcinoma                                                      |                                      |
| Onartuzumab (MetMAb)                      | Safety/efficacy | I     | Chinese patients with locally advanced or metastatic solid tumors                  |                                      |
| Onartuzumab (MetMAb)                      | Efficacy   | III   | Met-positive, incurable stage IIIb or IV NSCLC                                      | Erlotinib                            |
| Foretinib (GSK1363089)                    | Efficacy   | II    | Genomic subpopulations of NSCLC                                                     |                                      |
| LY2875358                                 | Safety/efficacy | I/Ii  | Advanced cancer                                                                     | Ramucirumab                          |
| AMG 337                                   | Safety     | I/Ii  | Advanced solid tumor, gastric/esophageal adenocarcinoma or other solid tumors       |                                      |
| MSC2156119I                               | Safety/efficacy | I/Ii  | Second-line hepatocellular carcinoma                                                |                                      |
| Volitinib Savolitinib/AZD6094/HMPL-50     | Safety/efficacy | I/Ii  | Papillary renal cell cancer                                                         |                                      |
| Crizotinib (PF02341066)                   | Efficacy   | II    | Patients with stage IV NSCLC that has progressed after crizotinib treatment         | Pemetrexed disodium                  |
| Rilotumumab (AMG 102)                     | Efficacy   | III   | Gastric cancer                                                                     | Cisplatin and capcitabine vs placebo |
| Volitinib Savolitinib/AZD6094/HMPL-50     | Safety/efficacy | I/Ib  | EGFR mutation-positive advanced lung cancer                                          | AZD9291                              |
| INCB28060 (INC280)                        | Safety/efficacy/PK | I     | Squamous cell carcinoma of head and neck                                            | Cetuximab                            |
| INCB28060 (INC280)                        | Safety/efficacy/PK | I     | Metastatic colorectal cancer                                                        |                                      |
Experimental Cancer Therapeutics Targeting the HGF/MET Pathway

The prevalence of HGF/MET pathway activation in human malignancies has driven rapid growth in drug development programs. The most advanced agents currently under development as HGF/MET pathway inhibitors include mAbs directed at HGF and low molecular weight compounds that competitively antagonize ATP binding to MET (Table 2). Although some of the multi-kinase inhibitors that target MET have received regulatory approval in several indications, it remains unclear whether the MET kinase is a primary target. None of the more selective MET inhibitors have shown efficacy in phase II or III clinical trials, although few of these agents have reached this level of development.

### Table 2 (Continued)

| Drug                          | Design          | Phase | Patient population                                                                 | Combinations                                         |
|-------------------------------|-----------------|-------|-----------------------------------------------------------------------------------|-------------------------------------------------------|
| INC28060 (INC280)             | Safety/efficacy | II    | Chinese patients with advanced NSCLC                                              |                                                       |
| Ficlatuzumab (AV-299)         | Safety/efficacy | I     | Ficlatuzumab, cisplatin, and IMRT in locally advanced squamous cell carcinoma of the head and neck |                                                       |
| Ficlatuzumab (AV-299)         | Safety/efficacy | I     | Recurrent/metastatic squamous cell carcinoma of the head and neck                  |                                                       |
| SALT301                       | Safety          | I     | Subjects with advanced c-MET-positive solid tumors followed by expansion in selected tumor types |                                                       |
| AMG 337                       | Safety/efficacy | I/II  | Advanced stomach or esophageal cancer                                              | Fluorouracil, oxaliplatin, leucovorin               |
| Volitinib Savolitinib/        | Safety/PK/preliminary efficacy | I     | Recurrent/metastatic squamous cell carcinoma of the head and neck                  |                                                       |
| AZD6094/HMPL-50               | Safety/efficacy | II    | Advanced gastric adenocarcinoma patients with MET overexpression as a second-line treatment | Docetaxel                                             |
| Crizotinib (PF02341066)       | Safety/efficacy | II    | Advanced gastric adenocarcinoma patients with MET overexpression as a second-line treatment | Docetaxel                                             |
| Volitinib Savolitinib/        | Safety/efficacy | I     | Patients with MET-dysregulated advanced solid tumors                              | Midazolam, caffeine                                   |
| AZD6094/HMPL-50               | Safety/PK/preliminary efficacy | II    | Advanced gastric adenocarcinoma patients with MET overexpression as a second-line treatment |                                                       |
| Rilotumumab (AMG 102)         | Efficacy        | III   | Stage IV SCLC                                                                     |                                                       |
| INC280                        | Safety/efficacy | I     | Glioblastoma multiforme, gliosarcoma, colorectal cancer, renal cell carcinoma      |                                                       |
| Capmatinib (INC280)           | Safety          | I     | Malignant NSCLC with exon14 alteration                                             |                                                       |
| JNJ-38877605                  | Safety/efficacy | I     | Advanced or refractory solid tumors                                               |                                                       |
| SGX523                        | Safety/efficacy | I     | Advanced cancer                                                                   |                                                       |

Experimental therapeutics (left column) are listed by generic name or alphanumeric identifier. For brevity, this table lists only those trials not tabulated in a prior comprehensive review by Cecchi et al. A complete listing of trials with links to several relevant cancer information sources can be found online (https://ccrod.cancer.gov/confluence/display/CCRHGF/Home). ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HSP90, heat shock protein 90; IMRT, intensity-modulated radiation therapy; mFOLFOX6, 5-fluorouracil, leucovorin, oxaliplatin; NSCLC, non-small-cell lung cancer; PD, pharmacodynamics; PK, pharmacokinetics; SCLC, small-cell lung cancer.

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A recent topic in HGF/MET pathway inhibition is clinical studies in lung cancer patients with MET-\textit{exon14} alteration. Paik et al.\textsuperscript{14} reported that \textit{MET-exon14} mutation is approximately 4% of lung adenocarcinoma, and three out of four patients with stage IV lung adenocarcinomas harboring \textit{MET-exon14} mutation had a response to MET TKI. Among 38 028 cancer patients, \textit{MET-exon14} mutations were found in 221 cases, and \textit{MET-exon14} mutations are detected most frequently in lung adenocarcinoma (3%), but also frequently in other lung neoplasms (2.3%) and brain glioma (0.4%).\textsuperscript{15} In 11 205 lung cancers profiled by comprehensive genomic profiling, 298 (2.7%) carcinomas harbored \textit{MET-exon14} alterations.\textsuperscript{17} Eight patients harboring \textit{MET-exon14} showed controlled responses, including four cases with partial responses, two cases with complete responses, and two cases with stable disease.\textsuperscript{17} Among 1296 Chinese patients with NSCLC, 12 patients (0.9%) had \textit{MET-exon14} mutation, suggesting a difference in frequency by ethnicity.\textsuperscript{76} It is anticipated that ongoing clinical studies will reveal the significance of \textit{MET-exon14} alteration as a biomarker and therapeutic target for clinical use of HGF-MET inhibitors.

**Conclusions**

Therapeutic resistance and metastasis are major obstacles to achieving durable clinical responses with molecular-targeted therapies. Signaling pathways driven by HGF and MET participate in invasion, metastasis, and resistance to molecular-targeted drugs. Although selective MET inhibitors have yet shown efficacy in phase II and III clinical trials, ongoing clinical trials have indicated favorable response to MET inhibitors in patients with NSCLC expressing variant MET deleted within the JM domain. Biomarker discovery and the utilization of appropriate biomarkers to validate HGF-MET signaling as a driver in cancer development, metastasis, and drug resistance appears to be key for regulatory approval of HGF-MET inhibitors for clinical use.

Because HGF is biosynthesized as a zymogen-like single chain inactive precursor (capable of MET binding but incapable of MET activation) and the processing to two-chain HGF is coupled to its activation, the measurement and evaluation of HGF activation is also key to understanding the tumor microenvironment that permits tumor metastasis and drug resistance. In the future, elucidation of the 3-D structure(s) of the HGF-MET complex and the MET activation process will provide an opportunity to discover molecular tools applicable to sensitive and specific detection of activation of HGF and MET for diagnosis and evaluation of therapeutic.

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