Novel therapeutic target for head and neck squamous cell carcinoma: HGF-MET signaling pathway

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Head and neck squamous cell carcinoma (HNSCC) represents a devastating type of malignancy characterized by its high incidence of regional and distant metastases at the time of diagnosis. Vital physiological functions in the upper aerodigestive tract are often impaired as a result of the disease and treatment for the disease, giving rise to severe morbidity in patients suffering from this type of cancer. It is crucial to delineate the aberrant growth signaling pathways in HNSCC cells and develop specific target therapies for the disease to improve the treatment outcome. Although the epidermal growth factor receptor pathway has been extensively studied in HNSCC and anti-epidermal growth factor receptor therapy has already shown promise in treating HNSCC in phase III clinical trials, the signaling pathway that accounts for the highly invasive phenotype of HNSCC needs to be defined and also therapeutically targeted. The hepatocyte growth factor-MET signaling pathway has been studied extensively over the past two decades and it is now clear that it plays an important role in mediating invasive growth of many types of cancer. Here, we review comprehensively the evidence on hepatocyte growth factor-MET cascade being a key in the signaling pathway in mediating invasive growth of HNSCC and the potential of this signaling pathway to be a therapeutic target for the treatment of HNSCC. *Anti-Cancer Drugs* **22:665–673 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Cancers arising from the head and neck region give rise to severe morbidity as vital functions such as speech and swallowing become impaired. The majority of head and neck cancers develop from the squamous epithelium that lines the upper aerodigestive tract. Common sites in which head and neck squamous cell carcinomas (HNSCC) develop include the oral cavity, tongue, oropharynx, hypopharynx, larynx, and nasopharynx in endemic areas. Approximately two-thirds of the patients with HNSCC present with disease at an advanced stage with regional lymph node metastasis [1], and this disease causes 350 000 cancer deaths worldwide each year [2]. In the United States, carcinoma of the oral cavity and pharynx was ranked in the top ten leading cancer types among estimated new cancer cases among men as reported in Cancer Statistics, 2009 [3]. The most important etiological factors for the development of HNSCC are tobacco smoking and alcohol consumption [4], and in the past decade human papilloma virus has also been identified as associated with the development of a subset of HNSCC such as cancer of the oropharynx [5]. Traditional treatment for HNSCC was extensive surgery with a poor functional outcome. Radiotherapy allows organ preservation, and the addition of chemotherapy concurrent with radiotherapy improves survival when compared with radiotherapy alone. Advances have been made in elucidating the molecular signaling pathways that are important for the development of HNSCC. For example, the epidermal growth factor receptor (EGFR) of the tyrosine kinase family has been shown to be implicated in the growth of HNSCC and therapeutically targeted [6,7]. Anti-EGFR therapy has shown a promising efficacy when combined with cytotoxic chemotherapy in treating advanced HNSCC [8]. The hepatocyte growth factor (HGF)-MET signaling cascade is another important cell signaling pathway for the development of HNSCC. There is now extensive evidence showing that this pathway could be a driving force for the invasive growth and early metastatic potential of HNSCC, and hence therapy targeting this pathway could be of great value in treating this devastating malignancy.

Molecular biology of the HGF-MET signaling pathway

HGF, also known as scatter factor, is a 90-kDa glycoprotein secreted by mesenchymal cell as an inactive single-chain polypeptide, which is then cleaved to its active heterodimer form by proteases [9]. MET is the transmembrane cell surface receptor for HGF [10,11]. Like HGF, the MET receptor is also a disulfide-linked heterodimer. The α-chain is heterodimerized to the amino-terminal of the β-chain and forms the major

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ligand-binding site in the extracellular domain of the receptor. HGF binding induces MET receptor homodimerization and phosphorylation of two tyrosine residues (Y1234 and Y1235) within the intracellular tyrosine kinase domain that activates its catalytic activity [12]. The carboxy-terminal of the β-chain harbors two other tyrosine residues (Y1349 and Y1356), which serve as docking sites for intracellular adaptor proteins when phosphorylated [13,14]. A variety of adaptor proteins including Grb2, SHC, and Gab1 mediate further downstream signaling by other downstream effectors [15]. HGF was first purified from human plasma and rat serum on the basis of its ability to stimulate growth of rat hepatocytes. It was found to be present in the plasma of man with fulminant hepatic failure and plasma of partially hepatectomized rats, which likely acts as a humoral factor for liver regeneration [16–18]. HGF was also purified from the human fibroblast culture medium and shown to act as a paracrine mediator of proliferation on a variety of epithelial cells and endothelial cells [19]. Although HGF expression is predominantly found in the fibroblasts and stromal cells in the mesenchyme of the mouse embryo, MET expression is predominantly found in cells of epithelial origin, and a paracrine mechanism of HGF-MET signaling exists between mesenchymal cells and epithelial cells during the development [20]. In particular, HGF-MET signaling could play a role in mediating epithelial cells to form lumen-like structures [21]. This pathway has normal physiological functions in regulating the embryonic development of a variety of organs including the kidney [22,23], mammary gland [24,25], muscle [26], neural tissues [27], and liver [28]. It also promotes angiogenesis [29,30] and facilitates wound healing [31].

HGF-MET signaling pathway and cancer development

MET and/or HGF expression has been found in many human cancers including carcinoma, sarcoma, and hematological malignancy, and is often associated with worse prognosis [9]. The HGF-MET signaling pathway has been shown to play an important role in causing cancer development and invasion in different animal and human cell line model systems [32]. Mouse and human cell lines that ectopically overexpress HGF and/or MET become tumorigenic and metastatic in athymic nude mice [33,34], while mouse models that express the receptor or ligand as a transgene develop different types of tumor and metastatic lesions [35–37]. Upon MET inhibition, either by small-hairpin RNA or small-molecule inhibitor, a decrease in the cell growth and viability was observed in a variety of cancer cells [38–40]. Amplification of the *MET* gene with consequent overexpression of the protein product has been reported in gastric and esophageal carcinomas [41–43], non-small-cell lung carcinomas (NSCLC) that have acquired resistance to EGFR inhibition [44], and liver metastasis from primary colorectal carcinoma [45]. Activating *MET* gene mutation has been detected in hereditary and sporadic papillary renal cell carcinoma [46] and gastric carcinoma [47]. Autocrine mechanism of the HGF-MET pathway activation with coexpression of HGF-MET in cancer cells has been described in glioma [48], breast carcinoma [49], and osteosarcoma [50]. The fact that HGF is frequently found to be expressed in the stroma of cancer cells suggests that a paracrine circuit could also operate in activating the HGF-MET signaling pathway in cancer cells [9]. It is interesting to note that other oncogenes such as activated Ras can induce MET overexpression through transcriptional mechanisms [51,52], suggesting that MET activation can also be a secondary event in promoting carcinogenesis in cancer cells.

HGF-MET signaling pathway and cancer invasion

In addition to promoting cell growth, dysregulated HGF-MET signaling also enhances the invasiveness and metastatic potential of malignant cells. A high level of MET expression was detected in human sarcoma, a malignancy with high metastatic potential [53,54]. An autocrine model of HGF-MET signaling in NIH 3T3 cells was shown to increase cell motility, collagenase activity, invasiveness *in vitro* and metastatic activity *in vivo* [33,55]. In the pleural fluid of patients whose cancer had metastasized to the pleura, a significant amount of HGF has been detected [56]. The molecular basis by which HGF-MET signaling enhances this invasive and metastatic phenotype is likely due to the increase in the level of cell proteases such as urokinase plasminogen activator, which mediates dissolution of the extracellular matrix and the basement membrane [57]. Moreover, HGF-MET signaling can induce several epithelial and mesenchymal cell types to undergo branching morphogenesis when the cells proliferate, migrate, and differentiate to form a connected series of tubules arranged like tree branches in a three-dimensional matrix [58–60]. Hypoxia-induced HGF-MET signaling model has been put forward [61]. In this model, hypoxia in the tumor mass induces HGF production in the stromal cells and MET expression in the cancer cells. This results in a paracrine HGF-MET signaling circuit, which can induce cancer cells to release protease to degrade the extracellular matrix and also factors that enhance angiogenesis, which helps to confer survival advantage to cancer cells under hypoxic stress when cells start to migrate, metastasize, and form new colonies for further proliferation and survival. In fact, the malignant property of cancer cells is further enhanced by the activity of the MET pathway in endothelial cells. HGF has been shown to promote endothelial cell growth and motility and is a potent angiogenic factor [29]. Sustained plasma levels of a MET inhibitor not only retard the growth of MET-positive xenografts, but also that of MET-negative tumor cells, indicating that a MET inhibitor could exert its effect by

inhibition of other mechanisms such as angiogenesis [62]. The Ras-mitogen-activated protein kinase (MAPK) signaling cascade, which operates as downstream effectors for the activated MET receptor, plays an essential role in cancer cell invasion by inducing epithelial-to-mesenchymal transition as a result of loss of intracellular adhesion by cadherins [63].

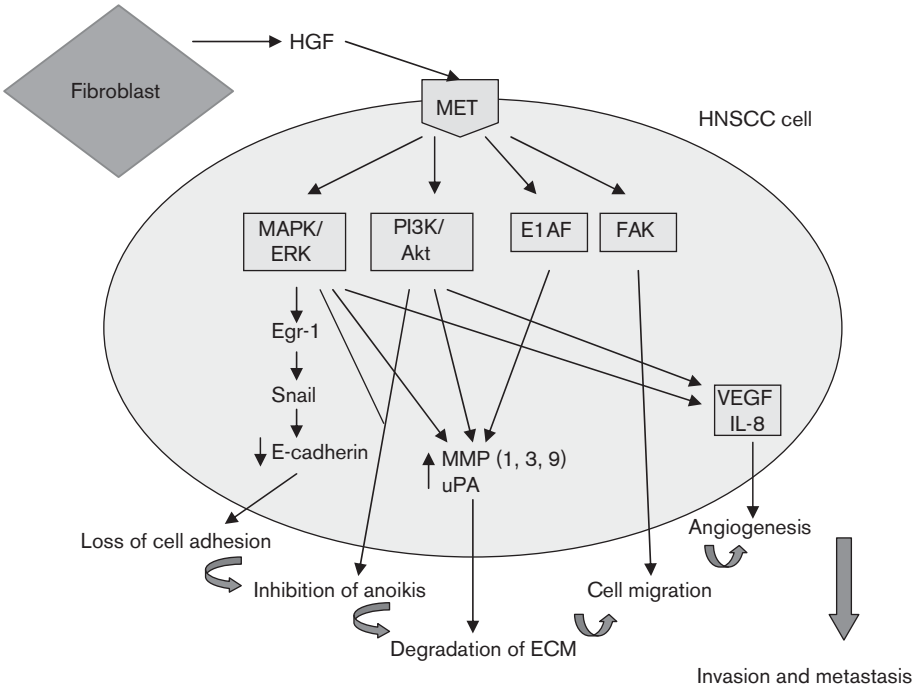
HGF-MET signaling pathway in head and neck squamous cell carcinoma

HNSCC is a highly invasive type of cancer, which often presents at an advanced stage of disease. Therefore, the HGF-MET signaling pathway, which is known to drive cancer cells to acquire an invasive phenotype, has become a major area of research on HNSCC in the past two decades. Carcinoma cells need to detach from the primary tumor mass, survive anoikis (a process in which cells undergo apoptosis when detached from its adjacent epithelium), undergo epithelial–mesenchymal transition, degrade the extracellular matrix and migrate through it, and form new blood vessels to colonize distant sites. It is now clear that the HGF-MET signaling pathway plays a role in all these steps that lead HNSCC cells to migrate and metastasize. Overexpression of the MET receptor protein has been shown in nearly all types of HNSCC, including cancer of the oral cavity, hypopharynx, and larynx, which often correlates with more advanced clinical stage especially the nodal stage [64–67]. MET expression in HNSCC is also associated with worse survival rate [68], and inferior response to both radiotherapy and chemotherapy [69,70]. Apart from the primary tumor, MET expression has also been consistently found in metastatic lymph nodes of HNSCC [71–74]. Activating mutations have been detected in the *MET* gene in the metastatic lymph nodes of HNSCC, and transfection of the mutant receptor confers invasive phenotype to cancer cells *in vitro* [75]. These observations suggest that the MET pathway could be implicated in nodal progression of HNSCC.

When HNSCC cell lines are treated with HGF *in vitro*, a dose-dependent increase in invasiveness was observed in cancer cells [76–78]. Cancer cells invade and migrate through its surrounding extracellular matrix in response to the stimulation of HGF by phosphorylation of focal adhesion kinase, which is a crucial signaling protein that is activated by numerous stimuli and functions as a biosensor or integrator to control cell motility. In oral SCC cell lines, it was found that gingival fibroblasts, rather than carcinoma cells, secrete large amount of HGF, and serum HGF level was also higher in patients with oral SCC when compared with normal individuals [79]. Hence, it is possible that HGF mediates its effect on HNSCC cancer cells by a paracrine mechanism. HGF decreases E-cadherin expression and induces E-cadherin translocation from the cell membrane to the cytoplasm in HNSCC cell lines [80], and it is known that the disruption of E-cadherin-mediated cell-to-cell adhesion will result in cancer cell invasion [81]. Therefore, HGF could mediate cancer invasion by its effect on E-cadherin, an important cell adhesion molecule, causing cancer cells to detach from their primary site. It has been shown that in HNSCC cell lines HGF-induced upregulation of the transcription factor, snail through the mitogen-activated protein kinase-Egr-1 signaling pathways, and snail, in turn, repressed the expression of E-cadherin [82]. Snail is required for HGF-induced cell scattering as small-hairpin RNA-mediated ablation of the snail expression prevented this process. A reverse correlation of E-cadherin and snail expression was also observed in HNSCC cell line [83]. Snail is implicated in the differentiation and transition of epithelial cells into mesenchymal cells during the embryonic development [84], and epithelial cells that ectopically express snail adopt a fibroblastoid phenotype with the acquisition of tumorigenic and invasive properties [85]. Snail has been shown to induce SCC cell lines to undergo transition of epithelial cells into mesenchymal cells, a process essential for invasiveness [86].

On loss of contact with the extracellular matrix, HNSCC cells undergo cell death (anoikis). HGF was found to protect HNSCC cells against anoikis, a process dependent on the extracellular signal-mediated protein kinase-Akt signaling pathways, as inhibition of the extracellular signal-mediated protein kinase-Akt pathways abolished the protective effect of HGF [87]. HGF also activates the extracellular signal-regulated protein kinase-Akt pathways to enhance the activity of matrix metalloproteinase (MMP)-9 and urokinase-type plasminogen activator, enzymes that degrade the extracellular matrix and facilitate cell migration [88]. In a highly invasive oral SCC cell line, HGF stimulated the expression of the Ets-oncogene family transcription factor E1AF and the treated cells also express higher levels of MMP-1, MMP-3, and MMP-9 [89]. When the cell line was transfected with the E1AF antisense expression vector, mRNA and protein levels of MMP-1, MMP-3, and MMP-9 decreased and the transfected cells also showed lower invasive potential [90]. These observations suggest that HGF induces HNSCC cells to express protein enzymes that degrade the extracellular matrix through the activation of E1AF, which is also an essential process for invasiveness. Finally, it has been shown that in HNSCC cell lines, HGF increased the production of angiogenic factors, interleukin-8 and vascular endothelial growth factor (VEGF) by cancer cells in a dose-dependent manner. Increased serum HGF level also correlated with higher levels of interleukin-8 and VEGF in patients with HNSCC [91,92]. Therefore, HGF could also mediate HNSCC hematological spread by its effect on cancer angiogenesis. As there is now abundant evidence suggesting that the HGF-MET signaling pathway is important in mediating invasive growth of HNSCC, this pathway has now become an attractive therapeutic target for drug development in treating HNSCC (Fig. 1).

Fig. 1



Schematic diagram showing the hepatocyte growth factor (HGF)-MET signaling pathway in mediating invasive growth of head and neck squamous cell carcinoma (HNSCC). MET activation could be ligand dependent from HGF secreted by surrounding fibroblast or ligand independent. Phosphorylated MET protein activates mitogen-activated protein kinase (MAPK)/extracellular signal-mediated protein kinase (ERK) and the phosphoinositide 3-kinases (PI3K)/Akt pathways in mediating loss of cell adhesion, inhibition of anoikis, production of proteolytic enzymes that degrade the extracellular matrix (ECM), and production of angiogenic factors [vascular endothelial growth factor (VEGF)/interleukin-8 (IL-8)] to promote cell invasion and metastasis by further downstream signaling/transcriptional mechanisms. MET also activates focal adhesion kinase (FAK) in promoting cell migration through the ECM. MMP, matrix metalloproteinase.

HGF-MET signaling pathway in nasopharyngeal carcinoma

Nasopharyngeal carcinoma (NPC) is a specific type of head and neck carcinoma that is endemic in South East Asia, especially in the Cantonese-speaking Chinese population residing in the southern part of China. Like other HNSCC, NPC is characterized by its invasive phenotype with high frequency of metastases to regional lymph nodes or distant organs at the time of diagnosis. It is also characterized by its high chemosensitivity [93]. Three types of NPC are recognized by the World Health Organization: type I, differentiated, keratinizing squamous cell carcinoma; type II, nonkeratinizing carcinoma; and type III, undifferentiated carcinoma, with type III accounting for the majority (95%) of NPCs in Southern China and Hong Kong. The World Health Organization type III NPC is nearly always associated with Epstein-Barr virus (EBV) infection. The expression of EBV-encoded viral oncoproteins, such as latent membrane protein-1 (LMP-1), promotes tumor cell growth and survival advantage [94]. MET expression in NPC cells has been reported in two major studies [95,96], and the association of MET expression with cervical lymph node metastases, more advanced clinical stage and poorer survival was also shown. HGF was mainly detected in the normal interstitial tissue surrounding the tumor, suggesting that MET signaling in NPC could act through a paracrine mechanism. The expression of LMP-1, transcription factor Ets-1, and MET correlated significantly in NPC cells, and transfection of LMP-1 expressing plasmid in an experimental model induced MET protein expression. Induction of MET expression by LMP-1 was suppressed by introducing a dominant negative form of Ets-1 in the LMP-1-expressing cells [96]. Transformation of epithelial cells is carried out by EBV, LMP-1-induced Ets-1 expression, and cell invasion [97]. These results suggest that in NPC, the EBV-encoded oncoprotein LMP-1 could upregulate the expression of MET protein by the transcription factor Ets-1, and MET is further activated by HGF produced by stromal cells in the surrounding interstitium in mediating cancer development.

Cancer drug treatment targeting the HGF-MET signaling pathway

In view of the large amount of evidence showing the importance of the HGF-MET signaling pathway in mediating invasive growth of different types of malignancy in the past two decades, multiple strategies have been

developed to inhibit this signaling pathway for cancer treatment. These include biological antagonists and decoy molecules, monoclonal antibodies, and small-molecule tyrosine kinase inhibitors (TKIs). Table 1 shows a list of drugs that target the HGF-MET signaling pathway in cancer. Although biological antagonists and decoy molecules are still at the stage of preclinical development [62,98], both monoclonal antibodies and small-molecule TKIs have already entered phase I and phase II clinical trials. AMG102 is a fully human IgG monoclonal antibody that selectively binds and neutralizes HGF, thereby preventing its binding to MET and subsequent activation [99,100]. An acceptable safety profile was shown in phase I and II clinical trials [101,102]. AMG102 has been shown to enhance the effects of various standard chemotherapeutic agents such as temozolomide and docetaxel *in vitro* and in tumor xenografts [103]. A phase I study on AMG102 in combination with antiangiogenetic agents such as bevacizumab or motesanib showed a best response of stable disease in eight out of 10 patients without dose-limiting toxicity [104]. MetMAb (OA5D5) is a humanized, monovalent anti-MET antibody, which binds to MET receptor with high affinity preventing HGF binding and subsequent pathway activity. It has shown potent effect in glioblastoma harboring MET-activating mutation in preclinical model [105]. The phase I clinical trial confirmed that MetMAb is safe and well tolerated as a single agent at doses up to 30 mg/kg [106].

As MET-pathway activation can be ligand dependent or independent, theoretically the most effective strategy in inhibiting this pathway in cancer cells is to inhibit the tyrosine kinase activity of the MET receptor thereby preventing the activation of its downstream signaling cascade. This led to the development of many small-molecule TKIs, which have nowadays entered phase I and phase II clinical trials. Some of these small-molecule TKIs are selective MET inhibitors (ARQ197, JNJ-38877605, and PF-04217903) while a few others are broad-spectrum TKIs that have inhibitory effects against other tyrosine kinase families (PF-02341066, XL880, XL184, MP470, MGCD265, and MK-2461). Early results are available for ARQ197, a highly selective MET inhibitor, which has shown a favorable safety profile and preliminary anticancer activity in advanced solid tumors in phase I trial [107]. PF-02341066 is a multitargeted TKI with activity against both MET and anaplastic lymphoma kinase. It has a potent inhibitory effects on MET-dependent proliferation, migration, and invasion of human tumor cells, and HGF-stimulated endothelial cell survival *in vitro* [110,111]. It also has a preferentially greater potent effect on cellular assays with specific MET mutation. In a phase I trial, PF-02341066 showed a manageable toxicity profile and promising clinical activity against advanced tumors carrying an activating anaplastic lymphoma kinase gene rearrangement [112]. XL880 is another multitargeted TKI that has high affinity for both MET and VEGFR. It has shown inhibition of tumor cell growth, invasion, metastasis, and angiogenesis in a preclinical model [113]. XL880 has good oral bioavailability and a manageable toxicity profile in phase I trials evaluating its effects on advanced solid tumors. Fifteen out of 41 treated patients achieved disease control with the longest response over 54 months [114–116]. Phase II trials are ongoing. There are at least two other selective MET inhibitors (JNJ-38877605 and PF-04217903) [108,109] and four other broad-spectrum multitargeted TKIs against MET in the ongoing phase I clinical trials (XL184, MP470, MGCD265, and MK-2461) [117–122].

Table 1 Classes of therapies that target the HGF-MET signaling pathway for cancer treatment and their stages of development

Class of drug that targets HGF-MET signaling pathway	Examples (stage of development)
HGF-MET biological antagonists	NK4 (preclinical) [98] Decoy MET molecule (preclinical) [62]
Monoclonal antibodies against HGF	AMG102 (phase I/II) [99–104]
Monoclonal antibodies against MET	MetMAb/OA5D5 (phase I) [105,106]
Small-molecule MET tyrosine kinase inhibitors (selective)	ARQ197 (phase I/II) [107] JNJ-38877605 (phase I) [108] PF-04217903 (phase I) [109]
Small-molecule MET tyrosine kinase inhibitors (broad-spectrum multikinase inhibitors)	PF-02341066 (phase I/II) [110–112] XL880 (phase I/II) [113–116] XL184 (phase I) [117–119] MP470 (phase I) [120] MGCD265 (phase I) [121] MK-2461 (phase I) [122]

HGF, hepatocyte growth factor.

In a preclinical model, invasion of HNSCC cells induced by HGF derived from tumor-associated fibroblasts was completely blocked by a HGF-neutralizing antibody, and the MET inhibitor PF-02341066 was able to cause a 50% decrease in HNSCC tumor growth *in vitro* with increased apoptosis within the tumors [123]. In another study, MET inhibition with small-molecule TKI SU11247 and PF-02341066 disrupted MET signaling, cell viability, motility, and migration *in vitro*, and tumor angiogenesis in xenograft of HNSCC. Interestingly, a greater-than-additive inhibitory effect on HNSCC cell growth was seen when the MET inhibitor was combined with the chemotherapeutic agent cisplatin or the EGFR-1 inhibitor erlotinib, and synergy was postulated to be mediated by EGFR-3 signaling [124]. In fact, in such MET-EGFR pathways cross-talk has been shown in NSCLC, in which MET amplification causes resistance to EGFR-1 blockade by activating EGFR-3 signaling [125]. MET and Src have been implicated in cooperating as mediators of EGFR tyrosine phosphorylation and cell growth in the presence of EGFR inhibitors [126], and the combination of the MET inhibitor and the EGFR

inhibitor erlotinib more potently inhibited NSCLC xenograft tumor growth in mice compared with either agent alone [127]. In other preclinical models, the triple combination of MET, EGFR, and VEGF inhibition resulted in more potent antitumor effects than any two agents alone [128], and the addition of an inhibitor of mammalian target of rapamycin reversed anti-EGFR resistance by MET inhibition [129]. Phase I clinical trial evaluating the effect of dual MET and EGFR blockade by TKI in NSCLC is ongoing [130]. MET amplification has been identified as a biomarker predictive of treatment sensitivity to MET inhibitor in epithelial cancers [131]. Further clinical studies on the effect of MET inhibition *in vivo* and biomarker predictive of response in HNSCC are much needed given the large amount of preclinical evidence showing its efficacy *in vitro* and promising results in early phase clinical studies on MET inhibition in other types of solid tumors.

Conclusion and perspectives

The role of the HGF-MET signaling pathway in promoting cancer growth, invasion, and metastases is now well established from numerous preclinical data. It has become an attractive pathway to study in cancers that are characterized by highly invasive phenotypes, such as HNSCC and NPC. Abundant evidence from preclinical models has shown that this pathway plays an important role in the invasive growth of HNSCC, and hence this pathway represents a promising novel therapeutic target in developing drug treatment for HNSCC. There are now many different drugs that target the HGF-MET signaling pathway in advanced solid tumors in phase I and phase II clinical trials, and it is anticipated that these drugs will be tested in HNSCC in clinical studies. Biomarkers predictive of response to HGF-MET pathway inhibition will also be needed to select patients who will most likely benefit from targeted treatment for this devastating malignancy.

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References

1 Ries LAG, Melbert D, Krapcho M, Mariotto A, Miller BA, Feuer EJ, *et al.* editors. SEER cancer statistics review 1975–SEER cancer statistics review 2004. Bethesda, MD: National Cancer Institute; 2006.

2 Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**:74–108.

3 Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics 2009. *CA Cancer J Clin* 2009; **59**:225–249.

4 Argiris A, Eng C. Epidemiology, staging, and screening of head and neck cancer. *Cancer Treat Res* 2003; **114**:15–60.

5 D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM, *et al.* Case–control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med* 2007; **356**:1944–1956.

6 Karamouzis MV, Grandis JR, Argiris A. Therapies directed against epidermal growth factor receptor in aerodigestive carcinomas. *JAMA* 2007; **298**:70–82.

7 Grandis JR, Tweardy DJ. Elevated levels of transforming growth factor alpha and epidermal growth factor receptor messenger RNA are early markers of carcinogenesis in head and neck cancer. *Cancer Res* 1993; **53**:3579–3584.

8 Vermorken J, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, *et al.* Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 2008; **359**:1116–1127.

9 Birchmeier C, Birchmeier W, Gheradi E, Van Woude GF. Met, metastasis, motility and more. *Nat Rev Mol Cell Biol* 2003; **4**:915–925.

10 Cooper CS, Park M, Blair DG, Tainsky MA, Huebner K, Croco CM, *et al.* Molecular cloning of a new transforming gene from a chemically transformed human cell line. *Nature* 1984; **311**:29–33.

11 Bottaro DP, Rubin JS, Faletto DL, Chan AM, Kmiecik TE, Vande Woude GF, *et al.* Identification of the hepatocyte growth factor receptor as the c-met protooncogene product. *Science* 1991; **251**:802–804.

12 Longati P, Bardelli A, Ponzetto C, Naldini L, Comoglio PM. Tyrosines 1234-1235 are critical for activation of the tyrosine kinase encoded by the MET protooncogene (HGF receptor). *Oncogene* 1994; **9**:49–57.

13 Ponzetto C, Bardelli A, Maina F, Longati P, Panayotou G, Dhand R, *et al.* A novel recognition motif for phosphatidylinositol 3-kinase binding mediates its association with the hepatocyte growth factor/scatter factor receptor. *Mol Cell Biol* 1993; **13**:4600–4608.

14 Ponzetto C, Bardelli A, Zhen Z, Maina F, dalla Zonca P, Giordano S, *et al.* A multifunctional docking site mediates signaling and transformation by the hepatocyte growth factor/scatter factor receptor family. *Cell* 1994; **77**:261–271.

15 Furge KA, Zhang YW, Vande Woude G. Met receptor tyrosine kinase: enhanced signaling through adaptor proteins. *Oncogene* 2000; **19**:5582–5589.

16 Michalopoulos G, Houck KA, Dolan ML, Leutteke NC. Control of hepatocyte replication by two serum factors. *Cancer Res* 1984; **44**:4414–4419.

17 Nakamura T, Nawa K, Ichihara A. Partial purification and characterization of hepatocyte growth factor from serum of hepatectomized rats. *Biochem Biophys Res Commun* 1984; **122**:1450–1459.

18 Gohda E, Tsubouchi H, Nakayama H, Hirono S, Sakiyama O, Takahashi K, *et al.* Purification and partial characterization of hepatocyte growth factor from plasma of a patient with fulminant hepatic failure. *J Clin Invest* 1988; **81**:414–419.

19 Rubin JS, Chan AM, Bottaro DP, Burgess WH, Taylor WG, Cech AC, *et al.* A broad-spectrum human lung fibroblast-derived mitogen is a variant of hepatocyte growth factor. *Proc Natl Acad Sci U S A* 1991; **88**:415–419.

20 Sonnenberg E, Weider KM, Birchmeier C. Expression of the MET-receptor and its ligand, HGF-SF during mouse embryogenesis. *EXS* 1993; **65**:381–394.

21 Tsarfaty I, Resau JH, Rulong S, Keydar I, Faletto DL, Vande Woude GF. The met proto-oncogene receptor and lumen formation. *Science* 1992; **257**:1258–1261.

22 Santos O, Barros E, Yang XM, Matsumoto K, Nakamura T, Park M, *et al.* Involvement of hepatocyte growth factor in kidney development. *Dev Biol* 1994; **163**:525–529.

23 Woolf AS, Kolatsi-Joannou M, Hardman P, Andermarcher E, Moorby C, Fine LG, *et al.* Roles of hepatocyte growth factor/scatter factor and the met receptor in the early development of the metanephros. *J Cell Biol* 1995; **128**:171–184.

24 Soriano JV, Pepper MS, Nakamura T, Orci L, Montesano R. Hepatocyte growth factor stimulates extensive development of branching duct-like structures by cloned mammary gland epithelial cells. *J Cell Sci* 1995; **108**:413–430.

25 Yang Y, Spitzer E, Meyer D, Sachs M, Niemann C, Hartmann G, *et al.* Sequential requirement of hepatocyte growth factor and neuregulin in the morphogenesis and differentiation of the mammary gland. *J Cell Biol* 1995;**131**:215–226.

26 Bladt F, Riethmacher D, Isenmann S, Aguzzi A, Birchmeier C. Essential role for the c-met receptor in the migration of myogenic precursor cells into the limb bud. *Nature* 1995; **376**:768–771.

27 Streit A, Stern CD, Thery C, Ireland GW, Aparicio S, Sharpe MJ, *et al.* A role for HGF/SF in neural induction and its expression in Hensen's node during gastrulation. *Development* 1995; **121**:813–824.

28 Schmidt C, Bladt F, Goedecke S, Brinkmann V, Zschiesche W, Sharpe M, *et al.* Scatter factor/hepatocyte growth factor is essential for liver development. *Nature* 1995; **373**:699–702.

29 Bussolino F, Di Renzo MF, Ziche M, Bocchietto E, Olivero M, Naldini L, *et al.* Hepatocyte growth factor is a potent angiogenic factor, which stimulates endothelial cell motility and growth. *J Cell Biol* 1992; **119**:629–641.

30 Grant DS, Kleinman HK, Goldberg ID, Bhargava MM, Nickoloff BJ, Kinsella JL, *et al.* Scatter factor induces blood vessel formation *in vivo*. *Proc Natl Acad Sci U S A* 1993; **90**:1937–1941.

31 Nusrat A, Parkos CA, Bacarra AE, Godowski PJ, Delp-Archer C, Rosen EM, *et al.* Hepatocyte growth factor/scatter factor effects on epithelia. Regulation of intercellular junctions in transformed and nontransformed cell lines, basolateral polarization of c-met receptor in transformed and natural intestinal epithelia. *J Clin Invest* 1994; **93**:2056–2065.

32 Jeffers M, Rong S, Vande Woude GF. Hepatocyte growth factor/scatter factor-Met signaling in tumorigenicity and invasion/metastasis. *J Mol Med* 1996; **74**:505–513.

33 Rong S, Segal S, Anver M, Resau JH, Vande Woude GF. Invasiveness and metastasis of NIH3T3 cells induced by Met-hepatocyte growth factor/scatter factor autocrine stimulation. *Proc Natl Acad Sci U S A* 1994; **91**:4731–4735.

34 Bellusci S, Moens G, Gaudino G, Comoglio P, Nakamura T, Thiery JP, *et al.* Creation of an hepatocyte growth factor/scatter factor autocrine loop in carcinoma cells induces invasive properties associated with increased tumorigenicity. *Oncogene* 1994; **9**:1091–1099.

35 Liang TJ, Reid AE, Xavier R, Cardiff RD, Wang TC. Transgenic expression of tpr-met oncogene leads to development of mammary hyperplasia and tumors. *J Clin Invest* 1996; **97**:2872–2877.

36 Takayama H, LaRochelle WJ, Sharp R, Otsuka T, Kriebel P, Anver M, *et al.* Diverse tumorigenesis associated with aberrant development in mice overexpressing hepatocyte growth factor/scatter factor. *Proc Natl Acad Sci U S A* 1997; **94**:701–706.

37 Wang R, Ferrell LD, Faouzi S, Maher JJ, Bishop JM. Activation of the Met receptor by cell attachment induces and sustains hepatocellular carcinomas in transgenic mice. *J Cell Biol* 2001; **153**:1023–1034.

38 Shinomiya N, Gao CF, Xie Q, Gustafson M, Waters DJ, Zhang YW, *et al.* RNA interference reveals that ligand-independent Met activity is required for tumor cell signaling and survival. *Cancer Res* 2004; **64**:7962–7970.

39 Ma PC, Jagadeeswaran R, Jagadeesh S, Tretiakova MS, Nallasura V, Fox EA, *et al.* Functional expression and mutations of c-Met and its therapeutic inhibition with SU11274 and small interfering RNA in nonsmall cell lung cancer. *Cancer Res* 2005; **65**:1479–1488.

40 Lutterbach B, Zeng Q, Davis LJ, Hatch H, Hang G, Kohl NE, *et al.* Lung cancer cell lines harboring MET gene amplification are dependent on Met for growth and survival. *Cancer Res* 2007; **67**:2081–2088.

41 Houldsworth J, Cordon-Cardo C, Ladanyi M, Kelsen DP, Chaganti RS. Gene amplification in gastric and esophageal adenocarcinomas. *Cancer Res* 1990; **50**:6417–6422.

42 Hara T, Ooi A, Kobayashi M, Mai M, Yanagihara K, Nakanishi I. Amplification of c-myc, K-sam, and c-met in gastric cancers: detection by fluorescence in-situ hybridization. *Lab Invest* 1998; **78**:1143–1153.

43 Miller CT, Lin L, Casper AM, Lim J, Thomas DG, Orringer MB, *et al.* Genomic amplification of MET with boundaries within fragile site FRA7G and upregulation of MET pathways in esophageal adenocarcinoma. *Oncogene* 2006; **25**:409–418.

44 Bean J, Brennan C, Shih JY, Riely G, Viale A, Wang L, *et al.* MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib. *Proc Natl Acad Sci U S A* 2007; **104**:20932–20937.

45 Di Renzo MF, Olivero M, Giacomini A, Porte H, Chastre E, Mirossay L, *et al.* Overexpression and amplification of the met/HGF receptor gene during the progression of colorectal cancer. *Clin Cancer Res* 1995; **1**:147–154.

46 Schmidt L, Duh FM, Chen F, Kishida T, Glenn G, Choyke P, *et al.* Germ line and somatic mutations in the tyrosine kinase domain of the MET protooncogene in papillary renal carcinomas. *Nat Genet* 1997; **16**:68–73.

47 Lee JH, Han SU, Cho H, Jennings B, Gerrard B, Dean M, *et al.* A novel germ line juxtamembrane Met mutation in human gastric cancer. *Oncogene* 2000; **19**:4947–4953.

48 Koochekpour S, Jeffers M, Rulong S, Taylor G, Klineberg E, Hudson EA, *et al.* Met and hepatocyte growth factor/scatter factor expression in human gliomas. *Cancer Res* 1997; **57**:P5391–P5398.

49 Tuck AB, Park M, Sterns EE, Boag A, Elliott BE. Coexpression of hepatocyte growth factor and receptor (Met) in human breast carcinoma. *Am J Pathol* 1996; **148**:225–232.

50 Ferracini R, Di Renzo MF, Scotlandi K, Baldini N, Olivero M, Lollini P, *et al.* The Met/HGF receptor is over-expressed in human osteosarcomas and is activated by either a paracrine or an autocrine circuit. *Oncogene* 1995; **10**:739–749.

51 Furge KA, Kiewlich D, Le P, Vo MN, Faure M, Howlett AR, *et al.* Suppression of ras-mediated tumorigenicity and metastasis through inhibition of the Met receptor tyrosine kinase. *Proc Natl Acad Sci U S A* 2001; **98**:10722–10727.

52 Ivan M, Bond JA, Prat M, Comoglio PM, Wynford-Thomas D. Activated ras and ret oncogenes induce over-expression of c-met (hepatocyte growth factor receptor) in human thyroid epithelial cells. *Oncogene* 1997; **14**:2417–2423.

53 Rong S, Jeffers M, Resau JH, Tsarfaty I, Oskarsson M, Vande Woude GF. Met expression and sarcoma tumorigenicity. *Cancer Res* 1993; **53**:5355–5360.

54 Rong S, Donehower LA, Hansen MF, Strong L, Tainsky M, Jeffers M, *et al.* Met proto-oncogene product is overexpressed in tumors of p53-deficient mice and tumors of Li-Fraumeni patients. *Cancer Res* 1995; **55**:1963–1970.

55 Giordano S, Zhen Z, Medico E, Gaudino G, Galimi F, Comoglio PM. Transfer of motogenic and invasive response to scatter factor/hepatocyte growth factor by transfection of human MET protooncogene. *Proc Natl Acad Sci U S A* 1993; **90**:649–653.

56 Kenworthy P, Dowrick P, Baillie-Johnson H, McCann B, Tsubouchi H, Arakaki N, *et al.* The presence of scatter factor in patients with metastatic spread to the pleura. *Br J Cancer* 1992; **66**:243–247.

57 Jeffers M, Rong S, Vande Woude GF. Enhanced tumorigenicity and invasion-metastasis by hepatocyte growth factor/scatter factor-met signaling in human cells concomitant with induction of the urokinase proteolysis network. *Mol Cell Biol* 1996; **16**:1115–1125.

58 Brinkmann V, Foroutan H, Sachs M, Weidner KM, Birchmeier W. Hepatocyte growth factor/scatter factor induces a variety of tissue-specific morphogenic programs in epithelial cells. *J Cell Biol* 1995; **131**:1573–1586.

59 Montesano R, Matsumoto K, Nakamura T, Orci L. Identification of a fibroblast-derived epithelial morphogen as hepatocyte growth factor. *Cell* 1991; **67**:901–908.

60 Niemann C, Brinkmann V, Spitzer E, Hartmann G, Sachs M, Naundorf H, *et al.* Reconstitution of mammary gland development *in vitro*: requirement of c-met and c-erbB2 signaling for branching and alveolar morphogenesis. *J Cell Biol* 1998; **143**:533–545.

61 Knudsen BS, Vande Woude G. Showering c-MET-dependent cancers with drugs. *Curr Opin Genet Dev* 2008; **18**:87–96.

62 Michieli P, Mazzone M, Basilico C, Cavassa S, Sottile A, Naldini L, *et al.* Targeting the tumor and its microenvironment by a dual-function decoy Met receptor. *Cancer Cell* 2004; **6**:61–73.

63 Boccaccio C, Comoglio PM. Invasive growth: a MET-driven genetic programme for cancer and stem cells. *Nat Rev Cancer* 2006; **6**:637–645.

64 Marshall DD, Kornberg LJ. Overexpression of scatter factor and its receptor (c-met) in oral squamous cell carcinoma. *Laryngoscope* 1998; **108**:1413–1417.

65 Chen YS, Wang JT, Chang YF, Liu BY, Wang YP, Sun A, *et al.* Expression of hepatocyte growth factor and c-met is significantly associated with the progression of oral squamous cell carcinoma in Taiwan. *J Oral Pathol Med* 2004; **33**:209–217.

66 Kim CH, Moon SK, Bae JH, Lee JH, Han JH, Kim K, *et al.* Expression of hepatocyte growth factory and c-met in hypopharyngeal squamous cell carcinoma. *Acta Otolaryngol* 2006; **126**:88–94.

67 Sawatsubashi M, Sasatomi E, Mizokami H, Tokunaga O, Shin T. Expression of c-met in laryngeal carcinoma. *Virchows Arch* 1998; **432**:331–335.

68 Lo Muzio L, Farina A, Rubini C, Coccia E, Capogreco M, Colella G, *et al.* Effect of c-met expression on survival in head and neck squamous cell carcinoma. *Tumour Biol* 2006; **27**:115–121.

69 Aebersold DM, Kollar A, Beer KT, Laissue J, Greiner RH, Djonov V. Involvement of the hepatocyte growth factor/scatter factor receptor c-met and of bcl-xL in the resistance of oropharyngeal cancer to ionizing radiation. *Int J Cancer* 2001; **96**: 41–54.

70 Akervall J, Guo X, Qian CN, Schoumans J, Leeser B, Kort E, *et al.* Genetic and expression profiles of squamous cell carcinoma of the head and neck correlate with cisplatin sensitivity and resistance in cell lines and patients. *Clin Cancer Res* 2004; **10**:8204–8213.

71 Murai M, Shen X, Huang L, Carpenter WM, Lin CS, Silverman S, *et al.* Overexpression of c-met in oral SCC promotes hepatocyte growth factor-induced disruption of cadherin junctions and invasion. *Int J Oncol* 2004; **25**:831–840.

72 Yucel OT, Sungur A, Kaya S. C-met overexpression in supraglottic laryngeal squamous cell carcinoma and its relation to lymph node metastases. *Otolaryngol Head Neck Surg* 2004; **130**:698–703.

73 Galeazzi E, Olivero M, Gervasio FC, De Stefani A, Valente G, Comoglio PM, *et al.* Detection of MET oncogene/hepatocyte growth factor receptor in lymph node metastases from head and neck squamous cell carcinomas. *Eur Arch Otorhinolaryngol* 1997; **254** (**Suppl 1**):S138–S143.

74 Cortesina G, Martone T, Galeazzi E, Olivero M, De Stefani A, Bussi M, *et al.* Staging of head and neck squamous cell carcinoma using the MET

oncogene product as marker of tumor cells in lymph node metastases. *Int J Cancer* 2000; **89**:286–292.

75 Di Renzo MF, Olivero M, Martone T, Maffe A, Maggiora P, De Stefani A, *et al.* Somatic mutations of the MET oncogene are selected during metastatic spread of human HNSC carcinomas. *Oncogene* 2000; **19**:1547–1555.

76 Morello S, Olivero M, Aimetti M, Bernardi M, Berrone S, Di Renzo MF, *et al.* MET receptor is overexpressed but not mutated in oral squamous cell carcinomas. *J Cell Physiol* 2001; **189**:285–290.

77 Kitajo H, Shibata T, Nagayasu H, Kawano T, Hamada J, Yamashita T, *et al.* Rho regulates the hepatocyte growth factor/scatter factor-stimulated cell motility of human oral squamous cell carcinoma cells. *Oncol Rep* 2003; **10**:1351–1356.

78 Matsumoto K, Matsumoto K, Nakamura T, Kramer RH. Hepatocyte growth factor/scatter factor induces tyrosine phosphorylation of focal adhesion kinase (p125FAK) and promotes migration and invasion by oral squamous cell carcinoma cells. *J Biol Chem* 1994; **269**:31807–31813.

79 Uchida D, Kawamata H, Omotehara F, Nakashiro K, Kimura-Yanagawa T, Hino S, *et al.* Role of HGF/c-met system in invasion and metastasis of oral squamous cell carcinoma cells *in vivo* and its clinical significance. *Int J Cancer* 2001; **93**:489–496.

80 Kim CH, Kim J, Kahng H, Choi EC. Change of E-cadherin by hepatocyte growth factor and effects on the prognosis of hypopharyngeal carcinoma. *Ann Surg Oncol* 2007; **14**:1565–1574.

81 Frixen UH, Behrens J, Sachs Eberle G, Voss B, Warda A, Lochner D, *et al.* E-cadherin-mediated cell–cell adhesion prevents invasiveness of human carcinoma cells. *J Cell Biol* 1991; **113**:173–185.

82 Grotegut S, Von Schweinitz D, Christofori G, Lehembre F. Hepatocyte growth factor induces cell scattering through MAPK-Egr-1-mediated upregulation of snail. *EMBO J* 2006; **25**:3534–3545.

83 Yokohama K, Kamata N, Hayashi E, Hoteiya T, Ueda N, Fujimoto R, *et al.* Reverse correlation of E-cadherin and snail expression in oral squamous cell carcinoma cells in vitro. *Oral Oncol* 2001; **37**:65–71.

84 Smith DE, Franco del Amo F, Gridley T. Isolation of *Sna*, a mouse gene homologous to Drosophila genes snail and escargot: its expression pattern suggests multiple roles during postimplantation development. *Development* 1992; **116**:1033–1039.

85 Cano A, Perez-Moreno MA, Rodrigo I, Locascio A, Blanco MJ, Del Barrio MG, *et al.* The transcription factor snail controls epithelial–mesenchymal transitions by repressing E-cadherin expression. *Nat Cell Biol* 2000; **2**:76–83.

86 Yokohama K, Kamata N, Fujomoto R, Tsutsumi S, Tomonari M, Taki M, *et al.* Increased invasion and matrix metalloproteinase-2 expression by snail-induced mesenchymal transition in squamous cell carcinomas. *Int J Oncol* 2003; **22**:891–898.

87 Zeng Q, Chen S, You Z, Yang F, Carey TE, Saims D, *et al.* Hepatocyte growth factor inhibits anoikis in head and neck squamous cell carcinoma cells by activation of ERK and Akt signaling independent of NFkB. *J Biol Chem* 2002; **277**:25203–25208.

88 Lim YC, Park HY, Hwang HS, Kang SU, Pyun JH, Lee MH, *et al.* (–)-epigallocatechin-3-gallate (ECGC) inhibits HGF-induced invasion and metastasis in hypopharyngeal carcinoma cells. *Cancer Lett* 2008; **271**:140–152.

89 Hanzawa M, Shindoh M, Higashino F, Yasuda M, Inoue N, Hida K, *et al.* Hepatocyte growth factor upregulates E1AF that induces oral squamous cell carcinoma cell invasion by activating matrix metalloproteinase genes. *Carcinogenesis* 2000; **21**:1079–1085.

90 Hida K, Shindoh M, Yasuda M, Hanzawa M, Funaoka K, Kohgo T, *et al.* Antisense E1AF transfection restrains oral cancer invasion by reducing matrix metalloproteinase activities. *Am J Pathol* 1997; **150**:2125–2132.

91 Dong G, Chen Z, Li ZY, Yeh NT, Bancroft CC, Van Waes C. Hepatocyte growth factor/scatter factor-induced activation of MEK and P13K signal pathways contributes to expression of proangiogenic cytokines interleukin-8 and vascular endothelial growth factor in head and neck squamous cell carcinoma. *Cancer Res* 2001; **61**:5911–5918.

92 Dong G, Lee TL, Yeh NT, Geoghegan J, Van Waes C, Chen Z. Metastatic squamous cell carcinoma cells that overexpress c-Met exhibit enhanced angiogenesis factor expression, scattering and metastasis in response to hepatocyte growth factor. *Oncogene* 2004; **23**:6199–6208.

93 Ma BB, Chan AT. Recent perspectives in the role of chemotherapy in the management of advanced nasopharyngeal carcinoma. *Cancer* 2005; **103**:22–31.

94 Tao Q, Chan ATC. Nasopharyngeal carcinoma: molecular pathogenesis and therapeutic developments. *Expert Rev Mol Med* 2007; **9**:1–24.

95 Qian CN, Guo X, Cao B, Kort EJ, Lee CC, Chen J, *et al.* Met protein expression level correlates with survival in patients with late-stage nasopharyngeal carcinoma. *Cancer Res* 2002; **62**:589–596.

96 Horikawa T, Sheen T, Takeshita H, Sato H, Furukawa M, Yoshizaki T. Induction of c-Met proto-oncogene by epstein-barr virus latent membrane protein-1 and the correlation with cervical lymph node metastasis of nasopharyngeal carcinoma. *Am J Pathol* 2001; **159**:27–33.

97 Kim KR, Yoshizaki T, Miyamori H, Hasegawa K, Horikawa T, Furukawa M, *et al.* Transformation of Madin–Darby canine kidney (MDCK) epithelial cells by Epstein-Barr virus latent membrane protein 1 (LMP1) induces expression of Ets1 and invasive growth. *Oncogene* 2000; **19**:1764–1771.

98 Matsumoto K, Nakamura T. NK4(HGF-antagonist/angiogenesis inhibitor) in cancer biology and therapeutics. *Cancer Sci* 2003; **94**:321–327.

99 Kakkar T, Ma M, Zhuang Y, Patton A, Hu Z, Mounho B. Pharmacokinetics and safety of a fully human hepatocyte growth factor antibody, AMG102, in cynomolgus monkeys. *Pharm Res* 2007; **24**:1910–1918.

100 Burgess T, Coxon A, Meyer S, Sun J, Rex K, Tsuruda T, *et al.* Fully human monoclonal antibodies to hepatocyte growth factor with therapeutic potential against hepatocyte growth factor/c-met-dependent human tumors. *Cancer Res* 2006; **66**:1721–1729.

101 Reardon DA, Cloughsey TF, Raizer JJ, Laterra J, Schiff D, Yang X, *et al.* Phase II study of AMG102, a fully human neutralizing antibody against hepatocyte growth factor/scatter factor, in patients with recurrent glioblastoma multiforme (Abstr 2051). *J Clin Oncol* 2008; **26** [Abstract].

102 Gordon MS, Mendelson DS, Sweeney C, Erbeck N, Patel R, Kakkar T, *et al.* Interim results from a first-in-human study with AMG102, a fully human monoclonal antibody that neutralizes hepatocyte growth factor (HGF), the ligand to c-Met receptor, in patients (pts) with advanced solid tumors (Abstr 3551). *J Clin Oncol* 2007; **25** [Abstract].

103 Jun HT, Sun J, Rex K, Radinsky R, Kendall R, Coxon A, *et al.* AMG102, a fully human anti-hepatocyte growth factor/scatter factor neutralizing antibody, enhances the efficacy of temozolomide or docetaxel in U-87MG cells and xenografts. *Clin Cancer Res* 2007; **13**:6735–6742.

104 Rosen PJ, Sweeney CJ, Park DJ, Beaupre DM, Deng H, Leitch IM, *et al.* A phase Ib study of AMG102 in combination with bevacizumab or motesanib in patients with advanced solid tumors. *Clin Cancer Res* 2010; **16**:2677–2687.

105 Martens T, Schmidt NO, Eckerich C, Fillbrandt R, Merchant M, Schwall R, *et al.* A novel one-armed anti-c-Met antibody inhibits glioblastoma growth *in vivo*. *Clin Cancer Res* 2006; **12**:6144–6152.

106 Salgia R, Peterson A, Eppler S. A phase I, open label, dose escalation study of the safety and pharmacology of MetMAb, A monovalent antagonist antibody to the receptor c-Met, administered IV in patients with locally advanced or metastatic solid tumors. Presented at the 20th Annual AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics; 2008 Oct 21-24; Geneva (Switzerland): Abstr 411.

107 Mekhail T, Rich T, Rosen L, Chai F, Semic-Suka Z, Savage RE, *et al.* Final results: a dose escalation phase I study of ARQ197, a selective c-Met inhibitor, in patients with metastatic solid tumors (Abstr 3548). *J Clin Oncol* 2009; **27** [Abstract].

108 Perera T, Lavrijssen T, Janssens B. JNJ-38877605: a selective Met kinase inhibitor inducing regression of Met-driven tumor models. Presented at the 99th AACR Annual Meeting; 2008 April 12–16; San Diego (CA): Abstr 4837.

109 Zou H, Li Q, Joseph L. PF-04217903, a novel selective c-Met kinase inhibitor with potent antitumor and anti-angiogenic properties in vitro and in vivo. Presented at the 99th AACR Annual Meeting; 2008 Apr 12–16; San Diego (CA): Abstr 4841.

110 Christiansen JG, Zou HY, Arango ME, Li Q, Lee JH, McDonnell SR, *et al.* Cytoreductive antitumor activity of PF-2341066, a novel inhibitor of anaplastic lymphoma kinase and c-Met, in experimental models of anaplastic large-cell lymphoma. *Mol Cancer Ther* 2007; **6**:3314–3322.

111 Zou HY, Li Q, Lee JH, Arango ME, McDonnell SR, Yamazaki S, *et al.* An orally available small-molecule inhibitor of c-Met, PF-2341066, exhibits cytoreductive antitumor efficacy through antiproliferative and antiangiogenic mechanisms. *Cancer Res* 2007; **67**:4408–4417.

112 Kwak EL, Camidge DR, Clark J, Shapiro GI, Maki RG, Ratain MJ, *et al.* Clinical activity observed in a phase I dose escalation trial of an oral c-met and ALK inhibitor, PF-02341066 (Abstr 3509). *J Clin Oncol* 2009; **27** [Abstract].

113 Qian F, Engst S, Yamaguchi K, Yu P, Won KA, Mock L, *et al.* Inhibition of tumor cell growth, invasion, and metastasis by EXEL-2880 (XL880, GSK1363089), a novel inhibitor of HGF and VEGF receptor tyrosine kinases. *Cancer Res* 2009; **69**:8009–8016.

114 Eder JP, Heath E, Appleman L, Shapiro G, Wang D, Malburg L, *et al.* Phase I experience with c-MET inhibitor XL880 administered orally to patients (pts) with solid tumors (Abstr 3526). *J Clin Oncol* 2007; **25** [Abstract].
115 LoRusso P, Appleman L, Zhu A. Pharmacodynamics of XL880, a novel spectrum selective kinase inhibitor (SSKI) administered orally in patients with advanced solid tumors (AST) (Abstr 404). *Eur J Cancer Suppl* 2006; **4** [Abstract].
116 Eder JP, Appleman L, Heath E. A phase I study of a novel spectrum selective kinase inhibitor (SSKI), XL880, administered orally in patients (pts) with advanced solid tumors (STs) (Abstr 3041). *J Clin Oncol* 2006; **24** [Abstract].
117 Jänne PA, Wax M, Leach J, Engelman JA. Targeting MET with XL184 to reverse EGFR tyrosine kinase inhibitor (TKI) resistance in NSCLC: impact of preclinical studies on clinical design (Abstr 552). *Eur J Cancer* 2008; **6** [Abstract].
118 Salgia R, Hong DS, Camacho LH, Ng S, Janisch L, Ratain MJ, *et al.* A phase I dose-escalation study of the safety and pharmacokinetics (PK) of XL184, a VEGFR and MET kinase inhibitor, administered orally to patients (pts) with advanced malignancies (Abstr 14031). *J Clin Oncol* 2007; **25** [Abstract].
119 Salgia R, Sherman S, Hong DS, Ng CS, Frye J, Janisch L, *et al.* A phase I study of XL184, a RET, VEGFR2, and MET kinase inhibitor, in patients (pts) with advanced malignancies, including pts with medullary thyroid cancer (MTC) (Abstr 3522). *J Clin Oncol* 2008; **26** [Abstract].
120 Tolcher A, Berk G, Fine G. MP470, a potent oral Rad51 suppressor is safe and tolerable in first-in-human study. Presented at the 99th AACR Annual Meeting; 2008 Apr 12–16; San Diego (CA): Abstr 4083.
121 Beaulieu N, Beaulieu C, Dupont I. Preclinical development of MGCD265, a potent orally active c-Met/VEGFR multi-target kinase inhibitor. Presented at the 99th AACR Annual Meeting; 2008 Apr 12–16; San Diego (CA): Abstr 4838.
122 Camacho LH, Moulder SL, LoRusso PM, Blumenschein GR, Bristow PJ, Kurzrock R, *et al.* First in human phase I study of MK-2461, a small molecule inhibitor of c-Met, for patients with advanced solid tumors (Abstr 14657). *J Clin Oncol* 2008;**26** [Abstract].
123 Knowles LM, Stabile LP, Egloff AM, Rothstein ME, Thomas SM, Gubish CT, *et al.* HGF and c-Met participate in paracrine tumorigenic pathways in head and neck squamous cell cancer. *Clin Cancer Res* 2009; **15**:3740–3750.
124 Seiwert TY, Jagadeeswaran R, Faoro L, Janamanchi V, Nallasura V, Dinali ME, *et al.* The MET receptor tyrosine kinase is a potential novel therapeutic target for head and neck squamous cell carcinoma. *Cancer Res* 2009; **69**:3021–3031.
125 Engelman JA, Zejnullahu K, Mitsudomi T, Song Y, Hyland C, Park JO, *et al.* MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science* 2007; **316**:1039–1043.
126 Mueller KL, Hunter LA, Ethier SP, Boerner JL. Met and c-Src cooperate to compensate for loss of epidermal growth factor receptor kinase activity in breast cancer cells. *Cancer Res* 2008; **68**:3314–3322.
127 Merchant M, Zhang Y-W, Su Y. Combination efficacy with MetMAb and erlotinib in a NSCLC tumor model highlight therapeutic opportunities for c-Met inhibitors in combination with EGFR inhibitors. Presented at 99th AACR Annual Meeting; 2008 April 12–16; San Diego (CA): Abstr 1336.
128 Merchant M, Zhang Y, Su Y. MetMAb significantly enhances anti-tumor activity of anti-VEGF and/or erlotinib in several animal tumor models. Presented at the 20th Annual AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics; 2008 October 21–24; Geneva (Switzerland): Abstr 556.
129 Nakachi I, Naoki K, Soejima K, Kawada I, Watanabe H, Yasuda H, *et al.* The combination of multiple receptor tyrosine kinase inhibitor and mammalian target of rapamycin inhibitor overcomes erlotinib resistance in lung cancer cell lines through c-Met inhibition. *Mol Cancer Res* 2010; **8**:1142–1151.
130 Laux I, Goldman J, Just R, Brady K, Li J, Schwartz B, *et al.* Phase I dose escalation trial (ARQ197-111) evaluating combination of selective c-Met inhibitor ARQ197 and erlotinib (Abstr 3549). *J Clin Oncol* 2009; **27** [Abstract].
131 Smolen GA, Sordella R, Muir B, Mohapatra G, Barmettler A, Archibald H, *et al.* Amplification of MET may identify a subset of cancers with extreme sensitivity to the selective tyrosine kinase inhibitor PHA-665752. *Proc Natl Acad Sci U S A* 2006; **103**:2316–2321.