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EDITORIAL

Promise and challenges on the horizon of MET-targeted cancer therapeutics

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Abstract

MET (MNNG HOS transforming gene) is one of the receptor tyrosine kinases whose activities are frequently altered in human cancers, and it is a promising therapeutic target. MET is normally activated by its lone ligand, hepatocyte growth factor (HGF), eliciting its diverse biological activities that are crucial for development and physiology. Alteration of the HGF-MET axis results in inappropriate activation of a cascade of intracellular signaling pathways that contributes to hallmark cancer events including deregulated cell proliferation and survival, angiogenesis, invasion, and metastasis. Aberrant MET activation results from autocrine or paracrine mechanisms due to overexpression of HGF and/or MET or from a ligand-independent mechanism caused by activating mutations or amplification of MET. The literature provides compelling evidence for the role of MET signaling in cancer development and progression. The finding that cancer cells often use MET activation to escape therapies targeting other pathways strengthens the argument for MET-targeted therapeutics. Diverse strategies have been explored to deactivate MET signaling, and compounds and biologics targeting the MET pathway are in clinical development. Despite promising results from various clinical trials, we are still waiting for true MET-targeted therapeutics in the clinic. This review will explore recent progress and hurdles in the pursuit of MET-targeted cancer drugs and discuss the challenges in such development.

Key words: MET; Hepatocyte growth factor; Targeted therapy; Receptor tyrosine kinase; Cancer therapeutics

Core tip: Aberrant activation of MET receptor tyrosine kinase signaling is frequently observed in many human cancers. Such activation not only affects cancer development and progression, but it also contributes to resistance against other cancer drugs. The inhibition of MET signaling is an attractive approach for cancer intervention, and pursuit of MET-targeted cancer therapeutics is underway. Even though promising results have been reported from various clinical trials, many challenges remain to be addressed before and even after the arrival of such drugs in the clinic.

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INTRODUCTION

It has been three decades since the discoveries of MET (MNNG HOS transforming gene) and its ligand, hepatocyte growth factor [HGF; also known as scatter factor (SF)][1-5]. MET, encoded by the proto-oncogene *MET* on chromosome 7 (7q31), is a receptor tyrosine kinase (RTK). Under physiological conditions, it is stimulated by HGF, mainly through a paracrine mechanism, which triggers a cascade of intracellular signaling networks. The signaling driven by this ligand-receptor pair is involved in mitogenesis, motility, and morphogenesis, and it is essential for many developmental and physiological processes[6-8]. Like that of many RTKs, MET signaling is tightly regulated, and its timely attenuation is crucial for proper regulation of its activities[9-11]. Inappropriate activation of this signaling cascade can cause hallmark cancer events that include deregulated cell proliferation, survival, transformation, angiogenesis, and invasion[12,13]. Several different mechanisms can lead to an aberrant MET signaling, including autocrine or paracrine activation resulting from overexpression of MET and or of HGF, and a ligand-independent mechanism caused by activating mutations or amplification of the *MET* gene[12].

Alteration of MET signaling has been reported in almost all types of human cancers and is often associated with poor prognosis[7,12] (http://www.vai.org/met/). The evidence provides a compelling rationale for targeting this pathway, and the rationale is strengthened by the fact that cancer cells often use the HGF-MET axis to escape therapies targeting other RTKs or signaling molecules[12,14-16]. Cancer treatment has been revolutionized by targeted therapy since the success of Gleevec (imatinib) for treating chronic myelogenous leukemia by inhibiting BCR-Abl tyrosine kinase activity[17]. Other targeted therapies include drugs targeting epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR)[11]. Targeted therapies are the trend in cancer treatment, even though not all such drugs have lived up to their promise, in part due to the complexity of the cancer genome[18-21]. Relative to how much we know about the molecular mechanisms of cancers and the numbers of suitable therapeutic targets that have been identified, the targeted therapies available in the clinic are quite limited. MET is one of the targetable molecules that are still lacking effective drugs for cancer treatment.

Over the years, diverse strategies have been explored to inhibit MET pathway activation, from blocking either ligand access or receptor dimerization to inhibiting MET kinase activity or preventing downstream signaling activation[12,22,23]. These efforts have led to the discovery of many MET inhibitors possessing distinct specificities and efficacies (Figure 1). There are hundreds of clinical trials aiming to bring MET inhibitors from the bench to bedside[12,23-25] (https://ccrod.cancer.gov/confluence/display/CCRHGF/Home). While many MET inhibitor trials have shown promising results, various challenges remain. For instance, which patient will benefit from MET-targeted therapeutics and what companion diagnostics will be needed for patient stratification? How can MET-targeted therapeutics be effectively used for tailoring a patient-oriented treatment plan?

MET SIGNAL TRANSDUCTION AND ACTIVITIES

MET is normally expressed in cells of epithelial or endothelial origin, while its ligand HGF is predominantly produced by mesenchymal cells[26]. This decoupling enables a tight regulation of MET signaling in tissues and cells where its activity is required, through the response of MET to gradients of HGF. When HGF binds, the MET receptor undergoes dimerization and a conformational change, leading to phosphorylation of its key tyrosine residues and recruitment of downstream signaling molecules. This recruitment triggers activation of important intracellular signaling pathways such as Ras-MAPK, PI3K-AKT, Src, STAT3, PLC-γ or Cdc42/Rac. Such activation is either mediated by scaffolding adaptors like Gab1 and Grb2 or by direct binding of signaling molecules to the multisubstrate-docking sites in the MET cytoplasmic region[27-30]. MET signaling is subject to timely attenuation that is regulated by several mechanisms, including phosphatase-mediated dephosphorylation, receptor turnover, and negative feedback inhibition[27,31-34]. Such regulation determines the duration and threshold of the MET signal output, how cells will respond, and what biological activities will be induced.

Diverse biological activities, from cell proliferation and survival to cell motility and invasion, can be induced by MET signaling, but it is still vague how the overall response to this signaling is produced. For instance, under what circumstances stimulated cells will proliferate rather than migrate or invade. Among many signaling pathways downstream of MET, activation of Ras-MAPK/ERK is crucial for cell proliferation; PI3K-Akt contributes more to cell survival; Cdc42/Rac activation induces cell motility; and STAT3 has been implicated in cell transformation and tubulogenesis[6-8,34]. Nonetheless, these intracellular pathways often have crossover activities, and they interplay to carry out many complicated biological roles driven by MET, such as invasion and branching morphogenesis[6-8,34]. The signal output and cellular response can be further complicated by crosstalk between the HGF-MET axis and many other cell-surface receptors or signaling pathways[12,34].

MET-mediated biological activities are part of many developmental and physiological processes. For example, the HGF-MET axis is essential for the developing placenta, embryonic liver, and limb muscles during embryogenesis[35-37], and it may be involved in the early development of the lungs, kidneys, and mammary glands[38-42]. HGF promotes formation of blood vessels and lymphatic vessels[43-45], and it plays a role in developing

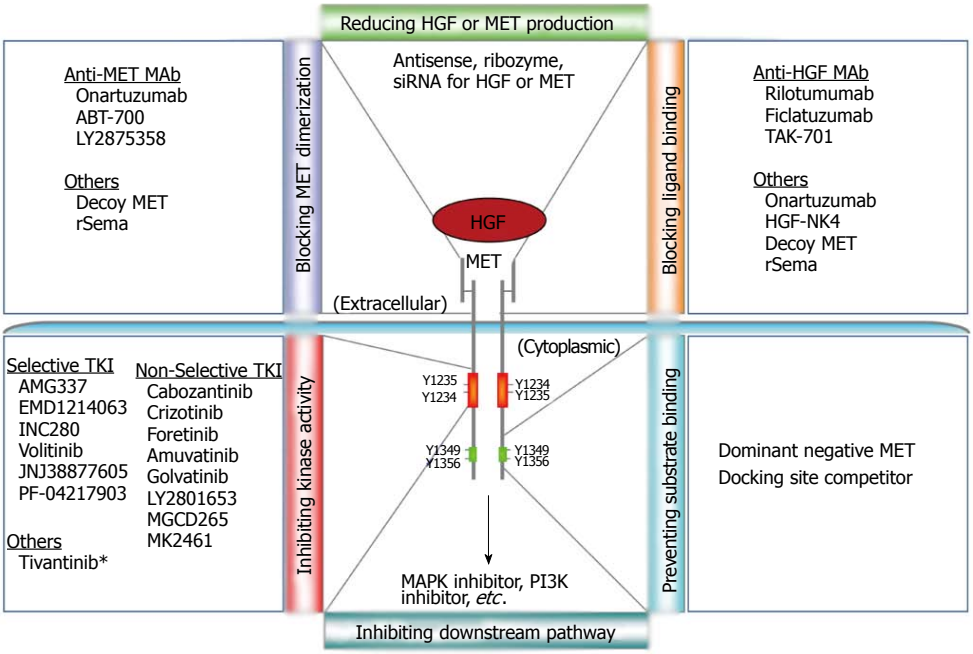

Figure 1 MET-targeted therapeutic strategies and inhibitors. Many strategies have been explored to inhibit MET signaling: blocking ligand binding or receptor dimerization; inhibiting MET kinase activity; preventing substrate binding; reducing hepatocyte growth factor (HGF) or MET production; and inhibiting downstream pathways. Shown in the diagram are representative inhibitors in each category, many of which are in clinical trials. Y1234 and Y1235 are two essential tyrosine residues in the TK-domain of MET, and Y1349 and Y1356 in its docking site are key tyrosine residues for substrate binding. Tivantinib is a non-ATP-competitive, selective MET inhibitor, but it also exhibits MET-independent antitumor activity by inhibiting microtubules. rSema: Recombinant MET Sema domain fragment.

neurons[46,47]. Physiologically, MET signaling is indispensable for liver regeneration and repair[48-50] and for skin wound healing[51]; it also contributes to insulin secretion and glucose metabolism[52,53]. A significant role of this signaling axis in the regulation of stem cell activity has also been found[54]. HGF can stimulate the migration and differentiation of mesenchymal stem cells (MSCs) while inhibiting their proliferation[55,56], and it can induce differentiation of bone marrow stem cells into hepatocytes[57,58].

MET SIGNALING IN CANCERS

The link of MET to cancer can be traced back thirty years. MET was originally cloned from a carcinogen-induced chromosome rearrangement in a human osteosarcoma cell line as part of the TPR-MET fusion[1,59], an oncogenic product which was also observed in human gastric carcinoma[60]. The most decisive evidence of MET signaling in cancers came from the identification of its germline and somatic mutations in papillary renal cell carcinomas (RCC)[61]. These mutations mainly locate in the tyrosine kinase (TK) domain of MET, resulting in constitutive activation of its signaling[62]. Such mutations have also been sporadically identified in childhood hepatocellular carcinoma (HCC) and head neck squamous cell carcinoma (HNSCC)[63,64]. Interestingly, MET mutations identified in other human solid cancers (such as lung and gastric cancers, and melanoma and thyroid carcinomas) are mostly in the extracellular semaphorin (Sema) domain and the juxtamembrane (JM) domain[65-69]. In lung adenocarcinoma, it is estimated that 4% of the tumors have exon 14 skipping in the MET mRNA due to splicing site mutations, and thus have JM-domain defect[20]. These non-TK-domain mutations likely affect ligand binding or CBL-mediated turnover of MET, thereby altering MET signal transduction. Besides genetic abnormalities, MET signaling is mostly altered through a paracrine or autocrine activation mechanism by inappropriate increases in MET and/or HGF expression. Evidence of such alterations has been documented in almost all types of human cancers, and high MET and HGF expressions are often correlated with invasive phenotype and poor prognosis[7,12]. Alternatively, aberrant MET activation in cancer cells can be the result of amplification of the *MET* gene, which is found in gastric, esophageal, lung, colorectal, and breast cancers[70-76].

Another important aspect of MET signaling in cancers emerged from studies of drug resistance. Activation of the HGF-MET axis has become one of the most crucial mechanisms that cancer cells adapt to bypass therapies targeting other oncogenic pathways. The first such evidence came from the analysis of non-small-cell lung cancer (NSCLC) patients treated with gefitinib (an EGFR inhibitor), which revealed amplification of *MET* as a mechanism for gefitinib resistance[14]. This mechanism accounts for acquired resistance to EGFR-targeted therapies (gefitinib and erlotinib) in about 5% of NSCLCs that harbor EGFR-activating mutations and are primarily sensitive to the treatment[77-80]. *MET* amplification is also associated with acquired resistance to cetuximab or panitumumab

(both EGFR-targeted monoclonal antibodies) in patients with metastatic colorectal cancer (mCRC)[81]. An alternative mechanism of resistance to EGFR-targeted therapies in lung cancer *via* MET signaling may be through up-regulation of HGF expression[82-84]. This mechanism could have a widespread impact on drug resistance to various anticancer kinase inhibitors[16]. For instance, stroma-derived HGF contributes to innate and acquired resistance to vemurafenib (RAF inhibitor) treatment of melanomas[15], and it may trigger resistance to ALK inhibitors in EML4-ALK lung cancer cells[85]. MET activation also confers tumor resistance to chemotherapy or radiotherapy.

Aberrant MET activation can elicit a multitude of biological consequences, ultimately leading to tumorigenesis and metastasis[6-8,12]. It causes oncogenic transformation and provides growth and survival signals to cancer cells by overactivating numerous downstream pathways (RAS-MAPK, PI3K-AKT, and STAT3, to name a few). In animal models, overexpression of MET in the liver results in HCC[86], while targeted expression of mutant MET in mammary epithelium leads to the development of breast cancers[87,88]. In parallel, MET causes invasive behavior of cancer cells, leading to metastasis; this is achieved by its abilities to up-regulate multiple extracellular matrix-degrading proteases, inducing the epithelial-to-mesenchymal transition and activating cell-mobilizing machinery[6-8,12]. The HGF-MET axis has also been implicated in the regulation of cancer stem cell activities in colon cancer and glioblastoma[89-91]. Besides direct contribution to the pathogenesis of cancer cells, MET signaling can enhance angiogenesis to strengthen tumor-supporting circuitry for promoting growth and survival[43,92,93].

DEVELOPMENT OF MET-TARGETED THERAPEUTICS: THE PROMISE

The indisputable role of MET signaling in cancer has made it a promising target for cancer intervention. Many approaches have been taken to try to effectively inhibit MET signaling activation in cancer cells[12,22-23]. Resulting from these efforts is a spectrum of targeted inhibitors having diverse biochemical and biological properties, including neutralizing antibodies to MET or HGF, small-molecule tyrosine kinase inhibitors (TKIs) of MET, and others (Figure 1). To date, more than two dozen MET-targeted inhibitors are in clinical development, with hundreds of trials conducted or underway, either as a single agent or in combination with other cancer drugs[12,23-25].

Ficlatuzumab (AV-299), rilotumumab (AMG102), and TAK-701 are humanized anti-HGF monoclonal antibodies that block HGF-dependent paracrine/autocrine MET activation. Ficlatuzumab, as a single agent for patients with advanced solid tumors, showed a partial benefit of stable disease in phase Ⅰ trials. Favorable responses were observed in a subgroup of NSCLC patients who had low MET expression when ficlatuzumab was used in combination with an EGFR inhibitor in a phase Ⅱ study[94-97]. Patients with refractory advanced solid tumors had a response of stable disease when treated with rilotumumab alone[98]. Recent phase Ⅱ clinical trials of rilotumumab in combination with chemotherapy extended progression-free survival (PFS) in patients with gastric cancer[99]. A benefit of combining rilotumumab with panitumumab was reported in a randomized phase Ⅱ trial of patients with mCRC who carry wild-type KRAS[100]. TAK-701, which has been tested in a phase Ⅰ trial, inhibits HGF-mediated resistance to gefitinib in an NSCLC tumor model[101,102].

Unlike HGF blockers, onartuzumab (MetMAb, a humanized monovalent antibody to MET) neutralizes MET by inhibiting HGF binding and receptor dimerization[103,104]. In a phase Ⅰ dose-escalation study, onartuzumab, as a single agent and in combination with bevacizumab, was well tolerated in patients with advanced solid tumors[105], while in a preclinical model it enhanced the antitumor efficacy of anti-VEGF biologics[106]. Several phase Ⅱ/Ⅲ trials of onartuzumab in combination with bevacizumab and or chemotherapeutic agents have been initiated for treating cancers such as mCRC, glioblastoma, NSCLC, breast cancer, and gastric cancer. In a randomized phase Ⅱ trial, onartuzumab and erlotinib in combination had a favorable outcome in MET-positive NSCLC patients, with MET expression of 2+ or 3+ scores based on immunohistochemical (IHC) staining[107]. This group of patients had a significant improvement of PFS (median 2.9 mo *vs* 1.5 mo) and overall survival (OS; median 12.6 mo *vs* 3.8 mo) relative to the placebo plus erlotinib controls. However in the MET-negative group, a worse OS was observed relative to the control group[107]. This result has led to a phase Ⅲ trial of onartuzumab plus erlotinib in MET-positive advanced NSCLC patients[108]. ABT-700 and LY2875358, two other antagonist antibodies against MET, are also being evaluated in early-phase trials[109,110].

While the anti-HGF and anti-MET biologics provide unique target specificity and long-lasting efficacy, the majority of potent MET inhibitors in clinical development are small-molecule TKIs. These are either selective or non-selective inhibitors of MET, and they mostly compete for the ATP-binding pocket in the TK-domain. Examples of selective inhibitors include AMG337, EMD1214063 (MSC2156119J), INC280 (INCB028060), and volitinib (HMPL-504); no significant safety concerns have been reported from early-phase studies of these oral inhibitors[111-114]. EMD1214063 is potent in suppressing the activities of both wild-type MET and its activating mutants in preclinical models[112,115,116], and ongoing phase Ⅰ/Ⅱ trials will evaluate its safety/efficacy in NSCLC and HCC. Several phase Ⅰ/Ⅱ trials of INC280 are recruiting patients with cancers including advanced cases of HCC, NSCLC, glioblastoma, or melanoma. A global phase Ⅱ study of volitinib has been initiated for papillary RCC[114]. PF-04217903, another potent selective TKI of MET, has been discontinued from trials due to a strategic

development decision[117].

Non-selective MET TKIs represent a different class of blockers; among them are crizotinib, cabozantinib, and foretinib. Crizotinib (Xalkori, PF-02341066), which was primarily designed for MET inhibition and displayed antitumor effects in MET-amplified NSCLC, is a multikinase inhibitor of MET, ALK, and ROS1[118-120]. Crizotinib is FDA-approved for treatment of ALK-fusion NSCLC patients, and it has shown antitumor activity in advanced ROS1-rearranged NSCLC[120]. A durable response to crizotinib was reported in an NSCLC patient with MET amplification but no ALK rearrangement[121]. Patients with MET-amplified esophagogastric adenocarcinoma or recurrent glioblastoma have also shown clinical responses to crizotinib treatment[122,123]. A cross-tumoral phase Ⅱ trial of crizotinib has been launched in patients with locally advanced and/or metastatic tumors that carry ALK and/or MET alteration. Ongoing trials also include crizotinib in combination with erlotinib or other inhibitors.

Cabozantinib (XL184) inhibits multiple molecular targets, including MET, VEGFR2, RET, AXL KIT, and FLT3, and it suppresses tumor growth, angiogenesis and metastasis[124]. Cabozantinib (Cometriq) was approved by the FDA as an orphan product for treating medullary thyroid cancer (MTC) in late 2012. A phase III trial for this rare human cancer showed a response rate of 28% for cabozantinib versus none for placebo (median PFS of 11.2 mo *vs* 4.0 mo), most likely due to its inhibitory activity on RET; it showed significant but manageable toxicity[125]. Cabozantinib phase Ⅱ trials displayed clinical activity in metastatic CRPC, resulting in improvement in PFS, bone scans, and pain, and a reduction of soft tissue lesions[126,127]. Clinical trials of cabozantinib are under way for several other cancer types, including NSCLC, glioblastoma, breast, ovarian, and urothelial cancers. Its combination with erlotinib has been tested in advanced NSCLC in an early-phase trial[128]; many other combination studies involving cabozantinib are under way.

Foretinib (XL880, EXEL-2880, and GSK1363089) is a multikinase inhibitor targeting MET, VEGFR2, RON, TIE-2, PDGFRβ, KIT, FLT3, and AXL. It has shown antitumor activity in xenograft tumors and in a phase Ⅰ trial of metastatic or unresectable solid tumors[129,130]. With a manageable toxicity profile, it demonstrated in a phase Ⅱ trial a high response rate in advanced papillary RCC patients who had germline MET mutations[131]. Phase Ⅱ trials are studying foretinib in metastatic gastric cancer, recurrent/metastatic HNSCC, and triple-negative breast cancer. Phase Ⅰ/Ⅱ trials also test combinations of foretinib with erlotinib against locally advanced/metastatic NSCLC or with lapatinib against HER2-overexpressing metastatic breast cancer. Other non-selective TKIs of MET include amuvatinib (MP470), golvatinib (E7050), LY2801653, MGCD265, and MK-2461, all of these inhibit both MET and other targets[132-136].

Tivantinib (ARQ197), unlike other MET TKIs, is a non-ATP-competitive small-molecule inhibitor of MET that has a broad spectrum of antitumor activity[137]. It selectively binds to inactive/unphosphorylated MET and inhibits its autophosphorylation[138]. Clinical development of tivantinib is being actively pursued. Examples from completed phase Ⅱ trials include tivantinib as a second-line treatment for advanced HCC, as well as its combination with erlotinib for previously treated NSCLC[139,140]. These results have led to the launches of phase Ⅲ trials of tivantinib either as a monotherapy or in combination, among many other ongoing clinical studies.

CHALLENGES OF MET-TARGETED THERAPEUTICS

Despite promising results, there have also been setbacks to MET-targeted therapeutics development, and numerous challenges remain to be addressed. For instance, rilotumumab in several phase Ⅱ trials showed no or limited efficacy in patients with metastatic RCC, castration-resistant prostate cancer (CRPC), or recurrent glioblastoma or ovarian cancer[141-144]. Foretinib as a single agent lacked efficacy in unselected patients with metastatic gastric cancer in a phase Ⅱ study[145]. The COMET-1 phase Ⅲ trial of cabozantinib in men with metastatic CRPC failed to meet its primary endpoint of demonstrating a statistically significant improvement of overall survival relative to prednisone treatment[146]. Further, the MARQUEE phase Ⅲ trial of tivantinib plus erlotinib and the MetLung phase Ⅲ trial of onartuzumab plus erlotinib in patients with advanced NSCLC were terminated following independent review board examination. Both trials failed to demonstrate any meaningful efficacy of combination compared with erlotinib alone[25,108,147]. Also, recent studies have demonstrated that tivantinib has cytotoxic activity independent of MET[148,149], raising the question of whether the clinical antitumor efficacy of this selective MET inhibitor was solely due to MET inhibition.

Such setbacks lead to the question of whether those clinical trials targeted the right groups of cancer patients for MET inhibition. One major challenge in patient selection is a lack of reliable biomarkers for companion diagnosis. IHC staining of MET has been widely used for assessing its protein status in tumors; patients with MET-IHC-positive gastric cancer displayed the greatest survival benefit from rilotumumab in combination with chemotherapy[99]. However, such staining unexpectedly failed in selecting patients for the MetLung phase Ⅲ trial, even though this biomarker was able to identify responders (MET-IHC score 2+ or 3+) for onartuzumab plus erlotinib treatment in a phase Ⅱ study[25,107,108,150]. It remains to be seen why MET-IHC biomarker failed in the latter trial and whether improvements in sensitivity and specificity would make it more reliable for patient stratification.

Other potential biomarkers include *MET* mutations

and *MET* amplification (gains in gene copy number or chromosome 7 polysomy). Germline *MET* TK-domain mutations are highly predictive for papillary RCC patients' response to foretinib treatment[131]. Nonetheless, *MET* mutation as a biomarker in general has its limitations, because a majority that are found in broader cancers are non-TK-domain mutations[20,65-69] whose value in predicting response to MET inhibitors remains undetermined. Fluorescence *in-situ* hybridization (FISH) of *MET* has been evaluated for a link between *MET* amplification and patient response in MET inhibitor trials[99,111,122,131,145,150]. Even though the sample sizes were mostly small for interpretation, patients with *MET*-amplified tumors usually have better response, indicating the value of *MET*-FISH as a predictive biomarker. The power of this biomarker will be further defined when results from several ongoing trials enrolling *MET*-amplified cancer patients become available. In addition, serum/plasma HGF and soluble MET concentrations have also been used in exploratory biomarker analyses[95,99,150].

While improved biomarkers are vital for better design and success of MET inhibitor trials, developing the proper therapeutic strategy to maximize drug efficacy in the clinic is equally important. The latter can be challenging, because alterations of MET signaling found in the majority of human cancers are not activating mutations or amplifications of *MET*, and the alterations are often accompanied by the activation of other pathways[7,12]. The use of MET-targeted drugs as a monotherapy has its own merit if MET alteration is the oncogenic driver; however, it might not perform well when different oncogenic pathway(s) is co-activated. The existence of crosstalk between MET and other pathways such as EGFR and VEGFR also complicates the outcome of MET-targeted monotherapy, providing further rationale for drug combination[12,34]. Clinical trials of various combination therapies have aimed to simultaneously inhibit MET and other molecular targets. However, determining what drug combination is best suited to which patient in the clinic demands a comprehensive platform of multiplexed molecular diagnoses. On the other hand, several targeted therapies, including those of EGFR and B-RAF, may theoretically benefit from combination with MET inhibitors to prevent MET signaling-mediated drug resistance[14-16,77-84]. Such combination strategies, nevertheless, are practically challenging because this resistance mechanism only accounts for a fraction of the resistant cases.

CONCLUSION

MET signaling is highly important in cancer malignancy, making it a promising molecular target for cancer intervention. The development of MET-targeted drugs is in full gear at multiple fronts, but numerous challenges remain. The failure of several late-stage clinical trials has put such development under scrutiny, but encouraging results are coming from other trials and new developments. Future trials should also put the activity of MET inhibitors on cancer invasion and metastasis in perspective. Inevitably, drug resistance will be expected for MET-targeted therapeutics, and such events have been observed in *in vivo* studies[151-154]. To enhance the performance of MET inhibition and to prevent cross-drug resistance, engineering bi-specific or multi-specific antibodies against MET and other cell surface receptors may provide a solution[155-157]. Many clinical benefits can be expected from the eventual approval of MET-targeted drugs.

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