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REVIEW ARTICLE

# MET As a Possible Target for Non–Small-Cell Lung Cancer

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A B S T R A C T

Lung cancer is a heterogeneous group of disorders that is now being subdivided into molecular subtypes with dedicated targeted therapies. The MET receptor tyrosine kinase has been identified as aberrantly overexpressed, potentially having activating mutations, and amplified in certain subsets of lung cancers. The ligand hepatocyte growth factor (HGF) can also be overexpressed in lung cancer or expressed in stroma, and both the MET receptor and the HGF ligand can be targets for therapeutics, especially in lung cancer. Activation of MET leads to a plethora of biochemical and biologic changes both in normal and cancerous cells. Preclinically, it has been shown that silencing or inactivating MET leads to decreased viability of cancer cells. There are a number of compounds against MET/HGF in clinical trials that have been shown to be active in lung cancers. This review will summarize the biology of MET as well as its therapeutic inhibition in lung cancer.

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## INTRODUCTION

Cancer treatment is being revolutionized by target-based therapeutic development. Cancers with oncogenic addiction to multiple genetic and epigenetic abnormalities have been well documented,[1-6] with inhibition of these abnormalities by monoclonal antibodies and small-molecule inhibitors presenting ideal clinical scenarios.[7] Recently, lung cancer biology and therapeutics have been revolutionized. With the discovery of epidermal growth factor receptor (*EGFR*) mutations, echinoderm microtubule-associated protein-like 4–anaplastic lymphoma kinase (*EML4-ALK*) translocations, and the reactive oxidant species 1 translocation, specific therapeutics designed to target these mutations and translocations have proved to be effective.[8-11] With the identification of molecular subsets in lung cancer, it is imperative that further studies be performed as to the various subclassifications.[12] Among many targets, the MET receptor tyrosine kinase (RTK) and its ligand hepatocyte growth factor (HGF) have been identified as important targets in lung cancer. The MET RTK and HGF are localized to chromosome 7q and can be overexpressed in lung cancer. The *MET* gene can have activating mutations, especially in the semaphorin (sema) domain and juxtamembrane (JM) domain, or be amplified.[13,14]

The protein product of the *MET* gene, HGF receptor (HGFR), has been implicated in various oncogenic processes including cell proliferation, survival, invasion, motility, and metastasis. There has been some headway in understanding mechanisms responsible for HGF-mediated mitogenesis and motogenesis. Phosphotidylinositol-3 kinase, required for HGF-induced mitogenesis and motogenesis, leads to decreased chemotaxis when inhibited.[15] Paxillin, which is highly overexpressed in non–small-cell lung cancer (NSCLC), shows increased phosphorylation in the presence of activating HGFR mutations (T1010I and R988C).[16] MET can be activated either by binding to its ligand HGF, overexpression/amplification, mutation, or decreased degradation. Degradation of MET is through the E3 ubiquitin ligase c-CBL. It has been identified that c-CBL is decreased via loss of heterozygosity and can sometimes be mutated in lung cancer.[17] Because there are various mechanisms for MET activation, these have now been therapeutically targeted in vitro, in xenograft models, in vivo, and in clinical trials.

The silencing (via small interference RNA or short hairpin RNA) or inactivation of MET via micro-RNA has been shown to be important in vitro for cell viability and downstream signaling, as well as for biologic properties such as cell motility, cell migration, and invasion. In vitro cell line inhibition and in vivo inhibition have been observed with small-molecule and antibody inhibition. There is also synergism of inhibition with cytotoxic, radiation, and novel therapies for MET. We have also shown in preclinical studies the synergistic effect of epidermal growth factor (EGF) and HGF on proliferation and downstream activation of signal transduction, along with an additive effect on motility in NSCLC cell lines. There is synergism of MET with other RTKs such as EGFR and RON (Fig 1). In particular, a combination of HGF and EGF tyrosine

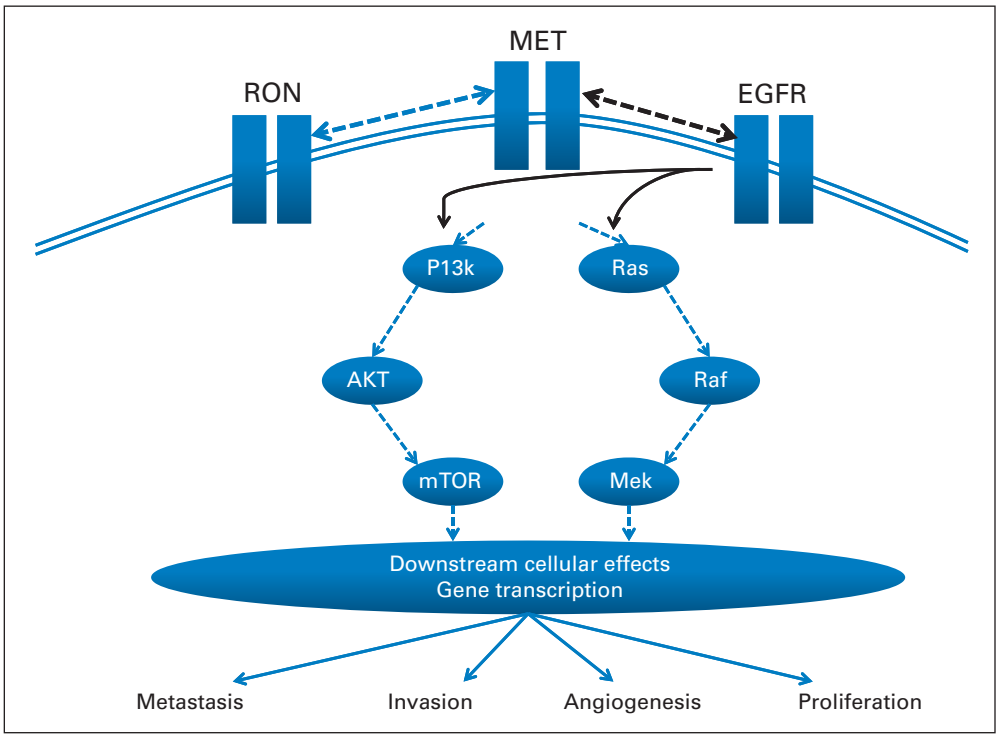


**Fig 1.** Synergism between MET/recepteur d'origine nantais (RON) and epidermal growth factor receptor (EFGR). mTOR, mammalian target of rapamycin.

kinase inhibitors in our preclinical work showed synergistic apoptotic effect.[18]

## STRUCTURE AND FUNCTION OF MET AND HGF

The human *MET* gene located at 7q21-q31 was discovered in 1984 as a fusion partner with Tpr in the transforming fusion oncogene *TPR-MET* in an immortalized osteosarcoma cell line.[14] With activation of MET, there is homodimerization and thus activation of kinase activity (Fig 2).[19] The MET precursor is post-translationally digested and glycosylated, leading to the formation of a 50-kDa extracellular $\alpha$-chain and transmembrane 140-kDa $\beta$-chain. The $\beta$-chain has homologous structural domains shared with other proteins, including the sema domain, plexin-semaphorin-integrin domain, four IPT (immunoglobin-like fold shared by plexins and transcription factors) repeats, a transmembrane domain, tyrosine kinase domain, and JM domain. HGF is the natural and only ligand for MET activation. HGF was identified initially as a growth factor for hepatocytes and as a fibroblast-derived cell motility factor.[20,21] HGF has six domains (an N-terminal domain, four kringle domains, and a C-terminal domain). HGF precursor secreted by mesenchymal cells is cleaved into disulfide-linked heterodimer.[22] It has been shown to bind with the sema domain of MET.[23,24]

## DYSREGULATION OF MET EXPRESSION

Regulation of MET activation in oncogenic addiction is different than normal MET signaling. Elevated MET levels are sufficient for oncogenic transformation, as shown by in vitro conversion of human osteoblasts into osteosarcoma cells.[25] NSCLC cell lines have shown MET overexpression, with high expression of both MET and HGF associated with higher pathologic tumor stage and worse prognosis.[26-28] Several factors influencing MET expression have been identified. Pennacchietti et al[29] have shown that hypoxic areas of tumors overexpress MET, with hypoxic activation leading to transcription of the *MET* proto-oncogene, higher MET levels, and amplification of HGF signaling. On inhibition of MET expression, hypoxia-induced invasive growth was prevented. The Wnt pathway has also been implicated in controlling MET expression in colorectal cancer.[30] PAX5 is a nuclear transcription factor required for B-cell development. In lung cancer, the PAX5 protein is strongly expressed in small-cell lung cancer (SCLC), whereas PAX8 is expressed in NSCLC.[31] PAX5 is frequently coexpressed with MET or phosphorylated MET in intermediate-grade and high-grade neuroendocrine tumors including atypical carcinoids, SCLCs, and large-cell neuroendocrine tumors. The transcriptional control of MET can be through PAX transcription factors.

## HGF-DEPENDENT SIGNALING THROUGH ITS RECEPTOR

Binding of soluble HGF to cell surface–expressed HGFR leads to receptor dimerization and tyrosine kinase activation with initiation of signaling cascades. In normal signaling through receptor activation, the transient signaling process is terminated by recruitment of CBL (E3 ubiquitin ligase), which binds to Y1003, an important regulatory site within the JM domain of HGFR, leading to ubiquitination of HGFR with internalization into clathrin-coated vesicles. In oncogenic ligand-independent signaling, HGFR containing the Y1003 mutation is not ubiquitinated, leading to decreased lysosomal degradation, increased stability, and continued oncogenic activation.[32] MET receptor activates a number of downstream signaling molecules that affect

  

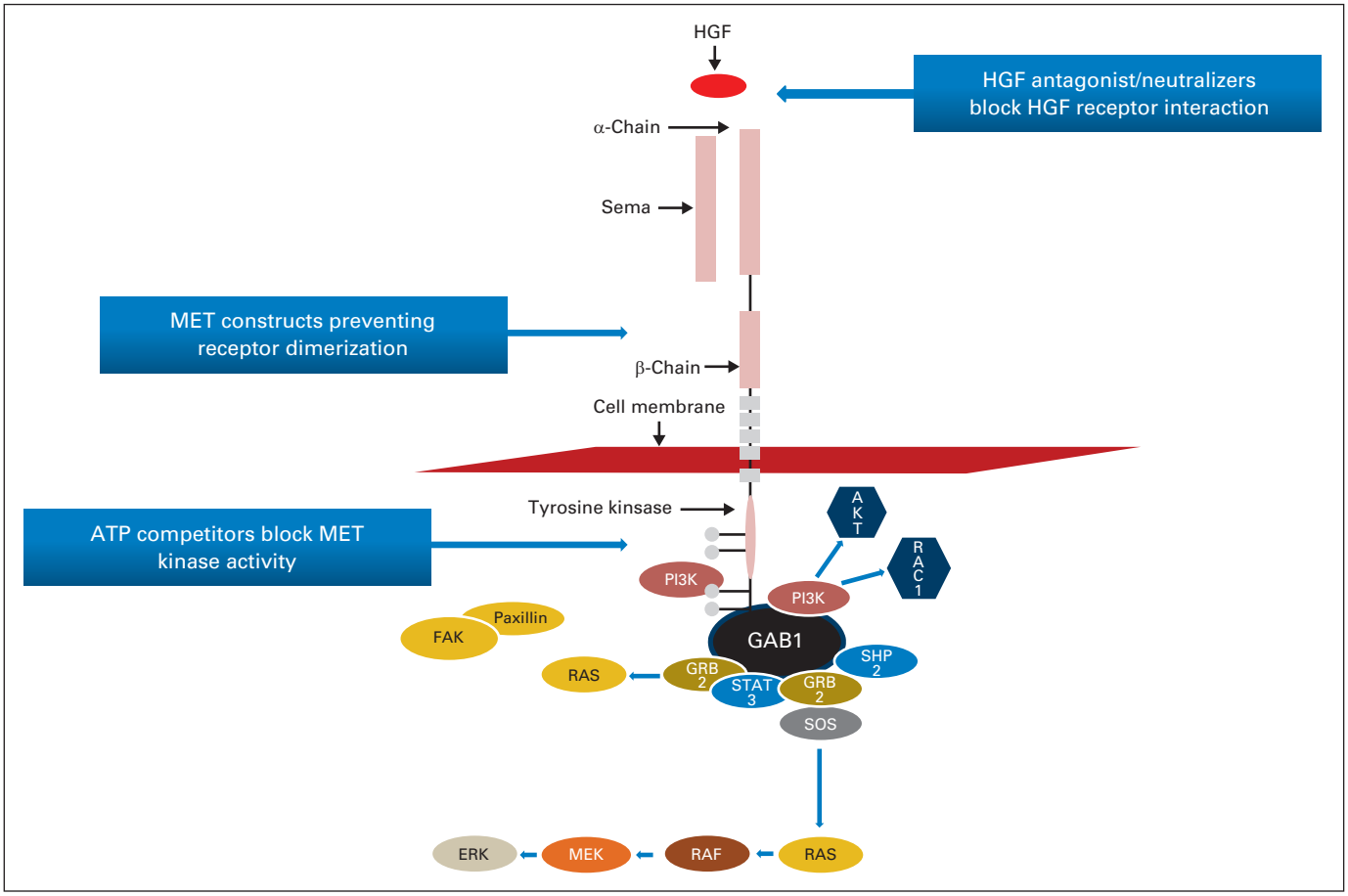


**Fig 2.** Targeting of the hepatocyte growth factor (HGF)/MET pathway. HGF-dependent activation of the MET pathway can be disrupted through extracellular therapies that interfere with HGF binding to MET. Intracellular approaches can inhibit HGF-dependent and -independent mechanisms that lead to phosphorylation of MET kinase substrates.

pathways for cell cycle, cytoskeletal function, cell survival/antiapoptosis, cell proliferation and differentiation, and a number of other functional pathways.[33]

## MUTATIONS AND AMPLIFICATION OF *MET* IN LUNG CANCER

*MET* gene mutations with both somatic and germline variants have been described in various human cancers, including hereditary papillary renal cell carcinoma (MET kinase mutations were first identified in hereditary papillary renal cell carcinoma) and thoracic malignancies.[34] In lung cancer, *MET* gene mutations are found both in extracellular and JM domains. The extracellular sema domain, encoded by exon 2, is required for receptor dimerization and activation.[35] The presence of these mutations has been clearly defined in lung cancer; however, because of certain histologic and ethnic variation, their biologic relevance still needs to be defined. JM domain mutations have been characterized in SCLC tissue samples and cell lines (S1040P, T992I, and R970C) and other cancers including melanoma (N930S) and gastric carcinoma (P991S). Kinase activity of HGFR is required for activation of downstream signaling pathways. No kinase domain mutations have been identified in lung cancer, but somatic and germline mutations have been reported in papillary renal cell carcinoma and hereditary papillary renal cell carcinoma, respectively.[36,37]

Although the EGFR tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib have shown activity in NSCLC, acquired resistance to these agents ultimately leads to disease progression. In 2007, Lutterbach et al[38] showed *MET* gene amplification and overexpression in NSCLC cell lines. Later, Engelman et al[39] showed that amplification of *MET* causes gefitinib resistance by driving ERBB3 (human epidermal growth factor receptor 3) -dependent activation of PI3K. Other studies showed a *MET* amplification rate of approximately 20% in patients with acquired EGFR TKI resistance.[40] As Pao and Chmielecki[42] have advocated, cells with *MET* amplification seem to undergo a kinase switch under EGFR blockade and bank on MET signaling instead to maintain activation of AKT through increased phosphorylation in the presence of EGFR-TKIs. In concept, this form of acquired resistance to EGFR blockade might be neutralized by simultaneous blockade of MET. Multiple studies have reported primary *MET* amplification in NSCLC adenocarcinoma ranging from 2% to 20%, particularly in EGFR-TKI–naive patients.[43-45] *MET* amplification leads to overexpression of the MET receptor and to activation of downstream signal transduction. In particular, the PI3K/AKT pathway is activated.

**Table 1.** Trials of Compounds Targeting MET/HGF

| Compound | Company | Mechanism of Inhibition | Phase of Study/Type of Tumor |
|---|---|---|---|
| Monoclonal anti-HGF antibodies | | | |
| AMG 102 (rilotumumab) | Amgen | Human IgG2 MoAb against HGF | Preclinical and phase I and II; active phase I/Ib/II studies in multiple solid tumors |
| Ficlatuzumab (AV-299; formerly SCH 900105) | AVEO | Anti-HGF/c-MET antibody | Preclinical and phase I and II; phase Ib/II study of AV-299 in combination with gefitinib in Asian patients with NSCLC |
| TAK 701 | Millennium | Humanized MoAb to HGF | Preclinical and phase I-III; phase I in solid tumors |
| Monoclonal anti-MET antibodies | | | |
| MetMab (onartuzumab) | Genentech | Single-armed humanized modified 5D5 anti-MET antibody | Preclinical and phase I-III; combination with erlotinib in NSCLC |
| DN30 | Metheresis | MoAb | Preclinical; reduces MET activation in GTL16 cells |
| CE-355621 | Pfizer | Monoclonal antibody that binds to the extracellular domain of MET | Preclinical |
| OA-5D5 | Genentech | One-armed (OA) variant of the anti-c-MET antibody 5D5 | Preclinical; inhibits HGF-induced MET phosphorylation, proliferation, and migration of U87-MG cells in vitro |
| Small-molecule MET inhibitors | | | |
| ARQ-197 (tivantinib) | ArQule | Non–ATP-competitive, MET-specific inhibitor | Preclinical and phase I-III; tivantinib plus erlotinib (MARQUEE and ATTENTION trials) |
| XL184 (cabozantinib) | Exelixis/Bristol-Myers Squibb | Dual inhibitor of MET and VEGF | Preclinical and phase I-III; phase III in medullary thyroid cancer |
| Crizotinib | Pfizer | MET and ALK kinase inhibitor | Preclinical and phase I-III |
| XL880 (foretinib) | Exelixis/GlaxoSmithKline | Tyrosine kinase (MET, VEGF, Flt-3, KIT, PDGFR-$\beta$, and Tie-2) inhibitor | Preclinical and phase I and II; active phase II study in renal papillary cell carcinoma |
| SGX523 | SGX Pharmaceuticals | ATP-competitive inhibitor of the MET receptor tyrosine kinase | Preclinical and phase I; phase I in advanced solid tumors |
| MGCD265 | MethylGene | MET and VEGF receptor tyrosine kinase inhibitor | Preclinical and phase I and II; phase I/II with erlotinib or docetaxel in patients with advanced malignancies or NSCLC |
| AMG 208 | Amgen | Small-molecule inhibitor of MET (ligand dependent and ligand independent) | Preclinical and phase I; phase I in advanced solid tumors |
| PF-04217903 | Pfizer | ATP-competitive small molecule inhibitor of MET kinase | Preclinical and phase I |
| BMS777607 | Bristol-Myers Squibb | Selective, orally available ATP-competitive MET kinase inhibitor | Preclinical and phase I; phase I in advance solid tumors |
| JNJ38877605 | Johnson & Johnson | Small-molecule inhibitor of MET | Preclinical and phase I; phase I in advance solid tumors |
| Decoy MET | | | |
| CGEN241 | Compugen | Decoy MET (truncated form of the c-MET receptor) | Preclinical and phase I |

Abbreviations: ATTENTION, Asian Trial of Tivantinib Plus Erlotinib for NSCLC Without EGFR Mutation; HGF, hepatocyte growth factor; IgG, immunoglobulin G; MARQUEE, MET Inhibitor ARQ 197 Plus Erlotinib Versus Erlotinib Plus Placebo in NSCLC; MoAb, monoclonal antibody; NSCLC, non–small-cell lung cancer; PDGFR, platelet-derived growth factor receptor; VEGF, vascular endothelial growth factor.

Small-molecule inhibitors are effective against *MET*-amplified tumors.[46] A number of trials have studied MET/HGF, and these are summarized in the next section (Table 1).

## CURRENT CLINICAL ADVANCES IN LUNG CANCER MET INHIBITION

### *MET Inhibitors for Preclinical Use*

There has been extensive preclinical work done on MET inhibitors, which has paved the way for further clinical trials with these agents. K252a (Fermentek Biotechnology, Jerusalem, Israel), a staurosporine analog isolated from *Nocardiopsis* soil fungi, showed inhibition of both the wild-type (WT) and the mutant (M1268T) *MET* function at nanomolar concentrations.[47] SU11274 (Sugen, Redwood City, CA), a MET-specific kinase inhibitor, has demonstrated inhibition of HGF-induced motility and invasion of epithelial and carcinoma cells.[48] PHA-665752 (Pfizer, New York, NY), a MET-specific kinase inhibitor, demonstrated suppression of both HGF-dependent and constitutive MET phosphorylation.[49] Furthermore, some tumors harboring *MET* amplifications were noted to be highly sensitive to treatment with PHA-665752. CGEN241 (Compugen, Tel Aviv, Israel), a decoy MET (soluble truncated MET receptor), inhibits MET activation mediated by both HGF-dependent and -independent mechanisms, because decoys prevent both ligand binding and MET receptor homodimerization. This agent was noted to be highly efficient in inhibiting tumor growth and preventing metastasis in animal models.[50] OA-5D5 (Genentech, South San Francisco, CA), a one-armed antibody, inhibits HGF-induced MET phosphorylation, proliferation, and migration of U87-MG cells along with enhancement of staurosporin-induced apoptosis in vitro. Local treatment

  

inhibited growth of intracranial U87-MG xenografts with evidence of reduced angiogenesis.[51]

### Clinical Data of MET Inhibitors in Lung Cancer

There are a number of clinical trials for MET and HGF that have come to fruition recently. Emphasized in the next section are some of the trials that have been preliminarily reported and some that are ongoing. As more therapeutic responses are identified, we believe that a number of trials will also be forthcoming against lung cancer (Table 1).

## THERAPEUTIC MONOCLONAL ANTIBODIES SPECIFIC TO MET/HGF

### AMG 102

AMG 102 (rilotumumab; Amgen, Thousand Oaks, CA) is a humanized monoclonal antibody directed against HGF that interferes with the interaction between HGF and MET, preventing MET activation.[52] Immunoprecipitation experiments show that AMG 102 preferentially binds to the mature, active form of HGF.[53] AMG 102 has shown enhancement of efficacy of temozolomide or docetaxel in U87-MG cells and xenograft models.[54] A phase Ib study of AMG 102 in combination with bevacizumab or motesanib in advanced solid tumors showed acceptable toxicity, with treatment-emergent adverse events among patients receiving AMG 102 plus bevacizumab being generally mild and including fatigue (75%), nausea (58%), constipation (42%), and peripheral edema (42%).[55] Currently, a phase I/II study of AMG 102 and erlotinib in patients with recurrent or progressive advanced-stage NSCLC is being conducted (NCT01233687).

### Ficlatuzumab

Ficlatuzumab (AV-299; AVEO, Cambridge, MA), formerly known as SCH 900105, discovered by AVEO through its Human Response Platform, is a potent anti-HGF/MET antibody currently in phase II development. Clinical data from phase I studies of ficlatuzumab indicated a favorable tolerability profile[56,57] with good combinability with the EGFR inhibitors erlotinib and gefitinib and no dose-limiting toxicities up to the highest dose tested (20 mg/kg). In June 2011, patient enrollment was completed for an ongoing phase II trial evaluating ficlatuzumab in combination with gefitinib as first-line therapy for patients with WT and mutant EGFR NSCLC. Complete data from this study are still pending.

### MetMAb

Genentech developed a single-armed humanized modified 5D5 anti-MET antibody specifically designed as a monovalent antibody to avoid agonistic activity that may occur when a bivalent antibody binds two MET molecules.[58] MetMAb (onartuzumab; Genentech-Roche) binds to the sema domain of MET, inhibiting HGF from binding to MET, thereby blocking ligand-induced MET dimerization and activation of the intracellular kinase domain,[51] leading to inhibition of the downstream signaling activity and cellular response.[59] A phase Ib trial established the safety and recommended dose (15 mg/kg every 3 weeks). [60]

Efficacy data were recently presented for MetMAb from a global, randomized, double-blind phase II study comparing MetMAb plus erlotinib with placebo plus erlotinib in second- and third-line NSCLC. One hundred twenty eight patients were randomly assigned between two arms with 95%, 88%, and 75% tissue available for MET immunohistochemistry (IHC), *EGFR*/*KRAS* mutational analysis, and MET fluorescent in situ hybridization (FISH) analysis, respectively. In MET-positive NSCLC, which constituted more than half the population (54%), MetMAb plus erlotinib resulted in clinically and statistically improved progression-free survival and overall survival (OS), with OS benefit noted both in MET FISH ≥ five copies positive and FISH-negative/IHC 2+/3+ patients (n = 65; hazard ratio, 0.37; median OS, 12.6 months for MetMAb plus erlotinib *v* 4.6 months for placebo plus erlotinib; $P = .002$). The benefit observed in FISH-negative/IHC-positive patients ($P = .09$) signified that IHC might be a more sensitive MetMab response predictor.[61] Recently, Catenacci at al[62] showed a complete response for 2 years in a patient with chemotherapy-refractory metastatic gastric cancer with high *MET* gene polysomy and pretreatment evidence of autocrine production of HGF.

## MET KINASE INHIBITORS

### Tivantinib

Tivantinib (ARQ-197) is an oral, non–ATP-dependent selective MET inhibitor (ArQule [Woburn, MA] in partnership with Daiichi Sankyo [Tokyo, Japan] and Asian licensee Kyowa Hakko Kirin [Tokyo, Japan]) developed for the potential treatment of solid tumors, including NSCLC. Tivantinib inhibits MET autophosphorylation and is highly selective for the inactive or unphosphorylated form of MET.[63] Exposure to tivantinib results in the inhibition of proliferation of MET-expressing cancer cell lines as well as the induction of caspase-dependent apoptosis in cell lines with constitutive MET activity.[64] Tivantinib is metabolized rapidly by CYP2C19 and moderately by CYP3A4. Patients with functionally inferior CYP2C19 genotype (*2/*2,*2/*3*,*3/*3) are distinguished as poor metabolizers (PMs). Racial disparity was noted with the rate of PMs to be approximately 20% in Asians and 3% in whites in one Japanese study. CYP2C19 genotype noticeably affected the exposure to tivantinib, with CYP2C19 PMs showing higher exposure. This led to a 360-mg twice per day dose for extensive metabolizers and a 240-mg twice per day dose for PMs. Results from ARQ 197-209, a global randomized, placebo-controlled, phase II clinical trial of erlotinib plus tivantinib versus erlotinib plus placebo in previously treated, EGFR inhibitor–naive patients with locally advanced or metastatic NSCLC, were recently presented. One hundred sixty-seven patients were randomly assigned to erlotinib plus tivantinib (84 patients) or erlotinib plus placebo (83 patients), with some imbalances noted in treatment arms in NSCLC histology (adenocarcinoma in 54% of patients receiving erlotinib plus tivantinib and 64% receiving erlotinib plus placebo) and predictive molecular genotypes (*EGFR* mutations: 7% and 13% in tivantinib and placebo arms, respectively; *KRAS* mutations: 12% and 6% in tivantinib and placebo arms, respectively). Progression-free survival was prolonged with erlotinib plus tivantinib (hazard ratio, 0.81; 95% CI, 0.57 to 1.15; $P = .23$). It was particularly impressive in patients with nonsquamous histology, EGFR WT status, and *KRAS* mutations. Safety analysis revealed no major differences between arms with adverse events.[65] A follow-up phase III trial has been initiated. Nine hundred eighty-eight patients are planned to be stratified by the number of prior therapies, sex, smoking history, and *EGFR* and *KRAS* mutation

status. This study is powered to detect a significant improvement in median OS in the erlotinib plus tivantinib arm over erlotinib alone.[66] A similar study is under way in Osaka, Japan (sponsored by Kyowa Hakko Kirin), with a primary objective of determining whether the combination regimen of tivantinib with erlotinib will improve OS in EGFR WT patients with locally advanced or metastatic nonsquamous NSCLC (NCT01377376).

### Cabozantinib

Cabozantinib (XL184/BMS-907351; Exelixis [South San Francisco, CA]/Bristol-Myers Squibb [Princeton, NJ]) is a potent inhibitor of MET and vascular endothelial growth factor receptor 2 (VEGFR2) that also inhibits RET, KIT, AXL, and FLT3.[67] Cabozantinib has been shown to inhibit endothelial cell tubule formation, cellular migration and invasion, tumor cell proliferation in a variety of tumor types in vitro, and MET/VEGFR2 phosphorylation in vivo. It also disrupts the tumor vasculature, leading to tumor and endothelial cell death in a dose-dependent fashion. In a phase II study in men with metastatic castrate-resistant prostate cancer with up to one previous chemotherapy treatment, cabozantinib resulted in tumor response, partial or complete resolution of lesions on bone scan, and symptom relief.[68] Yakes et al[67] showed that treatment with cabozantinib did not result in any increase in lung tumor burden in an experimental model of metastasis, which has been observed with other vascular endothelial growth factor signaling inhibitors that do not target the MET pathway. Data from a phase Ib/II study of cabozantinib with and without erlotinib in patients with NSCLC were recently presented with the primary objectives being tolerability of erlotinib with cabozantinib, maximum-tolerated dose, and pharmacokinetic and pharmacodynamics parameters. Combination treatment resulted in a substantial decrease in pMET and pERK. There was no evidence of drug-drug interaction, with encouraging clinical activity of cabozantinib plus erlotinib in a largely erlotinib-pretreated population, including patients with $EGFR^{T790M}$ mutation and *MET* amplification. Interim results of a phase II randomized discontinuation trial in patients with advanced solid tumors were recently presented. All eligible patients had progressive measurable disease with or without bone metastasis. Patients received cabozantinib 100 mg daily over a 12-week lead-in stage. With nine different types of solid tumors, 398 of 483 patients (60 patients with NSCLC and 21 patients with SCLC) were evaluated. Forty percent of patients with NSCLC were on study treatment for more than 3 months. Results from the NSCLC cohort ($n = 60$) showed partial response in six patients (five with adenocarcinoma and one with squamous histology) with RECIST response ($\geq 30\%$) in 11 patients. Overall, 39 partial responses and one complete response were observed in 490 patients. Tolerability profile was consistent with that of other TKIs.[69]

### Crizotinib

The anaplastic lymphoma kinase (ALK) became a potential therapeutic target after the discovery of the fusion protein EML4-ALK in a small Japanese study.[70] Recently, the US Food and Drug Administration approved crizotinib (PF-2341066; Pfizer) for patients with NSCLC harboring *EML4-ALK* gene rearrangement. Interestingly, crizotinib was initially developed by Pfizer as an orally bioavailable, ATP-competitive, small-molecule MET inhibitor showing good efficacy in preclinical[71,72] and phase I studies.[73] Zou et al[71] showed that crizotinib potently inhibited HGF-stimulated endothelial cell survival and invasion, as well as serum-stimulated tubulogenesis in vitro. Crizotinib showed dose-dependent antitumor efficacy with strong correlation to inhibition of MET phosphorylation in vivo.[71] MET signaling inhibition by crizotinib in *MET*-amplified lung cancer cell lines has been shown to induce apoptosis along with inhibition of AKT and extracellular signal–regulated kinase phosphorylation.[74] Recently, there have been case reports of rapid durable clinical response with crizotinib in patients with NSCLC with absence of ALK rearrangement and de novo *MET* amplification. This clinical benefit most likely is attributable to the MET-inhibitory property of crizotinib.[46] Similar results were shown in another case report study showing rapid radiographic and clinical improvement after treatment with crizotinib in a *MET*-amplified recurrent glioblastoma multiforme.[75]

### Foretinib

Foretinib (XL880, EXEL-2880, GSK1363089; Exelixis/GlaxoSmithKline [Philadelphia, PA]) is a small-molecule kinase inhibitor that targets members of the HGF and vascular endothelial growth factor RTK families (dual VEGFR2/MET inhibitor). It also has inhibitory activity toward Flt-3, KIT, PDGFR-$\beta$, and Tie-2 but at significantly higher concentrations; therefore, it is not a potent inhibitor of these receptors particularly in vivo and in phenotypic assays. Three phase I studies have been completed studying the maximum-tolerated dose and bioavailability.[76] Two phase II studies have been completed in patients with head and neck cancer and gastric cancer. There is currently a randomized phase I/II trial looking at adverse effects of erlotinib with or without the MET/VEGFR2 inhibitor foretinib. This trial is designed to investigate how well foretinib works in treating patients with locally advanced or metastatic NSCLC who have not responded to previous chemotherapy.

## SUMMARY

There have been extensive preclinical/clinical studies performed to elucidate the mechanism of the MET/HGF inhibitory pathway in lung cancer and other solid malignancies. However, questions still remain regarding how to best use this pathway in NSCLC. We must determine, either on a clinical or molecular basis, the subset of patients with NSCLC who will benefit from MET inhibition therapy, as a single agent or in combination. Looking at *MET* amplification, mutation, and overexpression, as well as HGF levels in the context of EGFR and *KRAS* mutations, is important in determining the right cohort for these agents. Standardization and optimization of *MET* amplification/expression by FISH, chromogenic in situ hybridization, or IHC is going to be decisive in future clinical developments. It is crucial to develop a companion diagnostic, along with predictive biomarkers, for anti-MET/HGF therapeutics.

Furthermore, we must determine whether these agents should be used as first-line or second-line therapy and in combination or alone. Clinical trials with MetMab and tivantinib have been used in a primary setting with some emerging data regarding use of these agents either alone or in combination in EGFR-TKI–naive patients with NSCLC. However, cabozantinib has been used in the secondary setting. Ultimately, one could also envision using these inhibitors in earlier stages, as well as in combination with radiation therapies.

  

Looking at our experience with other TKIs in NSCLC, acquired resistance to these agents seems to be an unavoidable consequence. We still have to investigate this issue and make concerted efforts toward identifying potential mechanisms involved in resistance. With our deeper understanding of tumor biology and molecular pathways, evaluating rebiopsy specimens can be a valid option for finding areas of resistant disease in tumor samples and discovering new molecular mutations and treating them accordingly.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

## AUTHOR CONTRIBUTIONS

**Manuscript writing:** All authors
**Final approval of manuscript:** All authors

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