Review

Molecular Cancer Therapeutics

MET in Lung Cancer: Biomarker Selection Based on Scientific Rationale

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Abstract

MET or hepatocyte growth factor (HGF) receptor pathway signaling mediates wound healing and hepatic regeneration, with pivotal roles in embryonic, neuronal, and muscle development. However, dysregulation of MET signaling mediates proliferation, apoptosis, and migration and is implicated in a number of malignancies. In non–small cell lung cancer (NSCLC), aberrant MET signaling can occur through a number of mechanisms that collectively represent a significant proportion of patients. These include MET or HGF protein overexpression, *MET* gene amplification, *MET* gene mutation or fusion/rearrangement, or aberrations in downstream signaling or regulatory components. Responses to MET tyrosine kinase inhibitors have been documented in clinical trials in patients with *MET*-amplified or MET-overexpressing NSCLC, and case studies or case series have shown that *MET* mutation/deletion is a biomarker that is also predictive of response to these agents. However, other recent clinical data have highlighted an urgent need to elucidate optimal biomarkers based on genetic and/or protein diagnostics to correctly identify patients most likely to benefit in ongoing clinical trials of an array of MET-targeted therapies of differing class. The latest advances in the development of MET biomarkers in NSCLC have been reviewed, toward establishing appropriate MET biomarker selection based on a scientific rationale. *Mol Cancer Ther; 16(4); 555–65.* ©*2017 AACR.*

Introduction

The *MET* proto-oncogene was originally identified as a fusion partner with the translocated promoter region of the *TPR* gene in a chemically transformed osteosarcoma-derived cell line (1). The MET protein encoded by this proto-oncogene was later found to be a transmembrane receptor tyrosine kinase (RTK) activated by an endogenous ligand, scatter factor, or hepatocyte growth factor (HGF; refs. 2–5). Binding of HGF to MET [or HGF receptor (HGFR)] results in receptor dimerization and phosphorylation of tyrosine residues, ultimately leading to the phosphorylation of intracellular docking sites where adaptor proteins bind to activate downstream signaling (4, 6, 7). Activated signaling pathways include mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K)/AKT (protein kinase B), signal transducer and activator of transcription proteins, and nuclear factor-κB (8–10). In normal physiology, these signaling pathways promote activation of cytoplasmic and nuclear processes, which lead to a variety of cellular functions, including proliferation and protection from apoptosis (8–10). The MET pathway also mediates functions such as wound healing and hepatic regeneration, and has pivotal roles in normal liver development (11), embryonic placental development, and the formation of muscle and neurons (12–15).

HFG/MET in Lung Cancer

Dysregulation of MET signaling–mediated proliferation, apoptosis, and migration through overexpression of MET and amplification or mutation of the *MET* gene has been widely demonstrated in oncogenic processes across multiple tumor types and has been reviewed elsewhere (10, 16–18). Moreover, it is notable that all three of these mechanisms of MET/*MET* dysregulation have been documented in non–small cell lung cancer (NSCLC; refs. 19–22). Early studies established that MET can be overexpressed or activated [as measured by phosphorylation of the catalytic domain as well as juxtamembrane (JM) domain], or the gene mutated (in the semaphorin or JM domains) and/or amplified in lung cancer. For instance, studies on small cell lung cancer (SCLC) cell lines established the multipurpose nature of MET/HGF pathway activation during tumor progression and invasion, which occurs via dysregulation of diverse biological functions such as proliferation and differentiation, transcriptional control, cell-cycle G_1/S checkpoint, cytoskeletal functions, survival, motility, and apoptosis (23). Both epidermal growth factor receptor (EGFR) and MET are widely expressed on cancer cells, and both RTKs are implicated in these diverse signaling processes. Indeed, synergistic effects of epidermal growth factor (EGF) and HGF on proliferation, and additive effects on motility, were noted in preclinical studies in NSCLC cells. For example, increased membrane ruffling to form a motile cell surface was observed when cells were stimulated with HGF and EGF independently, and when these growth factors were combined, an additive effect was observed (24). These preclinical studies suggested that the combination of inhibitors for MET and EGFR RTKs could potentially produce synergistic antitumor effects (24). Indeed, a synergistic effect on inhibition of cell proliferation and apoptosis was

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Note: Supplementary data for this article are available at Molecular Cancer Therapeutics Online (http://mct.aacrjournals.org/).

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seen when a novel first-generation MET inhibitor, SU11274, was combined with EGFR inhibitors such as AG1478 or gefitinib (24). The synergism and cross-talk of EGFR and MET pathways in NSCLC, and the potential of simultaneous inhibition, were thus recognized in these studies.

Therapy combining various targeted agents or other standard therapies with MET inhibitors has also been explored in other preclinical studies, including synergistic effects of when MET and EGFR inhibitors were combined in NSCLC cell lines, and head and neck squamous cell carcinoma (SCCHN) cells (24, 25). Combined inhibition of MET and mammalian target of rapamycin resulted in cooperative inhibition of cell growth in *TPR-MET* transformed cells expressing a constitutively active variant of MET, and in MET-expressing NSCLC cells (26). MET inhibition is also synergistic with cisplatin in SCCHN cancer cell lines (25) and also appears to be synergistic with radiation in cell lines in some studies, although crizotinib (Pfizer), an inhibitor of MET, anaplastic lymphoma kinase (ALK), and ROS1 kinases, failed to enhance the effects of radiation in SCCHN xenograft models (27). Furthermore, MET inhibition was synergistic with topoisomerase-I inhibition in SCLC cell lines, with a significant positive correlation observed between *MET* gene copy number (GCN) and topoisomerase-I nuclear expression (28).

Role of MET and HGF in Induction of Drug Resistance

Several RTKs often expressed on cancer cells activate signaling pathways that converge on common downstream effectors. This "overlap" may, in part, be implicated in resistance to RTK-based treatment, which is commonly observed in cancer patients. Resistance to targeted agents may be mediated by the stroma, and preclinical investigations of growth-factor–driven resistance have shown that increasing levels of ligands with a similar signaling output, such as PI3K or MAPK, may confer innate or acquired resistance to inhibitors of an oncogenic kinase (29, 30).

Loss of drug sensitivity in tumor cells through exposure to RTK ligands in the tumor microenvironment was demonstrated in *BRAF*-mutant melanoma cells, with HGF conferring resistance to the BRAF inhibitor PLX4032 (vemurafenib; ref. 30). Stromal secretion of HGF resulted in activation of MET, thereby reactivating the MAPK and PI3K/AKT pathways (30). Consequently, in cell models at least, it is feasible that dual inhibition of RAF and MET can reverse drug resistance (30). These data highlight the redundancy of RTK-transduced signaling in cancer cells and the wide-ranging effects of RTK ligands that lead to innate and acquired resistance, which may potentially be overcome through combinations of targeted agents (29, 30).

MET amplification in NSCLC is implicated in acquired resistance to EGFR inhibitors and has been reported in approximately one-fifth of cases with EGFR inhibitor resistance (31–34). This provides further therapeutic rationale for combinations of MET inhibitors with EGFR inhibitors to treat selected patients with NSCLC.

MET Biomarkers in NSCLC

The varied mechanisms of MET activation in lung cancer, including overexpression of MET and/or its ligand, HGF, and genetic alterations to *MET* (e.g., mutations, amplification, translocation, or dysregulated transcription), and impaired degradation of MET, provide an array of potential biomarkers (Table 1). The challenge now faced is to identify which of these biomarkers holds the most promise to select appropriate patients for MET-targeted treatment with the array of agents currently in development.

Expression of MET/p-MET and HGF proteins

Human tissue microarray studies reveal that while HGF is widely expressed in both tumor and nonmalignant tissue, MET is differentially expressed in solid tumors (35). Positive staining for MET and HGF, which is thought to have a progenitor role, was observed in the bronchioalevolar junctions of lung tumors (35). Overexpression of MET occurs with a high frequency (35%–72%) in NSCLC tumors (Table 1). For example, in a recent study of more than 200 NSCLC samples, 37% were scored as immunohistochemistry (IHC) $\geq 2+$ for MET expression (36). In another study, MET was detected in eight of nine NSCLC cell lines and in all of 23 NSCLC tumor samples examined (37). Furthermore, 61% of tumor tissues strongly expressed MET, with high MET expression being confirmed as particularly common in adenocarcinoma (67%). It is noteworthy that increased levels of circulating MET mRNA, which were 1.4–8 times above normal concentrations in 68% of patients with overexpression of MET in their tumors, have been found to correlate with early disease recurrence in NSCLC patients (38).

In addition to total levels of the protein, MET activated by ligand to induce phosphorylation of the JM domain can be assayed via phospho-MET (p-MET). Using IHC, specific expression of p-MET has been observed in approximately two-thirds of lung cancer samples and has also been reported to be preferentially expressed at the invasive fronts of NSCLC tumors (35, 37). In a study of the expression and prognostic role of MET, p-MET, and HGF in patients with NSCLC and SCLC ($N = 129$), high expression of two specific forms of p-MET—cytoplasmic expression of Y1003 and nuclear expression of Y1365—was associated with significantly worse overall survival [OS; $P = 0.016$; hazard ratio (HR), 1.86; 95% confidence interval: 1.12–3.07; and $P = 0.034$; HR: 1.70; 95% confidence interval: 1.04−2.78, respectively]. Consequently, specific forms of p-MET may also serve as potential biomarkers in lung cancer (39).

Serum HGF (s-HGF) is also feasible as a biomarker in MET-addicted cancer. Levels of s-HGF were significantly elevated in patients with SCLC compared with healthy individuals (0.40 ± 0.17 vs. 0.26 ± 0.093, $P = 0.0083$; ref. 40). A high s-HGF level has also been shown to be associated with epithelial-to-mesenchymal transition in patients with SCLC ($N = 112$; ref. 41). Of these patients with stage IV disease, increased s-HGF levels at response evaluation ($P = 0.042$) and at progression ($P = 0.003$) were associated with poor outcome (41).

MET mutations

Mutations in the splice site of *MET* that result in skipping of exon 14 are important molecular drivers in NSCLC (37, 42). Such mutations have recently been shown to occur in 3% to 4% of NSCLC adenocarcinomas, 2% of squamous cell carcinomas, and 1% to 8% of other subtypes of lung cancer (Table 1; refs. 43–46). Novel JM domain (exon 14/15) mutations in *MET* were first identified in SCLC, in three of 10 cell lines and in four of 32 SCLC tumor tissue samples examined (42). *MET* alterations included two different missense mutations in the JM domain (R988C found in NCI-H69 and H249 cell lines; and T1010I in SCLC

Table 1. Reported incidence and functional consequences of MET biomarkers in lung cancer

MET dysregulation	Functional consequences	Biomarker	Reported incidence in samples from lung cancer patients	Reference
Gene overexpression	Reduces or removes the requirement for ligand activation, leading to sustained or altered signaling properties of the receptor	MET/p-MET expression by IHC	NSCLC	
			37% IHC ≥2+	(36)
			61% IHC ≥2+	(37)
			ADC	
			35%	(76)
			67% IHC ≥2+	(37)
			72%	(77)
			SCC	
			38%	(77)
			p-MET in NSCLC	
			67%	(35, 37)
HGF expression	Ligand-induced activation could cause sustained or altered signaling	Circulating plasma HGF	Elevated in SCLC	(40)
Gene mutation	*MET* mutation can lead to reduced degradation, with consequent overexpression and sustained or altered signaling	*MET* exon 14 skipping mutation	ADC	
			3%	(43–46)
			4%	(43, 44, 46, 78)
			SCC	
			2%	(45)
			Other lung cancer subtypes	
			2%	(43, 44, 46)
			1%–8%	(45)
Gene amplification	Can lead to overexpression and reduce or remove the requirement for ligand activation, leading to sustained or altered signaling properties of the MET receptor	*MET* GCN MET/CEP7 ratio	Newly diagnosed ADC	
			2%	(46)
			4%	(21, 56)
			5%	(55)
			EGFR TKI-resistant ADC	
			5%	(57, 58)
			17%	(33)
			21%	(31)
			22%	(34)
Gene rearrangement	May reduce or remove the requirement for ligand activation, leading to sustained or altered signaling properties of the MET receptor	*MET* rearrangement	Identified in an ADC patient	(67)
Downstream MET signaling alteration	Decreases RTK turnover to perpetuate oncogenic activation of MET	*CBL* mutation or LOH	Detected in NSCLC patients	(69)

Abbreviations: ADC, adenocarcinoma; CEP, chromosome enumeration probe; SCC, squamous cell carcinoma.

tumor sample). Also, a semaphorin domain missense mutation (E168D in SCLC tumor sample), two-base-pair insertional mutations [IVS13-(52–53)insCT in SCLC tumor samples] within the pre-JM intron 13, as well as an alternative transcript involving exon 10 (H128 cell line), were identified (42). The two reported JM mutations affected cell proliferation, resulting in small but significant growth factor independence in the IL3-dependent BaF3 cell line, and were found to regulate cell morphology and adhesion, and enhanced tumorigenicity when introduced into an SCLC cell line (42). The JM mutations also altered MET RTK signaling, resulting in preferentially increased constitutive tyrosine phosphorylation of various cellular proteins, with significant implications in cytoskeletal functions and metastatic potential. These novel *MET* JM gain-of-function somatic mutations associated with a more aggressive phenotype were among those mutations subsequently identified in NSCLC adenocarcinoma tissues (R988C, R988C + T1010I, S1058P, and an alternative exon 14 splice variant product skipping the entire JM domain; ref. 37).

Using NSCLC tissues and cell lines, we (37) and Kong-Beltran and colleagues (22) functionally characterized tumor-specific somatic intronic *MET* mutations, which immediately flank exon 14 (22). Exon 14 was found to encode the JM domain and Y1003 residue that serves as the binding site for casitas B-lineage lymphoma (CBL), the E3 ubiquitin ligase that controls MET turnover (22). In each case of *MET* exon 14 skipping, confirmed by reverse transcriptase polymerase chain reaction, the result was a decrease in the ubiquitination of MET and consequent delayed receptor downregulation after stimulation with HGF. Downstream ligand-dependent signaling through MAPK was also prolonged in cells transfected with a *MET* exon 14 splice variant (22). Furthermore, a xenograft model of Rat1A fibroblasts stably transfected with a *MET* exon 14 splice variant developed particularly aggressive tumors compared with wild-type *MET* (22). Overall, the biological effects of *MET* JM mutations are increased tumorigenicity, reduced adhesion, and disorganized cytoarchitecture compared with wild-type, increased cell survival, motility and migration, increased phosphorylation of focal adhesion proteins, such as paxillin, and HGF independence (23, 37, 47).

Elegant studies have validated the nematode *C. elegans* as a model for rapid screening of the functional aspects of mutant forms of cancer genes, with METR988C and METT1010I harboring wild-type or frequently seen mutant forms of MET in lung cancer (48). Expression of these mutations in this model led to low fecundity and abnormal vulval development characterized by hyperplasia. In addition, exposure of *MET*-mutant transgenic worms to nicotine resulted in enhanced abnormal vulval

Table 2. Case reports and series of patients with lung adenocarcinomas and *MET* exon 14 alterations responding to MET inhibitors

Patient no.	Age and gender	Smoking status	*MET* exon 14 alterations	MET IHC	*MET* amp	Best response	Reference
1	86 M	NS	Splice acceptor deletion	2+	NA	PR to crizotinib	Jenkins *et al*., 2015 (50)
2	71 M	ES	D1028H Splice donor mutation	NA	No	PR to crizotinib	Waqar *et al*., 2015 (51)
3	76 F	ES	D1010H	NA	NA	PR to crizotinib	Mendenhall *et al*., 2015 (52)
4	80 F	NS	Splice donor mutation	3+	Yes	CR (PERCIST) to cabozantinib	Paik *et al*., 2015 (44)
5	78 M	ES	Splice donor deletion	3+	NA	PR to crizotinib (lung) PD to crizotinib (liver)	Paik *et al*., 2015 (44)
6	65 M	ES	Splice donor mutation	NA	NA	PR to crizotinib	Paik *et al*., 2015 (44)
7	90 F	NS	Splice donor mutation	NA	NA	PR to crizotinib	Paik *et al*., 2015 (44)
8	67 F	NS	D1028N Splice donor mutation	NA	NA	PR to crizotinib	Mahjoubi *et al*., 2016 (79)

Abbreviations: CR, complete response; ES, ever-smoker; F, female; M, male; NA, not available; NS, never-smoker; PERCIST, PET Response Criteria in Solid Tumors; PR, partial response.

development, fecundity, and locomotion (48). This model also demonstrated colocalization of MET and EGL5 (PAX8 ortholog) proteins in embryos of the organism (49). PAX8 provides signals for growth and motility of NSCLC cells and is required for MET and RON expression; also, it may have therapeutic potential (49).

Responses to the MET inhibitors crizotinib and cabozantinib have been documented in case reports of patients with lung adenocarcinoma and *MET* exon 14 alterations (Table 2; refs. 44, 50–52). In phase I clinical studies of the investigational MET inhibitor capmatinib (INC280, Novartis), two patients with MET-dependent NSCLC and *MET* exon 14 alterations were identified by comprehensive genomic profiling. In one patient with large-cell carcinoma who was treated for over 5 months, there was a partial response comprising a 53% reduction in tumor, and in the other patient, who had squamous NSCLC that had failed prior therapies and was treated for 13 months, there was a partial response comprising a 61% reduction in tumor (43). *MET* mutations in the semaphorin domain have been shown to affect ligand binding: MET-N375S, the most frequent mutation of MET, most common among male smokers and squamous cell carcinoma, confers resistance to MET inhibition based on HGF binding, molecular modeling, and apoptotic susceptibility to MET inhibitor studies (53).

Larger clinical studies focusing on patients with *MET* mutations, particularly exon 14 alterations, are now required to prospectively obtain response rates associated with MET inhibitors in this patient population. These studies will also need to evaluate any association of MET inhibitor efficacy with known disease driving mutations such as KRAS, EGFR, BRAF, or ALK (54). Nonetheless, because the potentially actionable genetic alterations within exon 14 are diverse, in-depth molecular profiling of all lung cancer patients, irrespective of additional disease driving mutations, is recommended (54).

MET amplification

In NSCLC, amplification of *MET* typically occurs in about 2% to 5% of newly diagnosed adenocarcinomas (Table 1; refs. 21, 46, 55, 56). Interestingly, a much greater incidence of *MET* amplification, ranging from 5% to 22%, has been reported in patients with NSCLC following treatment with erlotinib/gefitinib (Table 1; refs. 31, 33, 34, 57, 58). Amplification of *MET* (and overexpression of the protein) is also a common event in brain metastases of NSCLC (59). Furthermore, fluorescence *in situ* hybridization (FISH)–positive *MET* status predicts worse survival in patients with advanced NSCLC (56, 60). An analysis of OS based on MET FISH status-derived GCN revealed that increased GCN is an independent negative prognostic factor in surgically resected NSCLC, with OS of 25.8 months for patients with *MET* $\geq$5 copies/cell compared with 47.5 months for patients with *MET* <5 copies/cell ($P = 0.0045$; ref. 21). These data support further investigation of anti-MET therapeutic strategies in appropriately selected patients (21). The question remains as to how biomarkers should be best utilized for patient selection.

While preclinical studies indicated that agents targeting MET are effective in the presence of high levels of *MET* gene amplification (61, 62), there is currently no clear consensus on how best to determine *MET* gene amplification in the clinical setting. In a phase I study of capmatinib, preliminary antitumor activity was seen in patients with *EGFR*-wild-type NSCLC and a high level of *MET* amplification (*MET* GCN $\geq$6; ref. 63), while a study of capmatinib plus gefitinib in patients with *EGFR*-mutant, *MET*-positive NSCLC reported an overall response rate of 50% in patients with *MET* GCN $\geq$6 (64). Although, based on preliminary data, *MET* GCN appears to be a good predictive biomarker, the FISH MET/chromosome enumeration probe 7 (CEP7) ratio is also a relatively simple primary measure of amplification. In a study of crizotinib in *MET*-amplified NSCLC, as determined by MET/CEP7 ratio [$\geq$1.8 to $\leq$2.2 (low), >2.2 to <5 (intermediate) and $\geq$5 (high)], antitumor activity was seen in patients with intermediate and high ratios, with a high response to therapy only observed in individuals in the gene ratio $\geq$5 category (65). One possible drawback of using the MET/CEP7 gene ratio is that this technique may not identify all amplified patients due to the unique pathophysiology of NSCLC. In some cases, amplicons occur that include the centromere control protein and the *MET* gene or the centromere protein but not the *MET* gene; in the latter case, the ratio may be falsely lowered (66).

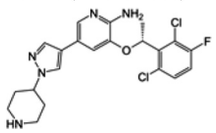
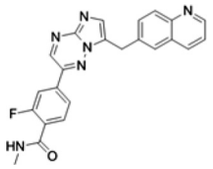
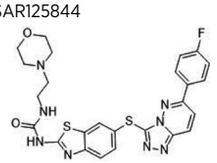
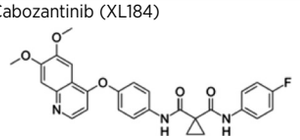
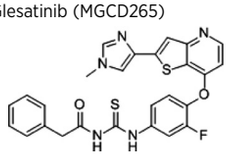
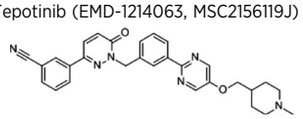
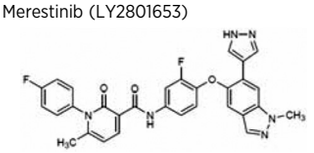
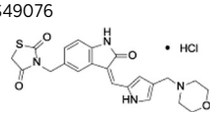
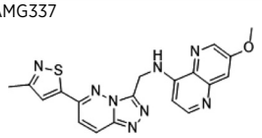
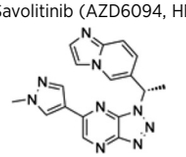
MET rearrangement

Compared with mutations and amplification of *MET*, gene rearrangements are less well documented. However, the kinase fusion *KIF5B–MET* has been identified in a case of lung adenocarcinoma, and it is feasible that this translocation event could potentially account for a significant portion of MET-driven oncogenesis (67). This fusion-driven activation of MET is most likely due to constitutive dimerization and is likely to be an actionable target for drug-induced inhibition, similar to other fusions in lung cancer such as those involving *ALK*, *ROS1*, and *RET* (67).

MET processing: degradation/transcription

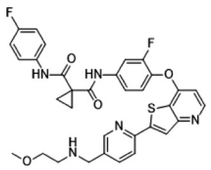
CBL is a mammalian gene encoding an E3 ubiquitin ligase and adaptor protein involved in cell signaling and protein ubiquitination (68). CBL thus has an important role in RTK downregulation and degradation (68). Somatic mutations [or loss of

Table 3. MET-targeted therapies in development for NSCLC and/or solid tumors

Agent and structure	Target(s)	Company	Status (MET$^+$ indications)
Small molecule tyrosine kinase inhibitors			
Crizotinib (PF-02341066) 	ALK/ROS/MET	Pfizer	Phase II (NSCLC, GC, UC, pRCC)
Capmatinib (INC280, INCB28060) 	MET	Novartis	Phase II (NSCLC, HCC, pRCC, CRC, HNSCC)
SAR125844 	MET	Sanofi	Phase II (NSCLC)
Cabozantinib (XL184) 	MET/RET/others	Exelixis	Phase II (NSCLC)
Glesatinib (MGCD265) 	MET/AXL/others	Mirati Therapeutics	Phase II (NSCLC)
Tepotinib (EMD-1214063, MSC2156119J) 	MET	Merck KGaA	Phase II (NSCLC, HCC)
Merestinib (LY2801653) 	MET/ROS1/AXL/FLT3/others	Eli Lilly	Phase II (NSCLC)
S49076 	MET/AXL/FGFR1–3	Servier	Phase I/II (NSCLC)
AMG337 	MET	Amgen	Phase I (GC, ST)
Savolitinib (AZD6094, HMPL-504, volitinib) 	MET	AstraZeneca/Hutchison Medi Pharma	Phase I (pRCC, GC, NSCLC)

(Continued on the following page)

Table 3. MET-targeted therapies in development for NSCLC and/or solid tumors (Cont'd)

Agent and structure	Target(s)	Company	Status (MET$^+$ indications)
Sitravatinib (MGCD516)	MET/VEGFR/others	Mirati Therapeutics	Phase I (NSCLC, ST)
			
Monoclonal antibodies			
Emibetuzumab (LY2875358)	MET	Eli Lilly	Phase II (NSCLC, GC)
Ficlatuzumab (AV-299)	HGF	AVEO	Phase II (NSCLC); Phase I (HNSCC)

Abbreviations: CRC, colorectal cancer; FGFR, fibroblast growth factor receptor; FLT3, Fms-related tyrosine kinase 3; GC, gastric or esophageal carcinoma; HCC, hepatocellular carcinoma; HNSCC, squamous cell carcinoma of the head and neck; pRCC, papillary renal cell carcinoma; ST, solid tumors; UC, urothelial cancer; VEGFR, vascular endothelial growth factor receptor.

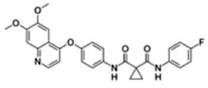
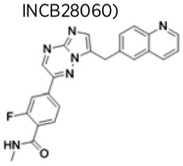
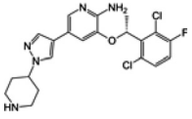
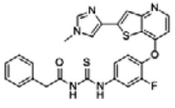
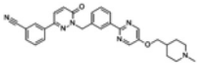
heterozygosity (LOH)] in *CBL* have been detected in NSCLC patients, and expression of these mutations in cell lines was found to result in increased proliferation and cell motility (69). CBL LOH is associated with either *MET* or *EGFR* mutations and may contribute to their oncogenic potential (69). As already described, it is noteworthy that the JM domain of MET is involved in the binding and E3 activity of CBL, and *MET* JM mutations (e.g., Y1003) therefore affect CBL binding and decrease RTK turnover to perpetuate oncogenic activation of MET (22, 70).

Discussion: Potential of MET as a Biomarker in Lung Cancer

The growing prominence of MET inhibition in lung cancer is reflected in the number of molecular aberrations with oncogenic potential that occur in this disease, and in the number and diversity of MET-targeted agents in clinical development in this indication. These include the monoclonal antibodies emibetuzumab, ficlatuzumab, and rilotuzumab, and tyrosine kinase inhibitors (TKI) such as crizotinib, tepotinib, cabozantinib, and capmatinib (Table 3). Recent negative or disappointing clinical trials results pose the question as to whether the biomarkers and their related cutoff values have been chosen appropriately to select patients for enrollment in all studies to date. For instance, despite positive phase II data (71), the phase III METLung trial ($N = 499$) of onartuzumab plus erlotinib failed to show clinical benefit compared with placebo plus erlotinib in patients with MET$^+$ NSCLC (Table 4; ref. 72). In this study, patient biomarker–based selection of patients with MET-overexpressing tumors as measured by IHC (MET SP44) was used to determine eligibility. These negative data suggest that IHC may not be sufficiently sensitive as a diagnostic tool for MET positivity; its use as a standard biomarker for overexpression is further compromised by the lack of standardized interpretation or consensus on optimized cutoff values. Moreover, MET protein expression may have a low predictive value as a tool to detect MET activation and may not always reflect tumor dependency on MET signaling (73). Heterogeneity in the expression of MET within a tumor or across metastatic sites may also lead to unreliable results.

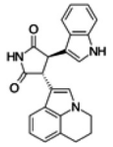
Circulating HGF (cHGF) or MET are attractive potential alternative biomarkers for ligand or receptor overexpression, respectively. For example, elevated cHGF, as measured by ELISA, has been used as a pharmacodynamic biomarker of activity with onartuzumab (74). However, in cases of ligand-independent activation of MET, it is feasible that monoclonal antibody therapy, without drug internalization, may be a less effective therapeutic strategy than TKIs that target the receptor protein kinase directly. Recent data suggest that HGF/MET protein expression alone may be an oversimplification of the oncogenic driver status of "MET-positive" NSCLC, where mutations or translocations and amplification reduce the requirement for ligand activation and lead to sustained or altered signaling properties of the receptor. Although IHC data have been shown to correlate with *MET* amplification (66), clinical study biomarker data (summarized in Table 4) have not confirmed any clear-cut relationships between *MET* mutation, amplification, and overexpression, when collectively applied as predictive biomarkers for MET-targeted therapy. IHC-based MET expression has not been a successful biomarker approach in clinical studies of monoclonal antibodies, and current clinical and biomarker data suggest that genetic changes in *MET*, in particular gene amplification, may be the preferred biomarkers for MET TKI therapy (21, 63–65). The data summarized in Table 4 also indicate that biomarkers for MET TKI therapy need to be optimized based on not only *MET* amplification but also *MET* mutation or translocation status, which constitutes an additional and numerically significant (>4%) molecular subgroup of NSCLC (46). Mutations or altered expression of signaling proteins downstream of MET signaling, such as CBL mutation, are also emerging biomarkers in NSCLC and extend further the range and diversity of potential MET-related biomarkers in this disease. There is therefore an urgent need to elucidate both optimal biomarkers for MET dysregulation, and their application, based on our growing understanding of this oncogenic driver in NSCLC. To facilitate this goal, the medical oncologist and pathologist now have at their disposal a panel of genetic and protein biomarkers for MET dysregulation that together constitute a significant proportion of lung cancer molecular subgroups. Indeed, current data indicate that panels of MET biomarkers are likely to be necessary in the future, and measurements of potential biomarkers should therefore be included in new clinical trial designs for MET inhibitors to facilitate the robust definition of appropriate therapies for specific MET-dysregulated NSCLC subsets. Furthermore, the recent report of a response to crizotinib in a patient with lung adenocarcinoma with MET copy-number gain but without a high-level MET/CEP7 ratio, MET overexpression, or exon 14 splicing mutation (75) indicates that the list of independent predictive biomarkers for response to MET inhibitors may well be extended further. Importantly, since alterations in *MET* gene status have been found to occur in both untreated patients and those who have developed resistance to other targeted therapies, new clinical study designs should consider both patient groups. This

Table 4. Predictive biomarkers evaluated in clinical studies of MET-targeted therapies in patients with NSCLC

Agent	Study	Biomarker (assay)	Comment	Reference
		Tyrosine kinase inhibitors		
Cabozantinib (XL184) 	Phase II cabozantinib + erlotinib in pretreated *EGFR*-mut NSCLC ($N = 37$)	*MET* amplification/GCN (FISH)	Clinical activity (ORR/DCR 8%/65%) was unrelated to *MET* amplification (not detected in any patients)	Reckamp *et al.*, 2015 (80)
Capmatinib (INC280, INCB28060) 	Phase I MET+ (H-score ≥150 or *MET*/centromere ratio ≥2.0 or *MET* GCN ≥5, or ≥50% of tumor cells IHC 2/3+ or IHC 3+ [expansion]) NSCLC ($N = 55$)	MET expression (IHC) *MET* amplification/GCN (FISH) *METΔex14* mutation (NGS)	10/18 MET IHC 3+ patients showing tumor shrinkage also had MET GCN ≥6 ORR/DCR 20%/51% in all patients; ORR/DCR 47%/80% in patients with *MET* GCN ≥6 and 24%/60% in patients with IHC 3+ Preliminary median PFS 3.6 months, increased to 7.4 months for patients with *MET* GCN ≥6 Preliminary activity in patients with either a high level of *MET* amplification and/or *cMETΔex14* mutation	Schuler *et al.*, 2016 (63)
	Phase II capmatinib + gefitinib in MET+ (*MET* GCN ≥4, or ≥50% of tumor cells IHC 3+)/*EGFR*-mut NSCLC	MET expression (IHC) *MET* amplification/GCN (FISH)	ORR/DCR 31%/81% GCN <4: ORR/DCR 14%/77% 4 ≤ GCN <6: ORR/DCR 24%/88% GCN >6: ORR/DCR 50%/84%	Wu *et al.*, 2016 (64)
Crizotinib (PF-02341066) 	Phase I MET+ (*MET*-amplified) NSCLC (PROFILE 1001; $N = 14$)	*MET* amplification as MET/CEP7 ratio (FISH)	Tumor shrinkage seen in intermediate MET (MET/CEP7 ratio >2.2 to <5; ORR 17%) and high MET (MET/CEP7 ratio ≥5; ORR 67%) cohorts	Camidge *et al.*, 2014 (65)
	Phase I *MET* exon 14 altered NSCLC (PROFILE 1001; $N = 21$)	*METΔex14* (NGS)	Clinically meaningful antitumor activity in this subgroup ORR/DCR 44%/94%	Drilon *et al.*, 2016 (78)
Glesatinib (MGCD265) 	Phase I advanced solid tumors ($N = 25$) including NSCLC ($n = 11$)	*MET* mutation or amplification	The first three NSCLC patients (two with *METΔex14* and one with *MET* GCN gain) demonstrated tumor regression	Kollmannsberger *et al.*, 2015 (81)
Tepotinib (EMD-1214063, MSC2156119J) 	Phase I advanced solid tumors/NSCLC ($N = 143$)	MET expression (IHC) *MET* amplification/GCN (FISH)	Exploratory biomarker analyses suggested MET expression and amplification were associated with response	Falchook *et al.*, 2015 (82)

(Continued on the following page)

Table 4. Predictive biomarkers evaluated in clinical studies of MET-targeted therapies in patients with NSCLC (Cont'd)

Agent	Study	Biomarker (assay)	Comment	Reference
Tivantinib (ARQ197) 	Phase II tivantinib + erlotinib (T + E) in advanced NSCLC ($N = 167$)	*MET* amplification/GCN (FISH)	Patients with increased *MET* GCN demonstrated a trend towards PFS benefit from T + E *MET* GCN 2, 3, 4, and 5 revealed PFS HRs of 0.92, 0.75, 0.71, and 0.42, respectively Similar but less vigorous trend for OS No evidence that T + E was worse than E + placebo in patients with low *MET* GCN (<2 or <3)	Sequist *et al.*, 2011 (83)
	Phase III erlotinib ± tivantinib in advanced NSCLC ($N = 1{,}048$)	MET expression (IHC) *MET* amplification/GCN (FISH)	Exploratory subgroup analysis suggested OS improvement in patients with high MET expression (HR 0.70) Longer OS in patients with tumors with *MET* GCN >4 (HR 0.83), but limited sample size Study discontinued for futility	Scagliotti *et al.*, 2015 (84)
	Phase III (Asia) erlotinib ± tivantinib in advanced NSCLC (ATTENTION; $N = 307$)	MET expression (IHC) *MET* amplification/GCN (FISH) HGF expression (IHC) Serum HGF (ELISA)	Tivantinib was associated with a weak OS benefit in patient with high MET expression (HR 0.83) Significant OS benefit in patients with normal *MET* GCN (<4, HR 0.51) Significant OS benefit in patients with high HGF expression (H-score ≥200; HR 0.54) Favorable effect on OS in patients with high serum HGF concentration Enrollment stopped for safety reasons (ILD incidence)	Yoshioka *et al.*, 2015 (85)
		Monoclonal antibodies		
Emibetuzumab (LY2875358)	Phase I MET$^+$ (IHC ≥2+) solid tumors ($N = 62$), including NSCLC ($n = 19$)	MET expression (IHC)	Preliminary, but limited, single-agent clinical activity was observed (DCR 26% in patients with MET IHC ≥2+ NSCLC) IHC was not considered to be a sufficient predictive biomarker	Banck *et al.*, 2015 (86)
Ficlatuzumab	Phase II (Asia) gefitinib ± ficlatuzumab (G + F) in lung adenocarcinoma ($N = 188$)	MET expression (IHC) HGF expression (IHC)	No statistically significant improvement in ORR/PFS Notable difference seen in low MET group (ORR 41% vs. 22%) and median PFS (7.3 vs. 2.8 months) favoring G + F Preliminary OS favored G + F in patients with high stromal HGF ($P = 0.03$) and high MET ($P = 0.18$) biomarkers	Mok *et al.*, 2012 (87)
Onartuzumab	Phase I (Japan) solid tumors and MET$^+$ lung cancer	MET expression (IHC)	PR observed in a patient with an IHC 3+ tumor	Nishio *et al.*, 2015 (88)
	Phase II onartuzumab + erlotinib in advanced NSCLC ($N = 137$)	MET expression (IHC)	Benefit maintained in patients with IHC 2/3+ Detriment in patients with IHC 0/1+ Benefit was proportional to the intensity of expression	Spigel *et al.*, 2013 (71)
		MET expression (IHC) *MET* amplification/GCN (FISH) *MET* mRNA expression (RT-PCR) *HGF* mRNA (RT-PCR) Circulating plasma HGF (ELISA) *MET* exon 14 (RT-PCR)	MET IHC was the most robust predictor of OS and PFS benefit Non-significant OS improvement in patients with high *MET* GCN (mean ≥5 copies/cell) Benefit maintained in MET IHC$^+$/MET FISH$^-$ patients (HR 0.37; $P = 0.01$) *MET* and HGF mRNA levels did not predict significant benefit; nonsignificant OS improvement in patients with high tumor *MET* mRNA levels (HR 0.59) OS favored onartuzumab in patients with low baseline plasma HGF (HR 0.52; $P = 0.09$)	Koeppen *et al.*, 2014 (89)
	Phase III onartuzumab + erlotinib in advanced MET+ (IHC 2/3+) NSCLC ($N = 499$)	MET expression (IHC)	No improvement in OS, PFS, or ORR Trial stopped for futility	Spigel *et al.*, 2014 (72)

Abbreviations: DCR, disease control rate; ELISA, enzyme-linked immunosorbent assay; ILD, interstitial lung disease; *METΔex14*, MET exon 14 deletion; NGS, next-generation sequencing; ORR, overall response rate; PFS, progression-free survival; PR, partial response; RT-PCR, reverse transcription polymerase chain reaction.

highlights the future importance of both upfront and resistance-based genetic testing in lung cancer patients, which should include MET as the probable next major biomarker in lung cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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