REVIEW ARTICLE

Targeting MET in Lung Cancer: Will Expectations Finally Be MET?

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ABSTRACT

The hepatocyte growth factor receptor (MET) is a potential therapeutic target in a number of cancers, including NSCLC. In NSCLC, MET pathway activation is thought to occur through a diverse set of mechanisms that influence properties affecting cancer cell survival, growth, and invasiveness. Preclinical and clinical evidence suggests a role for MET activation as both a primary oncogenic driver in subsets of lung cancer and as a secondary driver of acquired resistance to targeted therapy in other genomic subsets. In this review, we explore the biology and clinical significance behind MET proto-oncogene receptor tyrosine kinase (*MET*) exon 14 alterations and *MET* amplification in NSCLC, the role of *MET* amplification in the setting of acquired resistance to EGFR tyrosine kinase inhibitor therapy in *EGFR*-mutant NSCLC, and the history of MET pathway inhibitor drug development in NSCLC, highlighting current strategies that enrich for biomarkers likely to be predictive of response. Whereas previous trials that focused on MET pathway–directed targeted therapy in unselected or MET-overexpressing NSCLC yielded largely negative results, more recent investigations focusing on *MET* exon 14 alterations and *MET* amplification have been notable for meaningful clinical responses to MET inhibitor therapy in a substantial proportion of patients.

Keywords: *MET* exon 14 skipping alterations; *MET* amplification; non-small cell lung cancer; crizotinib; MET inhibitor; MET overexpression

Introduction

Phase III randomized trials of tyrosine kinase inhibitor (TKI) therapy for *EGFR*-mutant and anaplastic lymphoma receptor tyrosine kinase (*ALK*)-rearranged lung cancers have documented improvements in response and progression-free survival (PFS),[1,2] and seven TKIs have gained regulatory approval for the treatment of patients with these tumors. The treatment landscape continues to evolve as durable responses to targeted therapy have been reported in a growing number of other genomic subsets.[3,4]

The path to approval of targeted therapy for lung cancers with alterations of the MET proto-oncogene receptor tyrosine kinase (*MET*), however, has not been straightforward. First discovered in the mid-1980s, the hepatocyte growth factor receptor (MET) pathway was found in the 1990s to be dysregulated in lung cancer (Fig. 1*A*).[5,6] More than 20 agents targeting MET or its ligand, hepatocyte growth factor (HGF), have undergone preclinical and clinical study, but findings have ranged from relatively high response rates in molecularly preselected subtypes of NSCLC in single-arm trials to the prominent failure of large phase III studies in different trial populations.

This review summarizes MET pathway dysregulation in lung cancers and critiques different scientific methods and clinical trial approaches taken for translating these into predictive biomarkers of benefit from MET inhibition.

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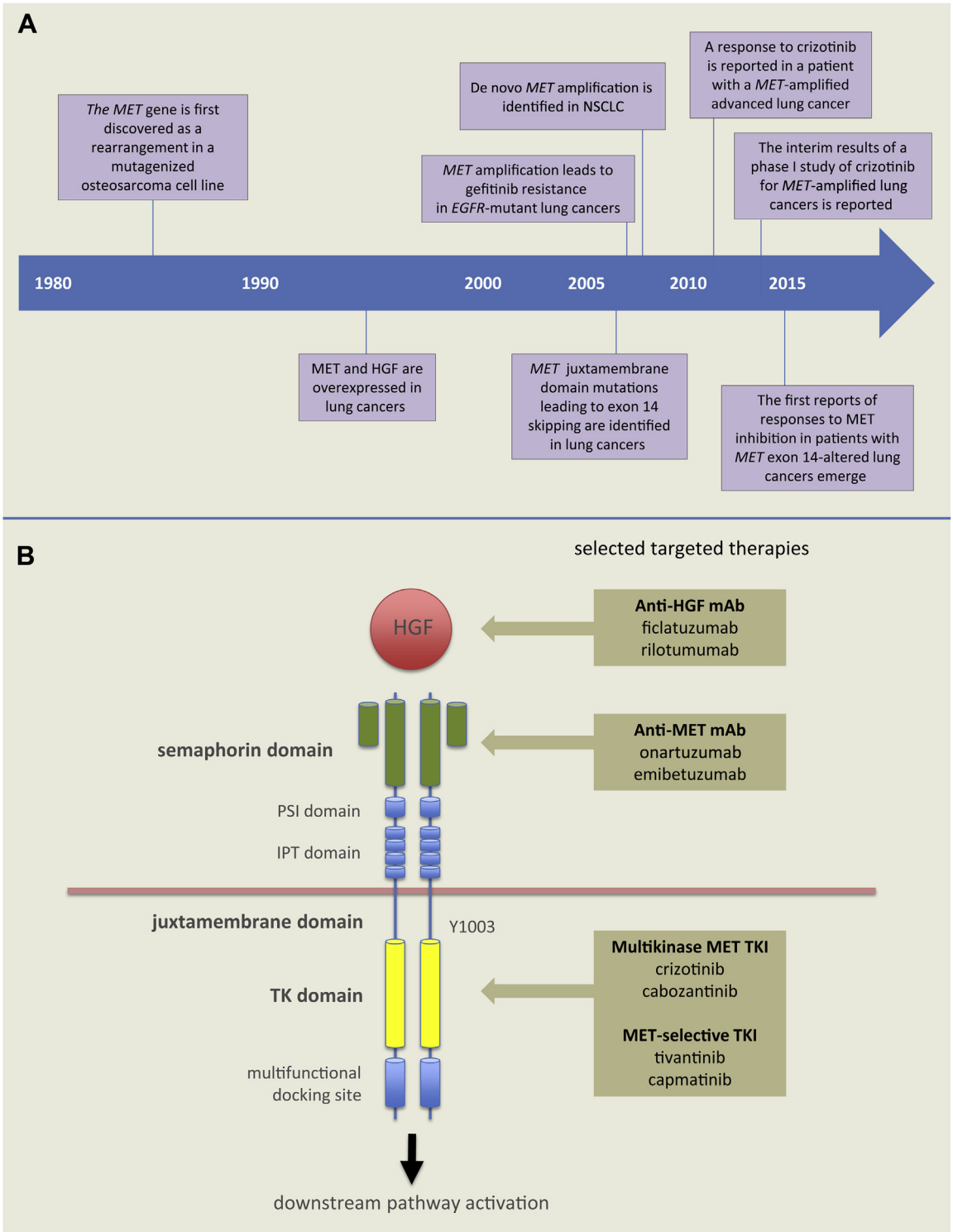

Figure 1. (*A*) Time line of discovery in lung cancers harboring alterations of the hepatocyte growth factor receptor (MET) pathway. (*B*) The MET receptor and selected MET pathway-directed targeted therapies. *MET*, MET proto-oncogene receptor tyrosine kinase; HGF, hepatocyte growth factor; mAb, monoclonal antibody; PSI, plexin-semaphorin-integrin; IPT, immunoglobulin-plexin transcription; TKI, tyrosine kinase inhibitor.

The MET Pathway and Targeted Therapy

The *MET* gene, located on chromosome 7q21–q31, is approximately 125 kilobases long, with 21 exons.[7,8] The 150-kDa MET polypeptide undergoes glycosylation to a 190-kDa glycoprotein that functions as a transmembrane receptor tyrosine kinase.[8] The extracellular region of MET contains semaphorin, cysteine-rich, and immunoglobulin domains; the intracellular region consists of a

juxtamembrane domain, a tyrosine kinase catalytic domain, and a carboxy terminal docking site (Fig. 1*B*).[9,10]

MET is activated when the HGF ligand binds to the MET receptor, inducing homodimerization and phosphorylation of intracellular tyrosine residues.[8] This activates the downstream RAS/ERK/MAPK, PI3K/AKT, Wnt/β-catenin, and STAT signaling pathways. Depending on the cellular context, these pathways can drive cell proliferation, survival, migration, motility, invasion, angiogenesis, and the epithelial-to-mesenchymal transition.[9,11] In embryonic development, MET and HGF are important in placental trophoblast and hepatocyte formation.[12] In adults, both are broadly expressed in a variety of tissues and can be up-regulated in response to tissue injury.[8]

Dysregulation of the MET pathway in lung cancer occurs through a variety of mechanisms, including gene mutation, amplification, rearrangement, and protein overexpression. *MET* was first discovered as an oncogene with the identification of a translocated promoter region, nuclear basket protein gene (*TPR*)-*MET* fusion in a mutagenized osteosarcoma cell line. The fusion oncoprotein lacked the juxtamembrane Y1003 and was unaffected by c-Cbl recruitment and ubiquitination.[13] A kinesin family member 5B gene (*KIF5B*)-*MET* fusion has since been detected by The Cancer Genome Atlas by RNA sequencing in a sample from a patient with lung adenocarcinoma[14]; however, *MET* rearrangements are likely rare events in lung cancers.

Several agents have been developed to target MET or HGF (see Fig. 1*B*). These are divided into small molecule inhibitors and monoclonal antibodies. The small molecule TKIs are further subdivided into multikinase and selective MET inhibitors. Examples of multikinase MET inhibitors include crizotinib, cabozantinib, MGCD265, AMG208, altiratinib, and golvatinib. Selective MET inhibitors include the adenosine triphosphate–competitive agents capmatinib and tepotinib (MSC2156119J)[15,16] and the adenosine triphosphate–noncompetitive agent tivantinib.[17] Monoclonal antibody therapy is divided into anti-MET antibodies (e.g., onartuzumab and emibetuzumab [LY2875358])[18–20] and anti-HGF antibodies (e.g., ficlatuzumab [AV-299] and rilotumumab [AMG 102]).[10,21]

In recognition of the diversity of putative alterations resulting in MET pathway activation in NSCLC, the challenge has been to determine the best way to distinguish a true sensitizing MET signature, either as a primary driver state or as a codriver state in the setting of acquired resistance to EGFR-directed therapy. For diagnostic purposes, this would involve selection from a combination of continuous and potentially overlapping MET-related biomarkers.

MET as a Primary Driver in NSCLC

By analogy with *ALK* rearrangements and *EGFR* mutations, it is conceivable that some NSCLCs may be primarily driven by, and therefore addicted to, the MET pathway alone. In the presence of an active MET inhibitor, precedent from other driver states suggests that monotherapy against MET should display clear evidence of anticancer activity. To date, two partially overlapping MET-related states in NSCLC have shown promise: *MET* exon 14 (*MET*ex14) alterations and *MET* gene amplification.

MET*ex14-Altered Lung Cancers*

Whereas tumors such as sporadic and hereditary renal cell carcinomas harbor activating mutations of the *MET* kinase domain,[22] lung cancers frequently harbor mutations in the extracellular/juxtamembrane domains.[23] The extracellular semaphorin domain is thought to be required for receptor activation and dimerization[24]; however, the relevance of mutations in this domain remains unclear. In contrast, juxtamembrane domain mutations often result in *MET*ex14 alterations.

Cancers with *MET*ex14 alterations, a prime example of the association between aberrant splicing and oncogenesis, were initially reported in SCLC and NSCLC in 2003 and 2005, respectively.[25,26] Normally, introns flanking *MET*ex14 in pre-mRNA are spliced out, resulting in mRNA containing *MET*ex14 that is translated into a functional MET receptor (Fig. 2*A*). *MET*ex14 encodes part of the juxtamembrane domain containing Y1003, the c-Cbl E3 ubiquitin ligase binding site.[27] Ubiquitination tags the MET receptor for degradation. Juxtamembrane domain mutations that disrupt splice sites flanking *MET*ex14 result in aberrant splicing (Fig. 2*B*). These mutations result in *MET*ex14 skipping, producing a truncated MET receptor lacking the Y1003 c-Cbl binding site. Losing this binding site results in decreased ubiquitination and degradation of the MET protein, sustained MET activation, and oncogenesis.[28] Decreased degradation of the MET receptor is thought to potentially cause MET overexpression on some tumors that is detectable by methods such as immunohistochemistry (IHC).

*MET*ex14 alterations are extremely diverse. Base substitutions or indels disrupt several gene positions important for splicing out introns flanking *MET*ex14,[29] including the branch point, the polypyrimidine tract, the 3′ splice site of intron 13, and the 5′ splice site of intron 14.[27,28,30] The Cancer Genome Atlas project identified *MET*ex14 alterations resulting in incomplete splicing from the mature mRNA, leaving low-level expression of untruncated MET.[31] Notably, point mutations or deletions within *MET*ex14 can affect the Y1003

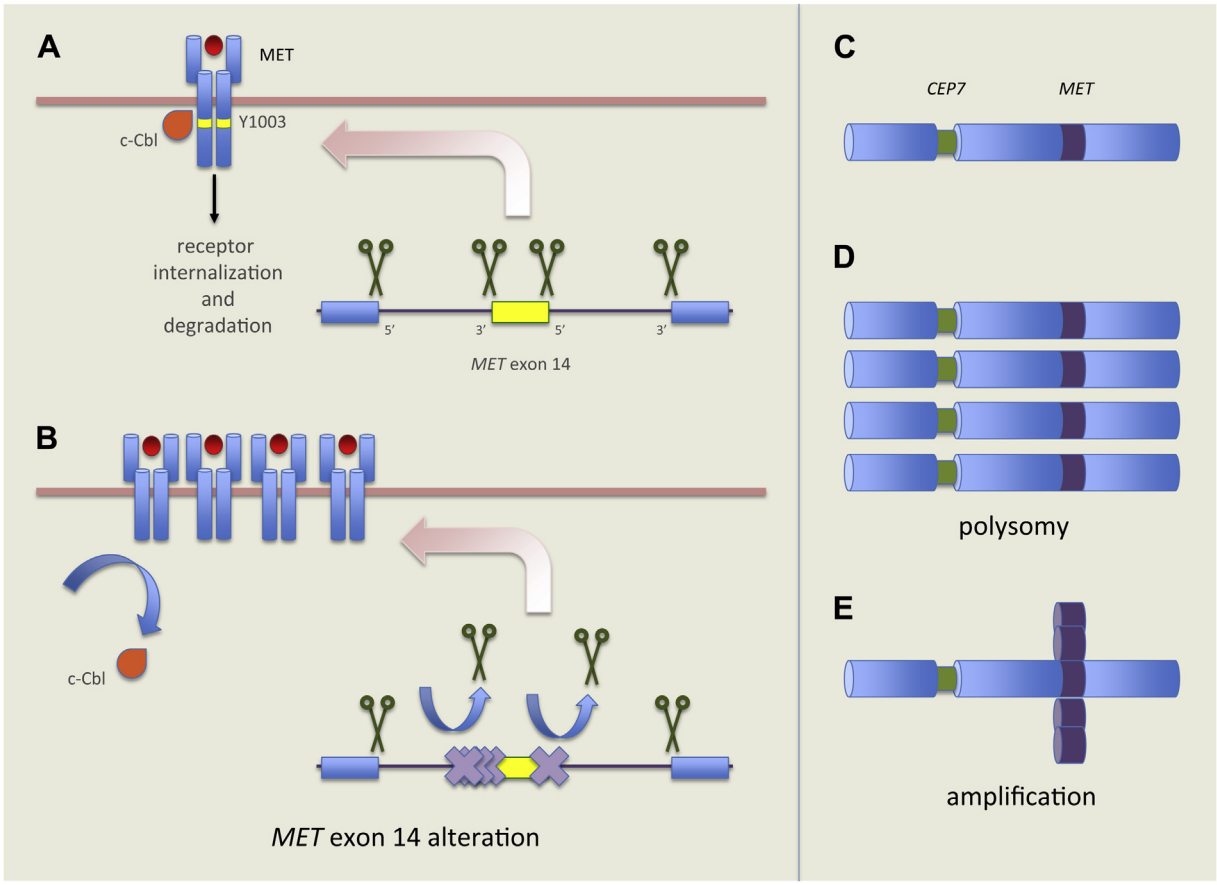

Figure 2. The pathobiology of MET proto-oncogene receptor tyrosine kinase (*MET*) exon 14 alterations and *MET* amplification. MET, hepatocyte growth factor receptor; CEP7, centromeric portion of chromosome 7.

residue, resulting in c-Cbl binding site loss of function without necessarily causing *MET*ex14 skipping.[29–31]

The diversity of *MET*ex14 alterations presents challenges for diagnostic testing.[12,29] Algorithms for molecular profiling will need to rapidly move toward comprehensive clinical sequencing platforms permitting routine detection of these mutations.[32] Currently, DNA-based broad, hybrid capture next-generation sequencing (NGS) represents the most frequently used tool. RNA-based sequencing using anchored multiplex polymerase chain reaction[33] or NanoString technology (NanoString Technologies, Inc., Seattle, WA) provide complementary tools.[32] It should be noted that NGS is a platform, not a standardized test, and detection of specific genomic alterations crucially depends on the primers within the NGS panel. It cannot be assumed that the wide array of *MET*ex14 variants will be equally detected (or detected at all) by every NGS panel used in clinical practice. Similarly, RNA-based testing, although a means of getting around the underlying variety of DNA-based changes by focusing on the more uniform resultant RNA-related splice-altered message, is not routinely performed in the clinic. Furthermore, the amount of tissue available after DNA-based NGS can be scant and inadequate for further RNA-based testing. Future diagnostic investigation must explore tests that will detect these changes in a manner suitable for widespread clinical use.

Lung cancers harboring *MET*ex14 alterations have been found to overexpress MET by means of IHC (3+ in 100% of cells in select cases).[32] MET overexpression is not found in all cases documented in the literature. In one series, stage IV *MET*ex14-altered lung cancers were more likely to display strong MET IHC expression compared with stage IA–IIIB *MET*ex14-altered lung cancers.[30] Rapid initial IHC screening has been proposed to narrow the population to undergo more comprehensive molecular profiling. To estimate the validity of this approach, better data on the prevalence of MET IHC 3+ cases that contain *MET*ex14 variants are required.[34]

*MET*ex14 alterations are detected in 3% to 4% of lung adenocarcinoma samples (Table 1),[27,29,31,34–36] a prevalence comparable to that in *ALK*-rearranged lung cancers.[37] These mutations occur in tumors from older patients, with a lower percentage of never-smokers than in the case of patients with tumors harboring other

Table 1. Prevalence of *MET* Exon 14 Alterations and *MET* Amplification in NSCLC Using Different Testing Methods

Study	Genomic Alteration	Diagnostic Method	Prevalence
*MET*ex14 alterations			
The Cancer Genome Atlas. 2014[31]	Exon 14 alterations	WES	4.3% (10 of 230)
Frampton et al. 2015[29]	Exon 14 alterations	Parallel DNA sequencing	3% (131 of 4402)
Okuda et al. 2008[35]	Exon 14 alterations	Direct sequencing	1.7% (3 of 178)
Onozato et al. 2009[27]	Exon 14 alterations	Direct sequencing	3.3% (7 of 211)
Tong et al. 2016[34]	Exon 14 alterations	Direct sequencing	2.6% (10 of 392)
MET amplification			
Cancer Genome Atlas. 2014[31]	Somatic copy number	WES	5.2% (12 of 230)
Capuzzo et al. 2009[36]	*MET* copy number $\geq$5 (polysomy + gene amplification)	FISH	11.1% (48 of 435)
	MET copy number $\geq$5 (gene amplification only)		4.1% (18 of 435)
Okuda et al. 2008[35]	*MET* copy-number >3	qRT-PCR	5.6% (12 of 213)
Tong et al. 2016[34]	*MET*/CEP7 ratio $\geq$5	FISH	1.0% (4 of 392)
Onozato et al. 2009[27]	*MET* amplification	qRT-PCR	1.4% (2 of 148)
	MET splice mutations	Direct sequencing	3.3% (7 of 211)

MET, MET proto-oncogene receptor tyrosine kinase; *MET*ex14, *MET* exon 14; WES, whole-exome sequencing; FISH, fluorescence in situ hybridization; qRT-PCR, quantitative real-time polymerase chain reaction.

oncogenes.[30] In a series of 687 Asian patients with resected NSCLC, *MET*ex14 alterations were poor prognostic factors for overall survival (OS).[34]

*MET*ex14 alterations are mutually exclusive with other lung cancer drivers, suggesting they represent a true oncogenic driver state.[29] In a study of 933 patients with nonsquamous NSCLC,[30] no patients with *MET*ex14 alterations had activating mutations in *KRAS*, *EGFR,* or erb-b2 receptor tyrosine kinase 2 gene (*ERBB2*), or rearrangements involving *ALK, ROS1,* or ret proto-oncogene (*RET*).[30] In contrast, *MET*ex14 alterations can overlap with other alterations such as *MET* and MDM2 proto-oncogene (*MDM2*) amplification. *MET*ex14 alterations can co-occur with *MET* copy number gain/amplification, with the frequency of overlap being heavily influenced by the definition of amplification used.[34]

Although many cases of *MET*ex14 alterations are found in lung adenocarcinomas, these events have a much higher incidence in pulmonary sarcomatoid carcinomas. Approximately 20% to 30% of sarcomatoid carcinomas harbor *MET*ex14 alterations.[34,38] In one series, these were more likely to be associated with sarcomatoid carcinomas with an adenocarcinoma component,[38] suggesting the possibility of a shared tumor origin. The therapeutic implications of *MET*ex14 alterations in sarcomatoid carcinomas are discussed later.

*MET*ex14 alterations are likely to be highly predictive of response to MET inhibition (Table 2).[29,30,32,38–44] Dramatic and durable partial responses (PRs) to crizotinib were first reported in mid-2015 in patients with advanced lung cancers with *MET*ex14 alterations.[32] The same authors reported a complete metabolic response (according to the Positron Emission Tomography Response Criteria in Solid Tumors) to cabozantinib therapy (stable disease by the Response Evaluation Criteria in Solid Tumors). Durable PRs to capmatinib or crizotinib have been reported in patients with advanced *MET*ex14-altered lung cancers.[29] Subsequent case reports have confirmed these observations with use of different MET TKIs and in all NSCLC histologic types.[30,39–42]

Pulmonary sarcomatoid carcinomas were thought to be relatively refractory to cytotoxic chemotherapies; however, a dramatic PR was reported in a patient with advanced pulmonary sarcomatoid carcinoma harboring both a *MET*ex14 alteration and *MET* amplification. No responses to an anti-MET or anti-HGF monoclonal antibody in a patient with lung cancer with a *MET*ex14 alteration have been reported, although such a response is not unlikely given our knowledge of these tumors' biology, coupled with preclinical data supporting the use of these agents.[28]

Reports of response to MET inhibitors have prompted drug development plans focused on molecular enrichment for *MET*ex14 alterations. The phase I trial that resulted in approval of crizotinib for *ALK*- and *ROS1*-rearranged lung cancers (NCT00585195) is currently treating patients with advanced lung cancer with *MET*ex14 alterations in an enriched cohort.[41] Of the 18 response-evaluable patients at the latest available data cutoff, eight experienced a confirmed PR (overall response rate 44% [95% confidence interval: 22–69]) with tumor shrinkage in 14 of 18 patients.[45] We look forward to studies of potential mechanisms of acquired resistance to MET TKIs, but already *MET* D1228N has been reported as a putative mechanism.[46]

Table 2. Case Reports of NSCLCs with *MET* Exon 14 Alterations Responding to MET Inhibitors

Reference	Age/ Sex	Smoking History	*MET*ex14 Alteration	MET IHC	*MET* Amplification	Agent	Best Response
Awad et al. 2016[30]	64 F	Never	Splice donor mutation	NA	Yes	Crizotinib	PR
Frampton et al. 2015[29]	82 F	Former	Splice donor mutation	3+	Yes	Capmatinib	PR
Frampton et al. 2015[29]	66 F	Former	Splice donor mutation	3+	Not tested	Capmatinib	PR
Jenkins et al. 2015[39]	86 M	Never	Splice acceptor deletion	2+	NA	Crizotinib	PR
Jorge et al. 2015[40]	68 F	Former	Splice donor mutation	NA	NA	Crizotinib	PR
Lee et al. 2015[41]	61 M	Never	Splice donor deletion	NA	NA	Crizotinib	PR
Liu et al. 2015[38]	74 F	Former	Splice site mutation	NA	NA	Crizotinib	PR
Mahjoubi et al. 2016[42]	67 F	Never	Splice donor mutation	NA	NA	Crizotinib	PR
Mendenhall et al. 2015[43]	76 F	Former	Splice donor mutation	NA	NA	Crizotinib	PR
Paik et al. 2015[32]	65 M	Former	Splice donor mutation	NA	NA	Crizotinib	PR
Paik et al. 2015[32]	78 M	Former	Splice donor deletion	3+	NA	Crizotinib	PR (lung) PD (liver)
Paik et al. 2015[32]	80 F	Never	Splice donor mutation	3+	Yes	Cabozantinib	CR (PERCIST)
Paik et al. 2015[32]	90 F	Never	Splice donor mutation	NA	NA	Crizotinib	PR
Waqar et al. 2015[44]	71 M	Former	Splice donor mutation	NA	No	Crizotinib	PR

MET, MET proto-oncogene receptor tyrosine kinase; *MET*ex14, *MET* exon 14; MET, mesenchymal epithelial transition receptor; IHC, immunohistochemistry; F, female; NA, not applicable/available; PR, partial response; M, male; PD, progressive disease; CR, complete response; PERCIST, Positron Emission Tomography Response Criteria in Solid Tumors.

MET-*Amplified Lung Cancers*

MET amplification is thought to dysregulate MET pathway signaling through protein overexpression and constitutive kinase activation. Identification of *MET* copy number gains in the setting of acquired resistance to EGFR TKI therapy in lung cancer stimulated interest in these alterations.

MET copy number gains arise from two distinct processes: polysomy and amplification.[47] High polysomy occurs when there are multiple copies of chromosome 7 in tumor cells secondary to factors such as chromosomal duplication.[48] True amplification occurs in the setting of focal or regional gene duplication through processes such as breakage-fusion-bridge mechanisms.[49] As opposed to polysomy, amplification is thought to represent a state of true biologic selection for MET activation as an oncogenic driver. Additionally, each type of *MET* gene copy number change represents a continuous variable. Placing a cutpoint to define *positivity* may dramatically alter the reported frequency, overlap with other NSCLC subtypes, and ultimately affect its potential to act as a predictive biomarker for benefit from MET inhibition.

With the use of fluorescence in situ hybridization (FISH), the ratio of *MET* to the centromeric portion of chromosome 7 (CEP7) can be used to distinguish between polysomy and true amplification. In polysomy, each copy of *MET* is associated with a corresponding centromere, preserving the *MET*/CEP7 ratio as copy number increases.[47] In true *MET* amplification, copy number increases without an increase in CEP7 and the *MET*/CEP7 ratio increases.[47] Broad, hybrid capture NGS assays are able to detect amplification events. Copy number changes can be identified by comparing sequence coverage of targeted regions in tumors relative to a diploid normal sample, and select platforms have been validated against tumor samples that previously tested positive for amplification of other genes such as *ERBB2* by FISH.[50,51] As with FISH, copy number gains detected by NGS are reported as continuous variables, and cutoffs can vary significantly between assays. In contrast to FISH, NGS and anchored multiplex polymerase chain reaction may provide additional information on other potentially clinically relevant, concurrent genomic alterations.[33]

No consensus on the definition of MET positivity based on gene copy number has yet been reached. Examples of a positive *MET* FISH result include five or more *MET* signals per cell (Cappuzzo scoring system),[36] and a *MET*/CEP7 ratio of 2 or higher (PathVysion kit [Abbott Molecular, Des Plaines, IL]).[34,52] *MET* amplification has also been classified by using the *MET*/CEP7 ratio as low ($\geq$1.8 to $\leq$2.2), intermediate ($>$2.2 to $<$5), and high ($\geq$5), as summarized in Table 3. Variation of classification thresholds between studies complicates comparisons of reported *MET* amplification/copy number gain relative to the underlying frequency, associated factors, and outcomes from therapy, although more rigorous data are now emerging.[11]

The reported prevalence of de novo *MET* amplification in NSCLC ranges from 1% to 5%, depending on the level of preselection, the assay, and the positivity cutpoint used (see Table 1).[27,29,35,36,53] In adenocarcinoma, because most true oncogenic drivers are mutually exclusive, so-called oncogene overlap analysis was used

Table 3. *MET*/CEP7 Ratio and Classification of *MET* Amplification

MET/CEP7 Ratio	*MET* Amplification Classification	Percentage of Total
<1.8	Negative	92.6
≥1.8 to ≤2.2	Low	3.6
>2.2 to <5.0	Intermediate	3.0
≥5.0	High	0.8
Total	—	100.0

Note: Data from a personal communication from L. Garcia (University of Colorado).
MET, MET proto-oncogene receptor tyrosine kinase; CEP7, centromeric portion of chromosome 7.

in 1164 cases to see whether there was a level of *MET* copy number gain by using either the mean number of copies of *MET* per cell (which would include high-polysomy cases) or the *MET*/CEP7 ratio, which could define a group in which the degree of overlap with other known oncogenic drivers (*EGFR*, *KRAS*, *ALK*, *ERBB2*, *BRAF*, *NRAS*, *ROS1*, or *RET*) disappeared.[54] Across all levels of mean increase in *MET* per cell (low, ≥5 to <6; intermediate, ≥6 to <7; and high, ≥7) oncogene overlap occurred in 41% to 63% of cases. Similarly, when the *MET*/CEP7 ratio was used, at low (≥1.8 to ≤2.2) and intermediate (>2.2 to <5) levels of *MET* amplification, oncogene overlap occurred in 52% and 50% of cases, respectively. However, zero oncogene overlap was seen in the high-*MET* amplification category (*MET*/CEP7 ratio ≥5). Only this high-level amplification category was associated with a dramatic rate of response to crizotinib. These data suggest that high *MET* copy number (*MET*/CEP7 ratio ≥5) represents the best case for a true *MET* copy number gain–dependent *MET*-driven state, whereas lower or different *MET* copy number definitions of positivity may more likely represent *MET* as a coincident event.[54]

There are two important issues related to exploring *MET* amplification as a predictive biomarker for benefit from MET inhibition. The first is that a *MET*/CEP7 ratio of 5 or higher represented only 0.34% of adenocarcinomas in a large series,[54] which is approximately 10% of the frequency of *MET*ex14 variants in the same population. The second is that the degree of benefit in this population independent of *MET*ex14 mutations remains under investigation. *MET*ex14 alterations harbor concurrent high-level *MET* copy number gain in approximately 20% of cases, with the degree of overlap increasing (just as with other known oncogenes) as less stringent definitions of *MET* amplification are used.[30,32,34] The case for *MET*ex14 variants to act as predictive biomarkers in the absence of *MET* amplification seems to have been made, as responses in this setting have been documented. Whether *MET* amplification is only a surrogate for some cases of *MET*ex14 (in which case testing should focus exclusively on the *MET*ex14 approach) or can truly function as an independent MET-addicted state capable of driving clinical responses without *MET*ex14 changes (requiring an all-inclusive testing approach for actionable abnormalities in lung cancer in addition to *MET*ex14 testing) is undetermined. Therefore, testing for both *MET* amplification and *MET*ex14 changes should be conducted in all MET TKI trials and then used to retrospectively investigate differential responses based on *MET* amplification status. As both *MDM2* and cyclin-dependent kinase 4 gene (*CDK4*) amplification are strongly coincident with *MET*ex14 alterations,[29] a similar approach could be taken to investigate MET TKI response with concurrent *MDM2* and *CDK4* amplification.

The first report of a response to MET inhibition in a patient with a de novo *MET*-amplified lung cancer was published in 2011. The patient was a 77-year-old woman with a 45 pack-year history of smoking and advanced lung adenocarcinoma. Her cancer had high-level *MET* amplification according to FISH (*MET*/CEP7 ratio >5). She was treated on the phase I trial of crizotinib (NCT00585195) and achieved a dramatic and durable PR.[55] Preliminary results were presented in 2014 and showed PRs in one of six patients (16.7%) with intermediate-level *MET* amplification (*MET*/CEP7 ratio >2.2 to <5) and in three of six patients (50%) with high-level *MET* amplification (*MET*/CEP7 ratio ≥5).[56] Responses were not seen in patients with low-level *MET* amplification (*MET*/CEP7 ratio ≥1.8 to ≤2.2).

MET as a Codriver in NSCLC

There is significant cross-talk between the MET pathway and other signaling pathways. Historically, many investigators have chosen to explore combination MET inhibitor and EGFR inhibitor therapy in clinical trials on patients with NSCLCs (Table 4). This strategy was partially based on the synergy of MET and EGFR in driving oncogenesis in both *EGFR* wild-type lung and mutant lung cancer models in the setting of acquired resistance to EGFR TKIs.[59,60] In 2007, *MET* amplification was found to be associated with acquired resistance to first-generation EGFR TKIs.[61] Although most EGFR-mutant lung cancers develop resistance to EGFR TKI therapy through acquired T790M mutation, activation of the MET pathway as a bypass tract represents a distinct acquired resistance mechanism driven by ERBB3-dependent phosphoinositide-3 kinase pathway

Table 4. Clinical Experience with Select MET- and HGF-Directed Targeted Therapies

Agent	Target(s)	Patients	Phase	Results
Multikinase MET TKIs				
Crizotinib	MET, ALK, ROS1	Crizotinib monotherapy Patients with *MET* exon 14-altered and *MET*-amplified NSCLC	I/II	*MET* exon 14–altered NSCLC: responses observed in 8 of 18 patients (44%); *MET*-amplified NSCLC: at data cutoff, partial responses were observed in 1 of 6 patients (16.7%) with a *MET*/CEP7 ratio of >2.2 to <5 and in 3 of 6 patients (50%) with a *MET*/CEP7 ratio of ≥5[56]
Cabozantinib	MET, RET, ROS1, VEGFR2	Erlotinib ± cabozantinib Patients with nonsquamous NSCLC and no *EGFR* mutation. MET expression assessed by IHC	II	Overall improvement in PFS with cabozantinib but MET IHC score was not predictive[57]
MET-selective TKIs				
Tivantinib	MET	Erlotinib ± tivantinib MARQUEE: Western cohort of patients with nonsquamous NSCLC. Not selected on the basis of MET analysis	III	Tivantinib was not associated with any improvement in OS, although PFS was increased in the tivantinib group compared with the group receiving erlotinib alone[58]
		Erlotinib ± tivantinib ATTENTION: East Asian cohort of patients with nonsquamous NSCLC. Not selected on the basis of MET analysis	III	Tivantinib was not associated with any improvement in OS, although PFS was increased in the tivantinib group compared with in the group receiving erlotinib alone. Trial terminated early because of an increase of interstitial lung disease in the tivantinib group[17]
Capmatinib	MET	Gefitinib + capmatinib Patients with *EGFR*-mutated NSCLC, refractory to EGFR TKIs, and *MET* amplification or MET overexpression	Ib/II	Partial responses in 6 of 41 patients (15%), all with either high *MET* amplification or MET overexpression[15]
Anti-MET monoclonal antibody				
Onartuzumab	MET	Erlotinib ± onartuzumab Patients with stage IIIB or IV NSCLC. MET expression evaluated at baseline	II	Onartuzumab plus erlotinib did not show an OS advantage, although an OS advantage was evident in the MET-positive subgroup[20]
		Erlotinib ± onartuzumab Patients with previously treated MET-positive stage IIIB or IV NSCLC	III	Stopped for futility as there was no improvement in OS, PFS, or ORR[19]
Emibetuzumab (LY2875358)	MET	Emibetuzumab monotherapy Patients with locally advanced or metastatic CRPC with bone metastasis, RCC, NSCLC, and HCC. Patients with RCC, NSCLC, and HCC were required to have ≥50% of tumor cells to be ≥2+ for MET expression by IHC	I	In patients with NSCLC, the disease control rate (PR + stable disease) was 26% (5 of 19), and the median duration of disease stabilization was 3.9 months (range 2.5-6.4) in NSCLC[18]
Anti-HGF monoclonal antibody				
Ficlatuzumab	HGF	Gefitinib ± ficlatuzumab Asian patients with stage IIIB or IV pulmonary adenocarcinoma. Patients were not selected on the basis of *MET* analysis	II	Failed to demonstrate significant improvement in PFS and overall response[21]
Rilotumumab	HGF	Erlotinib + rilotumumab Patients with recurrent or progressive NSCLC. Not selected on the basis of *MET* analysis	II	Ongoing (NCT01233687)

MET, hepatocyte growth factor receptor; HGF, hepatocyte growth factor; TKI, tyrosine kinase inhibitor; ALK, anaplastic lymphoma kinase; *MET*, MET proto-oncogene receptor tyrosine kinase; CEP7, centromeric portion of chromosome 7; RET, ret proto-oncogene; VEGFR, vascular endothelial growth factor receptor; PFS, progression-free survival; IHC, immunohistochemistry; OS, overall survival; ORR, overall response rate; CRPC, castration-resistant prostate cancer; RCC, renal cell carcinoma; HCC, hepatocellular carcinoma; PR, partial response.

activation. *MET* exon 14 alterations are generally thought to be mutually exclusive with other major lung cancer drivers and have not been associated with acquired resistance to EGFR TKI therapy in *EGFR*-mutant lung cancers.[27]

Unfortunately, significant variation in preselection criteria for identifying those patients who are potentially sensitive to EGFR and MET inhibition has contributed to some confusion over the results of trials combining EGFR and MET inhibition in NSCLC.

Combination Trials Not Focused on EGFR*-Mutant Lung Cancers*

Increased expression of MET alone is sufficient to induce oncogenic transformation in vitro and in vivo.[62,63] Although overexpression of both MET and HGF have been identified in unselected NSCLC specimens, the role of increased expression alone as a clinically relevant oncogenic driver has come into question.[5,6] The prevalence of MET overexpression in unselected NSCLCs ranges from 15% to 70%.[64–67] This frequency depends on the antibody, the assay, and the positivity cutpoint. Although MET protein expression has been associated with poor prognostic outcomes in lung cancer,[64,68] it has thus far served as a poor predictive biomarker of response to targeted therapy.

Interest in the treatment of patients with MET-overexpressing lung cancers was initially piqued by a subset analysis of a phase II combination trial of erlotinib and onartuzumab.[20] In this study, unselected second-line patients with advanced NSCLC were randomized to receive erlotinib with or without onartuzumab. Although the coprimary end points of OS (hazard ratio [HR] = 0.80, $p = 0.34$) and PFS (HR = 1.09, $p = 0.69$) were not met in the overall population, patients whose tumors expressed higher levels of MET (IHC result 2 to 3+) showed an improvement in both PFS (HR = 0.53, $p = 0.04$) and OS (HR = 0.37, $p < 0.05$).[20]

Disappointingly, a subsequent phase III trial randomizing 499 patients with advanced NSCLC with MET-overexpressing tumors (IHC result 2 to 3+) to erlotinib with or without onartuzumab was terminated early owing to futility.[19] The primary end point of OS was not different between groups (HR = 1.27, $p = 0.07$).[19] Median OS was numerically decreased in patients who received combination therapy, suggesting the possibility of harm.[19]

Two phase III combination studies of tivantinib that had reported anti-MET activity and treated largely unselected patients with NSCLC did not meet their primary end point. The ATTENTION trial randomized 307 patients with advanced, *EGFR* wild-type, nonsquamous NSCLC to receive erlotinib with or without tivantinib. Although the study was terminated early secondary to an increased incidence of interstitial lung disease in the tivantinib arm, the primary end point of OS was not significantly different between groups (HR = 0.89, $p = 0.43$).[17] The MARQUEE trial randomized 1048 patients with advanced, nonsquamous NSCLC to receive erlotinib with or without tivantinib. This trial was terminated early owing to an interim analysis revealing futility, and the primary end point of OS did not differ between groups (HR = 0.98, $p = 0.81$).[58] Although the secondary end point of PFS was improved by the combination in both trials, the absolute difference compared with single-agent erlotinib was small.[58] Of note, tivantinib is thought to potentially function as a mitotic spindle poison.[69]

Recently, a phase II study randomizing 118 patients with advanced, *EGFR* wild-type NSCLC to receive erlotinib, cabozantinib, or both in combination reached its primary end point of PFS (HR = 0.38, $p < 0.05$ for cabozantinib versus erlotinib; HR = 0.35, $p < 0.05$ for combination versus erlotinib). Unlike the MET-selective inhibitor tivantinib that was tested in the ATTENTION and MARQUEE studies, cabozantinib is a multikinase inhibitor with activity against several other potentially sensitive subgroups that may have been contained within this trial population, including both *ROS1*-rearranged and *RET*-rearranged lung cancers. This cohort of patients did not undergo comprehensive molecular profiling to rule out the presence of these alterations or other events, such as *MET*ex14 alterations. The contribution of these potentially undetected cases to these results remains unclear.

MET Inhibition in EGFR*-Mutant Lung Cancers*

The prevalence of *MET* amplification in *EGFR*-mutant lung cancers with acquired resistance to EGFR TKI therapy was initially reported at 15% to 20%.[61,70] A subsequent series noted a lower prevalence at 5% and found that *MET* amplification overlapped with other resistance mechanisms such as *EGFR* T790M acquisition or small cell transformation.[71] Unsurprisingly, the acquisition of *MET* amplification has also been reported as a mechanism of resistance to third-generation EGFR TKI therapy in patients with *EGFR* T790M–positive lung cancer.[72]

Clinical trials preselected or enriched for *EGFR*-mutant NSCLC exploring combined MET and EGFR inhibition have focused on either the EGFR TKI–naive setting as a means of preventing MET-driven resistance or the acquired resistance setting, with varying degrees of preselection to identify a MET-codriven state at the time of its emergence. The former approach does not depend on having specific biomarkers of MET activation. As an EGFR TKI is associated with significant benefit in an *EGFR*-mutant TKI-naive population, clinical investigations must rely on randomized data to make the case for combination therapy being superior to monotherapy with an EGFR TKI. In addition, this approach, with PFS as the primary end point, is inherently dependent on the expected underlying frequency of MET activation that would otherwise emerge to size the study to detect a change compared with the benefit from an EGFR TKI alone. The lower the frequency of MET as a predicted mechanism of acquired resistance, the larger the study must be to prove the combination adds unequivocal benefit. In a phase II

trial comparing emibetuzumab with or without erlotinib, in patients whose tumors developed acquired resistance to erlotinib and harbored MET overexpression, the overall response rate (ORR) was higher in both the combination and monotherapy arms (3.8% and 4.8%, respectively) for patients with at least 60% of cells determined to be MET positive by IHC (n = 74) than for patients with at least 10% of cells determined to be positive (n = 89), in which case the ORR was 3.0% in the combination arm and 4.3% in the monotherapy arm.[73] In the acquired resistance setting, the same challenges associated with defining the appropriate method and positivity cutpoint for identifying *MET* gene copy number gain as a primary driver apply to defining MET positivity as a codriver state. Data converging with the literature on primary drivers recently emerged from a small phase II study in *EGFR*-mutant patients with acquired resistance to an EGFR TKI who were then treated with the combination of gefitinib and capmatinib. When new biopsy specimens obtained at the time of acquired resistance were analyzed, the rate of response to the combination was 40% among those with a *MET* copy number of 5 or higher (the ratio was not reported), but zero among those with a copy number less than 5.[15] Clinical trials focusing on combination MET and EGFR inhibitor therapy for patients with acquired resistance to EGFR TKIs and using differing degrees of MET preselection are ongoing.[74]

Conclusions

Although research into the MET pathway as a driver of oncogenesis has stretched well over three decades, advances in technology and appropriate patient selection have reinvigorated the search for an effective targeted therapeutic for lung cancers harboring *MET*ex14 alterations and/or *MET* amplification as their primary oncogenic driver. Attempts to define the criteria for optimal use of a combination of MET and EGFR inhibitors in which MET acts as a targetable codriver, particularly in *EGFR*-mutant patients, continue. Ongoing and future drug development plans with a strong focus on molecular enrichment are likely to succeed in this arena. Both patients and providers look forward to eventual regulatory approval.

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