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

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Abstract

The mesenchymal epithelial transition factor receptor (MET) is a potential therapeutic target in a number of cancers, including non-small cell lung cancer (NSCLC). In NSCLC, MET pathway activation is thought to occur via a diverse set of mechanisms that influence properties affecting cancer cell survival, growth, and invasiveness. Preclinical and clinical evidence suggest 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* exon 14 (*MET*ex14) 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 that are likely to be predictive of response. While 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*ex14 alterations and *MET* amplification have been notable for meaningful clinical responses to MET inhibitor therapy in a substantial proportion of patients.

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Introduction

Phase III randomized trials of tyrosine kinase inhibitor (TKI) therapy for *EGFR*-mutant and *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* gene, however, has not been straightforward. First discovered in the mid-1980s, the MET pathway was found to be dysregulated in lung cancer in the 1990s (Figure 1A).[5, 6] More than twenty agents targeting MET or its ligand, hepatocyte growth factor (HGF), have undergone preclinical and clinical study, but findings have ranged from impressively large responses in molecularly pre-selected 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.

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 carboxyterminal docking site (Figure 1B).[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 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 upregulated in response to tissue injury.[8]

Dysregulation of the MET pathway in lung cancer occurs via a variety of mechanisms including gene mutation, amplification, rearrangement, and protein overexpression. *MET* was first discovered as an oncogene, with the identification of a *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 *KIF5B-MET* fusion has since been detected by The Cancer Genome Atlas via RNA sequencing in a sample from a patient with lung adenocarcinoma,[14] however, *MET* rearrangements are likely to be rare events in lung cancers.

Several agents have been developed to target MET or HGF (Figure 1B). 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 ATP-competitive agents capmatinib and tepotinib (MSC2156119J),[15, 16] and the ATP-non-competitive 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]

Recognizing 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 co-driver 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 monotherapy against MET should display clear evidence of anti-cancer activity. To date, two partially overlapping MET-related states in NSCLC have shown promise: *MET* exon 14 (*MET*ex14) alterations and *MET* gene amplification.

METex14-altered lung cancers

While tumors such as sporadic and hereditary renal cell carcinomas harbor activating mutations of the *MET* kinase domain,[22] lung cancers commonly 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 small cell lung cancer 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 (Figure 2A). *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 (Figure 2B). 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, polypyrimidine tract, 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 un-truncated MET.[31] Notably, point mutations or deletions within *MET*ex14 can affect the Y1003 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 commonly used tool. RNA-based sequencing using anchored multiplex polymerase chain reaction,[33] or NanoString (Seattle, WA) technology 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 via 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 to 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 3–4% of lung adenocarcinoma samples (Table 1),[29, 31] a prevalence comparable to *ALK*-rearranged lung cancers.[35] These mutations occur in tumors from older patients with a lower percentage of never-smokers compared to patients with tumors harboring other 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 *ERBB2*, or rearrangements involving *ALK, ROS1* or *RET*.[30] In contrast, *MET*ex14 alterations can overlap with other alterations such as *MET* and *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]

While many cases of *MET*ex14 alterations are found in lung adenocarcinomas, these events have a much higher incidence in pulmonary sarcomatoid carcinomas. About 20–30% of sarcomatoid carcinomas harbor *MET*ex14 alterations.[34, 36] In one series, these were more likely to be associated with sarcomatoid carcinomas with an adenocarcinoma component,[36] suggesting the possibility of a shared tumor origin. The therapeutic implications of *MET*ex14 alterations in sarcomatoid carcinomas are discussed below.

*MET*ex14 alterations are likely to be highly predictive of response to MET inhibition (Table 2). 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 (PERCIST) response to cabozantinib therapy (stable disease by RECIST). 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 using different MET TKIs and in all NSCLC histologies.[30, 37–40]

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 lung cancer patient 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 advanced lung cancer patients with *MET*ex14 alterations in an enriched cohort.[41] Of 18 response-evaluable patients, at the latest available data cutoff, 8 patients experienced a confirmed PR (overall response rate 44%, 95% CI: 22–69%) with tumor shrinkage in 14/18 patients.[41] 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.[42]

MET-amplified lung cancers

MET amplification is thought to dysregulate MET pathway signaling via 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.[43] High polysomy occurs when there are multiple copies of chromosome 7 in tumor cells, secondary to factors such as chromosomal duplication.[44] True amplification occurs in the

setting of focal or regional gene duplication, via processes such as breakage-fusion-bridge mechanisms.[45] 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 cut-point 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.

Using FISH, the *MET/CEP7* ratio 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.[43] In true *MET*-amplification, copy-number increases without an increase in *CEP7*, and the *MET/CEP7* ratio increases.[43] 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* via FISH.[46, 47] As with FISH, copy-number gains detected via NGS are reported as continuous variables, and cutoffs can vary significantly between assays. In contrast to FISH, NGS and anchored multiplex PCR 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 ≥5 *MET* signals per cell (Cappuzzo scoring system),[48] and a *MET/CEP7* ratio of ≥2 (PathVysion).[34, 49] *MET* amplification has also been classified via the *MET/CEP7* ratio as low (≥1.8, ≤2.2), intermediate (>2.2, <5), and high (≥5), 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 1–5%, depending on the level of preselection, the assay, and the positivity cut-point used (Table 1).[27, 29, 48, 50, 51] In adenocarcinoma, since most true oncogenic drivers are mutually exclusive, so called 'oncogene overlap analysis' was used in 1164 cases to see if there was a level of *MET* copy-number gain, using either the mean number of copies of *MET*/cell (which would include high polysomy cases) or the *MET/CEP7* ratio, that could define a group where the degree of overlap with other known oncogenic drivers (*EGFR*, *KRAS*, *ALK*, *ERBB2*, *BRAF*, *NRAS*, *ROS1*, or *RET*) disappeared.[52] Across all levels of mean *MET*/cell increase (low: ≥5, <6; intermediate: ≥6, <7; high ≥7) oncogene overlap occurred in 41–63% of cases. Similarly, using the *MET/CEP7* ratio, at both low (≥1.8, ≤2.2) and intermediate (>2.2, <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* ≥5). Only this high-level amplification category was associated with a dramatic response rate 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.[52]

There are two important issues related to exploring *MET* amplification as a predictive biomarker for benefit from MET inhibition. The first is that *MET/CEP7* ≥5 represented only 0.34% of adenocarcinomas in a large series,[52] ~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 ~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, then used to retrospectively investigate differential responses based on *MET* amplification status. As both *MDM2* and *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 female with a 45 pack-year history of smoking and advanced lung adenocarcinoma. Her cancer had high-level *MET* amplification via FISH (*MET/CEP7* ratio >5). She was treated on the phase I trial of crizotinib (NCT00585195) and achieved a dramatic and durable PR.[53] Preliminary results were presented in 2014and showed PRs in 1/6 (16.7%) patients with intermediate-level *MET* amplification (*MET/CEP7* >2.2, <5) and in 3/6 (50%) patients with high-level *MET* amplification (*MET/CEP7* ≥5).[54] Responses were not seen in patients with low-level *MET* amplification (*MET/CEP7* ≥1.8 to ≤2.2).

MET as a co-driver in NSCLC

There is significant cross-talk between the MET pathway and other signaling pathways. Historically, many investigators have chosen to explore combination MET- and EGFR-inhibitor therapy in clinical trials of 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.[55, 56] In 2007, *MET* amplification was found to be associated with acquired resistance to first-generation EGFR TKIs.[57] While the majority of EGFR-mutant lung cancers develop resistance to EGFR TKI therapy via acquired T790M mutation, activation of the MET pathway as a bypass tract represents a distinct acquired resistance mechanism driven by ERBB3-dependent PI3K pathway 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 defining those 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 patients

Increased expression of MET alone is sufficient to induce oncogenic transformation *in vitro* and *in vivo*.[58, 59] While 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%.[60–63] This frequency depends on the antibody, assay, and the positivity cut-point. While MET protein expression has been associated with poor prognostic outcomes in lung cancer,[60, 64] 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 advanced NSCLC patients were randomized to erlotinib ± onartuzumab. While the co-primary endpoints of OS (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 2–3+) 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 advanced NSCLC patients with MET overexpressing tumors (IHC 2–3+) to erlotinib ± onartuzumab was terminated early due to futility.[19] The primary endpoint of OS was not different between groups (HR 1.27, p=0.07).[19] Median OS was numerically decreased in patients that received combination therapy, suggesting the possibility of harm.[19]

Two phase III combination studies of tivantinib, which had reported anti-MET activity, that treated largely unselected NSCLC patients did not meet their primary endpoint. The ATTENTION trial randomized 307 patients with advanced, *EGFR* wild-type, non-squamous NSCLC to erlotinib with or without tivantinib. While the study was terminated early secondary to an increased incidence of interstitial lung disease in the tivantinib arm, the primary endpoint of OS was not significantly different between groups (HR 0.89, p=0.43).[17] The MARQUEE trial randomized 1,048 patients with advanced, non-squamous NSCLC to erlotinib ± tivantinib. This trial was terminated early due to an interim analysis revealing futility, and the primary endpoint of OS did not differ between groups (HR 0.98, p=0.81).[65] While the secondary endpoint of PFS was improved by the combination in both trials, the absolute difference compared to single-agent erlotinib was small.[65] Of note, tivantinib is thought to potentially function as a mitotic spindle poison.[66]

Recently, a phase II study randomizing 118 advanced, *EGFR* wild-type, NSCLC patients to erlotinib, cabozantinib, or both in combination reached its primary endpoint of PFS (HR

0.38, p<0.05 for cabozantinib vs erlotinib; HR 0.35, p<0.05 for combination vs 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*- 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 patients

The prevalence of *MET* amplification in *EGFR*-mutant lung cancers with acquired resistance to EGFR TKI therapy was initially reported at 15–20%.[57, 67] 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.[68] Unsurprisingly, the acquisition of *MET* amplification has also been reported as a mechanism of resistance to third generation EGFR TKI therapy in *EGFR* T790M-positive lung cancer patients.[69]

Clinical trials preselected or enriched for *EGFR*-mutant NSCLC exploring combined MET and EGFR inhibition have either focused on 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-co-driven 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 endpoint, is inherently dependent on the expected underlying frequency of MET activation that would otherwise emerge in order to size the study to detect a change compared to 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 ± erlotinib, the objective response rate (ORR) was higher in both the combination and monotherapy arms, 3.8% and 4.8%, respectively, for patients with ≥ 60% of MET positive cells by IHC (n=74) than for patients with ≥ 10% positive cells (n=89) where ORR was 3.0% in the combination arm and 4.3% in the monotherapy arm.[70] In the acquired resistance setting, the same challenges associated with defining the appropriate method and positivity cut point for identifying *MET* gene copy-number gain as a primary driver apply to defining MET positivity as a co-driver state. Data converging with the primary driver literature 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 biopsies at the time of acquired resistance were analyzed, the response rate to the combination was 40% among those with a *MET* copy-number ≥5 (ratio was not reported), but zero among those with copy-number <5.[15] Clinical trials focusing on combination MET and EGFR inhibitor therapy for patients with acquired resistance to EGFR TKIs employing differing degrees of MET preselection are ongoing.[71]

Conclusions

While 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 MET and EGFR inhibitor combination where MET acts as a targetable co-driver, 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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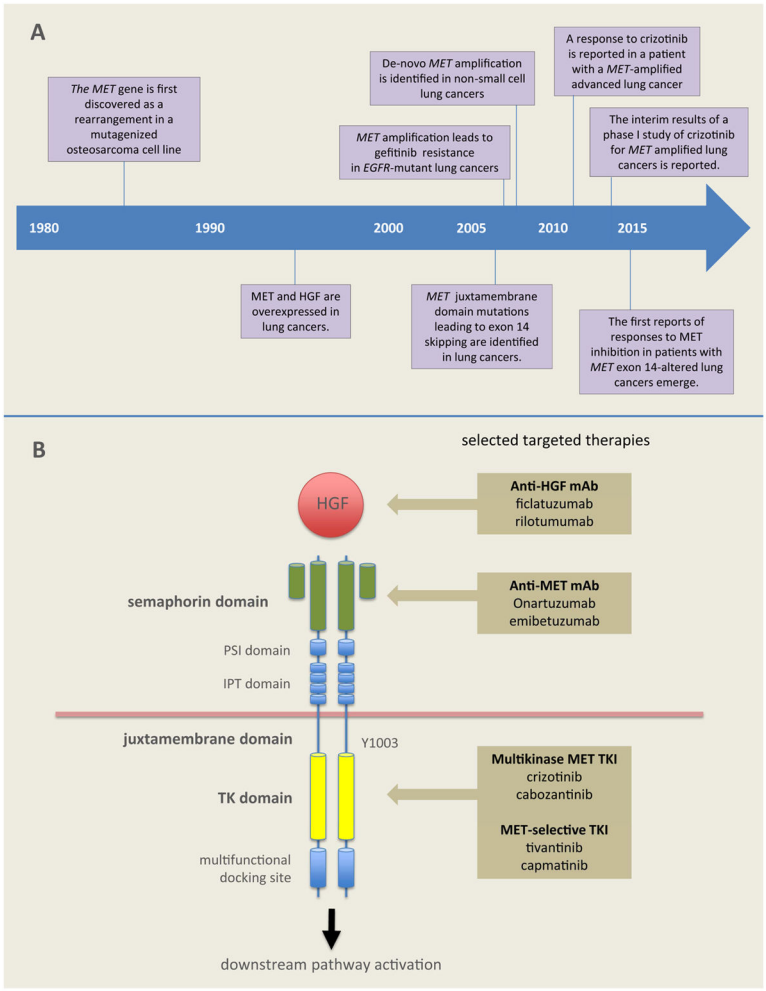

FIGURE 1.

A. Timeline of discovery in lung cancers harboring alterations of the MET pathway. **B.** The MET receptor and selected MET pathway-directed targeted therapies CEP7, centromeric portion of chromosome 7; HGF, hepatocyte growth factor; IPT, immunoglobulin-plexin transcription; mAb, monoclonal antibody; MET, mesenchymal epithelial transition receptor; PSI, plexin semaphoring integrin domain; TK, tyrosine kinase; TKI, tyrosine kinase inhibitor

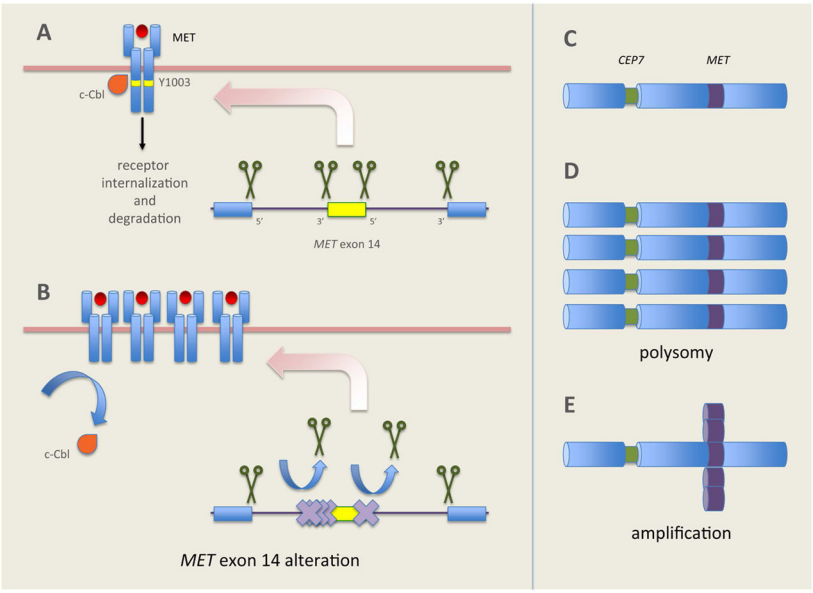

FIGURE 2.

The pathobiology of *MET*ex14 alterations and *MET* amplification CEP7, centromeric portion of chromosome 7; IPT, immunoglobulin-plexin transcription; MET, mesenchymal epithelial transition receptor; *MET*ex14, mesenchymal epithelial transition receptor exon 14; PSI, plexin semaphoring integrin domain

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**			
Cancer Genome Atlas. 2014[31]	Exon 14 alterations	WES	4.3% (10/230)
Frampton et al. 2015[29]	Exon 14 alterations	Parallel DNA sequencing	3% (131/4,402)
Okuda et al. 2008[50]	Exon 14 alterations	Direct sequencing	1.7% (3/178)
Onozato et al. 2009[27]	Exon 14 alterations	Direct sequencing	3.3% (7/211)
Tong et al. 2016[34]	Exon 14 alterations	Direct sequencing	2.6% (10/392)
***MET*-amplification**			
Cancer Genome Atlas. 2014[31]	Somatic copy-number	WES	5.2% (12/230)
Capuzzo et al. 2009[48]	*MET* copy-number ≥5 (polysomy + gene amplification	FISH	11.1% (48/435)
	MET copy-number ≥5 (gene amplification only)		4.1% (18/435)
Okuda et al. 2008[50]	*MET* copy-number >3	qRT-PCR	5.6% (12/213)
Tong et al. 2016[34]	*MET/CEP7* ratio ≥5	FISH	1.0% (4/392)
Onozato et al. 2009[27]	*MET* amplification	qRT-PCR	1.4% (2/148)
	MET Splice mutations	Direct sequencing	3.3% (7/211)

FISH, fluorescence in situ hybridization; MET, mesenchymal epithelial transition receptor; *MET*ex14, mesenchymal epithelial transition receptor exon 14; qRT-PCR, quantitative real-time polymerase chain reaction; WES, whole-exome sequencing

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[37]	86 M	Never	Splice acceptor deletion	2+	NA	Crizotinib	PR
Jorge et al. 2015[38]	68 F	Former	Splice donor mutation	NA	NA	Crizotinib	PR
Lee et al. 2015[40]	61 M	Never	Splice donor deletion	NA	NA	Crizotinib	PR
Liu et al. 2015[36]	74 F	Former	Splice site mutation	NA	NA	Crizotinib	PR
Mahjoubi et al. 2016[39]	67 F	Never	Splice donor mutation	NA	NA	Crizotinib	PR
Mendenhall et al. 2015[72]	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[73]	71 M	Former	Splice donor mutation	NA	No	Crizotinib	PR

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

TABLE 3

MET/CEP7 ratio and classification of *MET amplification* (Garcia, L. University of Colorado, personal communication)

***MET/CEP7* ratio**	***MET* amplification classification**	**Percentage of total**
<1.8	Negative	92.6
≥1.8–≤2.2	Low	3.6
>2.2–<5.0	Intermediate	3.0
≥5.0	High	0.8
Total	–	100.0

CEP7, centromeric portion of chromosome 7; MET, mesenchymal epithelial transition receptor

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 8/18 (44%) patients; *MET*-Amplified NSCLC: At data cut-off, partial responses were observed in 1/6 (16.7%) patients with a *MET/CEP7* ratio >2.2–<5 and in 3/6 (50%) patients with a *MET/CEP7* ratio ≥5[54]
Cabozantinib	MET, RET, ROS1, VEGFR2	Erlotinib +/− cabozantinib Patients with non-squamous NSCLC and no *EGFR* mutation. MET expression assessed by IHC	II	Overall improvement in PFS with cabozantinib but MET IHC score was not predictive.[74]
MET-Selective TKIs				
Tivantinib	MET	Erlotinib +/− tivantinib MARQUEE: Western cohort of patients with non-squamous NSCLC. Not selected based on *MET* analysis	III	Tivantinib was not associated with any improvement in OS, although PFS was increased in the tivantinib group compared with erlotinib alone.[65]
		Erlotinib +/− tivantinib ATTENTION: East Asian cohort of patients with non-squamous NSCLC. Not selected based on *MET* analysis	III	Tivantinib was not associated with any improvement in OS, although PFS was increased in the tivantinib group compared with erlotinib alone. Trial terminated early due to 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 15% [6/41] of patients, 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, but the *MET*-positive subgroup did.[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 + SD) was 26% (5/19), 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 based on *MET* analysis	II	Failed to demonstrate significant improvement in PFS and overall response.[21]
Rilotumumab	HGF	Erlotinib + rilotumumab	II	Ongoing (NCT01233687).

Agent	Target(s)	Patients	Phase	Results
		Patients with recurrent or progressive NSCLC. Not selected based on *MET* analysis		

+/−, with or without; ALK, anaplastic lymphoma kinase; ATP, adenosine triphosphate; CEP7, centromeric portion of chromosome 7; CRPC, castration-resistant prostate cancer; EGFR, epidermal growth factor receptor; FLT3, Fms-related tyrosine kinase 3; HCC, hepatocellular carcinoma; HGF, hepatocyte growth factor; IHC, immunohistochemistry; MET, mesenchymal epithelial transition receptor; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; RET, ret proto-oncogene; RON, Recepteur d'Origine Nantais; SD, stable disease; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor