Beyond epidermal growth factor receptor: MET amplification as a general resistance driver to targeted therapy in oncogene-driven non-small-cell lung cancer

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The rapidly changing treatment paradigm for patients with metastatic oncogene-driven lung cancer continues to evolve, and consequently our understanding of the landscape of resistance must also advance. MET amplification is an established and frequent driver of resistance in EGFR-mutant non-small-cell lung cancer (NSCLC). Recently, the combination of MET proto-oncogene (MET) and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) has shown promise in overcoming this molecularly defined resistance in clinical trials, and this combination strategy is being pursued in ongoing trials. Emerging data also demonstrate MET amplification as a resistance driver to TKI-treated ALK-, RET-, and ROS-1-fusion NSCLC, consistently at the range of 15%, while the resistance profiling data are maturing for other molecular targets. In this review, we discuss MET amplification as a driver of acquired resistance in well-defined molecular subsets of NSCLC, explore the biology behind this mechanism of resistance, and summarize the recently published clinical data, including the proposed combination strategies in the clinic achieving success in overcoming acquired MET amplification-dependent resistance.

Key words: EGFR, MET, amplification, resistance, NSCLC, targeted therapy

INTRODUCTION
Genomic profiling and the implementation of prospective tumor molecular analysis have revolutionized the way that lung cancer is diagnosed and treated in the clinic. As of 2021, various clinical guidelines [National Comprehensive Cancer Network (NCCN)/College of American Pathologists (CAP)/International Association for the Study of Lung Cancer (IASLC)/Association for Molecular Pathology (AMP)/American Society of Clinical Oncology (ASCO)/European Society of Medical Oncology (ESMO)] recommend genetic profiling of non-small-cell lung cancer (NSCLC) for > 10 genetic alterations, including EGFR, BRAF, KRAS, ERBB2 (HER2) mutations; ALK, ROS1, NTRK, RET fusions; and METex14 skipping and amplification to capture actionable molecular targets.1-7 Seven of these oncogene alterations now have Food and Drug Administration (FDA)-approved targeted therapies. With targeted therapies, patients with the oncogene-driven NSCLC have remarkable response rates and documented improved progression-free survival (PFS); however, resistance to these targeted therapies inevitably develops despite initial responses.

Understanding and addressing the development of targeted therapy resistance that occurs with tyrosine kinase inhibitors (TKIs) represent a key challenge of the precision medicine era. MET amplification is a well-established mechanism of acquired resistance to epidermal growth factor receptor (EGFR) inhibitors,8,9 and now increasing evidence, reported recently, suggests MET amplification is a consistent mechanism of acquired resistance in a number of other oncogene-driven molecular subsets of NSCLC post-tyrosine kinase inhibition. Combination strategies may overcome the genomic heterogeneity of drug resistance; however, the risk of overlapping toxicities and resulting dose adjustments can often hamper effective drug combinations.10 In this review, we discuss MET amplification as a driver of acquired resistance in NSCLC, review the clinical evidence to date in well-defined molecular subsets of NSCLC, discuss the possible mechanisms driving MET amplification in this setting, and summarize the proposed TKI combination strategies to overcome MET amplification-dependent resistance.

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**MET structure and function**

MET was first identified in a chemically transformed osteosarcoma-derived cell line.\(^\text{11}\) The proto-oncogene was later discovered to encode the receptor tyrosine kinase (RTK) MET, an RTK activated by an endogenous ligand, scatter factor, or hepatocyte growth factor (HGF).\(^\text{12-15}\) In general, RTKs such as MET contain an N-terminal extracellular binding domain, a single transmembrane α helix, and a cytosolic C-terminal domain with tyrosine kinase activity.\(^\text{16}\) MET is a disulfide-linked heterodimeric RTK consisting of an extracellular α chain, a β chain that encompasses the remainder of extracellular domain, the juxtamembrane, and the kinase domains (Figure 1). The intracellular component contains a juxtamembrane region responsible for signal downregulation and receptor degradation, a catalytic region with the enzyme activity, and a C-terminal region acting as a docking site for adaptor proteins, which leads to downstream signaling via phosphoinositide 3-kinase (PI3K), signal transducer and activator of transcription proteins (STAT), and mitogen-activated protein kinase (MAPK).\(^\text{17-19}\) HGF, typically produced and secreted by mesenchymal cells, is the only natural ligand of MET (Figure 1); binding of HGF to MET leads to receptor dimerization and phosphorylation of tyrosine residues in the kinase domain and autophosphorylation of the carboxy-terminal bidentate substrate-binding sites.\(^\text{20-22}\)

The resulting phosphotyrosines function as docking sites for other proteins involved in RTK-mediated signal transduction,\(^\text{20-22}\) and bind to activate distinct downstream signaling pathways,\(^\text{12,14,21}\) including PI3K/AKT (protein kinase B), MAPK, STAT, and nuclear factor-κB (NF-κB)\(^\text{23-25}\). MET signaling can become dysregulated through several mechanisms, including overexpression of MET protein or MET gene alterations, such as mutations, amplifications, or rearrangements.\(^\text{26,27}\) In this review, we focus on amplification of the MET gene in the setting of other oncogene-driven lung cancer.

**Detection of MET amplification**

**MET** amplification can occur as a focal amplification or as a result of chromosome 7 polysomy. Polysomy occurs when there are multiple copies of chromosome 7 in tumor cells, secondary to factors such as chromosomal duplication, whereas true amplification occurs in the setting of focal or regional gene duplication, via processes such as breakage–fusion–bridge mechanisms.\(^\text{28}\) Clinically, focal high-copy amplification of MET represents an oncogenic driver event for cancer, while polysomy is typically not.\(^\text{29}\)

Traditionally, MET amplification has been detected using a FISH method, with the challenges of the technical complexity and interpretation of the test.\(^\text{30}\) Using FISH, the mean MET per cell and chromosome 7 centromere ratio (MET/CEP7) ratio, the ratio of MET relative to chromosome 7 centromere, is 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, while in true MET amplification, copy number increases without an increase in CEP7, and the MET/CEP7 ratio increases.\(^\text{31}\)

In general, a cut-off of MET/CEP7 ≥ 2.0 is now used as the FISH criteria for MET amplification; however, historically various cut-offs have been used in studies for MET amplification and MET copy number gain: for instance, a MET/CEP7 threshold of 5 was set as minimum for high MET (FISH ≥ 5 MET signals/cell) in a study by Cappuzzo et al.,\(^\text{32}\) MET/CEP7 ratio of ≥ 2 was used by Tanaka et al.,\(^\text{33}\) and MET gene copy number (GCN) ≥ 10 was ultimately used in the GEOMETRY study.\(^\text{34}\)

Broad, hybrid-capture next-generation sequencing (NGS) assays are able to detect amplification events and are now increasingly used in clinical practice for MET amplification detection. In contrast to FISH for single-gene testing, NGS may provide additional information on other, potentially clinically relevant, concurrent genomic alterations.\(^\text{35}\) However, some NGS-based assays do not control for CEP7, and therefore may detect increase in copy number as in polysomy rather than true MET amplification. As with FISH, copy number gains detected via NGS are reported as continuous variables, and cut-offs can vary significantly between assays.

An ongoing difficulty with MET copy number studies has been to define a threshold for any given methodology for which MET-directed therapy will likely be active. In theory, increases in MET copy number are postulated to cause
excessive amounts of MET protein, and subsequent auto-
aggregation, ligand-independent MET signaling, and subse-
quent oncogenic addiction to the MET pathway.27 The
challenge is that changes in MET copy number represent a
continuous variable, and this variable has been assessed in
different ways, defined as either the ratio of MET relative to
another region of chromosome 7, such as CEP7, or the
absolute number of MET copies.27 A persistent challenge
with any defined cut-off criteria, however, is that a more
flexible criteria could include more patients but then dilute
the clinical benefit, and thus conversely, a more stringent
criteria while identifying fewer patients, may include pa-
ients who could potentially derive the greatest clinical
benefit. The risk is always the potential of excluding patients
who may still derive some benefit.

Very high level of MET amplification (MET/CEP7 ≥5 by
FISH) or GCN ≥ 10 by NGS often has an absence of other
oncogenic drivers, and is therefore viewed as a de novo
primary oncogene driver in NSCLC.36-38 In the setting of
acquired resistance, the definition of MET amplification can
be different; ongoing and future studies will inform the
selection criteria for this important biomarker.

**MET amplification as a resistance mechanism**

MET-dependent resistance is triggered by the activation of
common downstream pathways of oncogene receptors,
directly by the homodimer formation or indirectly by trans-
activating other tyrosine kinase receptors. In the setting of
EGFR-mutant NSCLC, MET amplification leads to resistance by
persistent activation of signaling pathways downstream of
EGFR, such as those mediated by MAPK, STAT, and PI3K/
AKT, independent of EGFR activation and signaling.89
Signaling occurs through two adaptors: human epidermal
growth factor receptor 3 (HER3 or ERBB3), when MET is
directly triggered by genomic amplification, or Grb2-associated
inhibitor 1 (GAB1), when MET is activated by HGF.89 Higher
levels of HGf expression have also been detected in tumor
samples from patients resistant to the EGFR TKI gefitinib or
erlotinib than in treatment-naïve tumor specimens.89
Resistance has been found even in the absence of MET
amplification via HGF-induced activation of the AKT
pathway.40,41 Thus, EGFR signaling becomes redundant and,
as preclinical and recent clinical studies suggest, targeting
both receptors by adding an anti-MET agent to EGFR TKIs is
required to obtain an effective antitumor activity.82 In other
oncogene-driven lung cancers, similar downstream signaling
pathways were activated, and MET amplification functions
similarly in a redundant manner to render resistance to TKI
treatment to the original driver oncogene.

**MET amplification in EGFR-mutant lung cancer**

Genomic alterations in the EGFR gene account for up to
50% of NSCLC in Asian patients and 10% in Western pa-
patients.43 While the resistance mechanism spectrum evolves
with the introduction of third-generation EGFR TKIs,
amplification of the MET gene as an acquired resistance
mechanism to EGFR TKI treatment has been reported in all
generations of TKIs.8,9,44-46 MET amplification as an ac-
quired mechanism resistance occurs in approximately 10%-15% of patients with NSCLC who have received erlotinib,
gefitinib, or afatinib.26,39,45 Osimertinib, a third-generation
EGFR TKI, is now used in the first-line setting for patients
with advanced EGFR-mutant NSCLC.47-49 Despite this more
potent inhibition to EGFR signaling, MET amplification re-
mains a major resistance mechanism, occurring still in about
15% of patients with treatment failure of first-line osi-
mertinib,50,51 and 10%-22% of patients following second-
line osimertinib.8,52,53 In the AURA3 study, MET amplifica-
tion was the most common (19%) resistance mechanism,52
where it co-occurred with EGFR C797S in 7% of cases, and
was also likely to be associated with CDK6 and BRAF
amplifications.54 Because of the relative proximity of CDK6,
MET, and BRAF on chromosome 7q (7q21.2, 7q31.2, and
7q34, respectively), a single genomic event could be hy-
pothesized to be responsible for gene amplifications.54 In
the FLAURA study, MET amplification was also the most
common acquired resistance mechanism (15%).55 MET
amplification can also occur as a mechanism of resistance to
third-generation EGFR TKIs, with or without loss of the
T790M mutation (Table 1).54,56,57 It is important to note that
using diverse patient materials, such as tissue or plasma for
analysis of MET amplification, may result in different
levels of MET amplification being detected, and so a
caveat should be that different levels of MET amplification
detected using different samples and techniques in various
studies may simply reflect these differences.

**Strategies to overcome resistance — MET TKI + EGFR TKI.**

Dual inhibition of EGFR and MET is a rationale treatment
strategy for overcoming acquired EGFR TKI resistance due
to MET amplification.26 Several preclinical studies have
demonstrated that concomitant use of MET inhibitors with
osimertinib overcame resistance in osimertinib-resistant
EGFR-mutant NSCLC cell lines with MET amplification.54,58
More recently, preclinical models using the potent and se-
lective MET TKI tepotinib with EGFR TKI (erlotinib, ge-

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This study
Table 1. Summary of key clinical studies identifying MET amplification as a mechanism of resistance in oncogene-driven NSCLC

| Molecular subset of NSCLC | Number of lung cancer samples | Type | Prior targeted therapy | Incidence of MET amplification | Method of MET amplification testing | Reference |
|---------------------------|-------------------------------|------|-----------------------|-------------------------------|------------------------------------|-----------|
| EGFR                      | 83                            | Plasma | Second-line osimertib: range 10%-22% | 19% (14/83) | NGS | 52 |
| EGFR                      | 32                            | Tumor tissue | MET overexpression (IHC3) particularly in NSCLC | 22% (7/32) | FISH | 8 |
| EGFR                      | 42                            | Tumor tissue | MET overexpression (IHC2) | 14% (6/42) | FISH and/or NGS | 54 |
| EGFR                      | 41                            | Tumor tissue | MET overexpression (IHC1) | 10% (4/41) | NGS and FISH | 53 |
| EGFR                      | 91                            | Plasma | First-line osimertib: range 7%-15% | 15% (14/91) | NGS | 59 |
| EGFR                      | 27                            | Tumor tissue | MET overexpression (IHC1) | 7.4% (2/27) | NGS | 51 |
| ALK                       | Post-treatment tissue (n = 101) or Plasma (n = 106) | Crizotinib, or next-generation ALK inhibitors (e.g. lorlatinib) | 11% (13%) | FISH and/or NGS | 77 |
| RET                       | 23                            | Selpercatinib or pralsetinib | 15% | FISH or NGS | 82 |
| ROS1                      | 17                            | Lorlatinib | 6% | NGS and FISH | 85 |
| KRAS                      | 10                            | Adagrasib | 20% | NGS | 95 |
| NGS, next-generation sequencing: NSCLC, non-small-cell lung cancer.

MET amplification in ALK-fusion-positive lung cancer

ALK-fusion-positive NSCLC is another established molecular subtype of lung cancer occurring in 3%-5% of lung adenocarcinomas. Similar to EGFR-mutant NSCLC, the clinical benefit of targeting anaplastic lymphoma kinase (ALK) using TKIs is limited by the emergence of drug resistance. Historically, the standard first-line therapy for advanced ALK-fusion NSCLC has been the multikinase ALK/ROS1/MET TKI crizotinib, which has recently been surpassed by more potent and selective second- and third- generation ALK TKIs, such as ceritinib, alectinib, brigatinib, and lorlatinib. Despite initial sensitivity to ALK TKIs, ALK-fusion-positive tumors invariably develop resistance, and a number of diverse mechanisms of resistance to ALK TKIs have now been discovered. In ~50% of cases, resistance to second-generation ALK TKIs is due to ALK-independent resistance mechanisms, most often due to activation of bypass signaling pathways, including activation of MET, EGFR, SRC, and IGF-1R. The availability of potent MET TKIs makes MET a particularly attractive target.

MET amplification has emerged as a prominent ALK-independent mediator of resistance, and recently MET amplification was detected in 15% of tumor biopsies from patients relapsing on selective ALK inhibitors, including 12% and 22% of biopsies from patients progressing on second-generation inhibitors and lorlatinib, respectively. Several clinical studies have investigated MET-targeted therapies in patients with ALK-fusion-positive NSCLC. In the TATTON study, a number of novel combinations were investigated in previously treated EGFR-mutant NSCLC, including the combination of MET TKI savolitinib with osimertinib. In this trial, patients with EGFR-mutant NSCLC had received prior EGFR TKI and had evidence of MET amplification, defined using FISH as ≥5 copies of MET averaged over 50 cells scored. The objective response rate was 44% (22%-69%) and 30% of patients progressing on a third-generation EGFR TKI showed an objective response. An expansion cohort of this trial included patients with EGFR-mutant T790M-negative NSCLC who had not previously received a third-generation EGFR TKI and, as such did not meet their primary endpoints.

The importance of selecting the appropriate drug—drug combination for the appropriate patient (here high-level MET amplification).

There are a number of ongoing studies aiming to bring the EGFR plus MET TKI combination to this EGFR-mutant MET-amplified NSCLC patient population, including INSIGHT 2 (NCT03940703; tepotinib and osimertinib) and SAVANNAH (NCT03778229; savolitinib and osimertinib).
case reports have also confirmed this, and suggest that the ALK/ROS1/MET TKI crizotinib may be able to overcome MET-dependent resistance.76,79

In a comprehensive analysis of MET alterations in ALK-fusion-positive NSCLC,77 FISH and/or NGS were performed on 207 post-treatment tissue (n = 101) or plasma (n = 106) specimens from patients with ALK-fusion-positive lung cancer to detect MET genetic alterations. The analysis also evaluated ALK inhibitor sensitivity in cell lines with MET alterations and assessed antitumor activity of the ALK/MET dual blockade in ALK-fusion cell lines and two subsequent patients with MET-dependent resistance. Eleven (13%) biopsies harbored MET amplification, including four with low-level MET amplification (MET/CEP7 2.4–3.9) and six with high-level MET amplification based on FISH (MET/CEP7 5.2 to >25) or NGS (16–19 MET copies). One sample had focal MET amplification by NGS, and FISH was too variable to estimate copy number. Of note, no coalterations in other genes potentially associated with resistance or bypass signaling were identified in the 11 biopsies, and MET amplification was mutually exclusive with ALK-resistance mutations, with the exception of one case.77 Patients treated with a second-generation ALK inhibitor in the first-line setting were more likely to develop MET amplification than those who had received next-generation ALK inhibitors after crizotinib (P = 0.019).77 This study demonstrated in preclinical models that treatment with MET-specific TKIs capmatinib or savolitinib, none of which have anti-ALK activity, partially suppressed proliferation.77 However, combination therapy using lorlatinib with capmatinib/savolitinib, or crizotinib potently suppressed cell proliferation and only dual inhibition of ALK and MET by crizotinib or by utilizing the combination of lorlatinib plus a MET TKI effectively suppressed both ALK and downstream signaling pathways.77 Based on these preclinical findings, two TKI-resistant ALK-fusion-positive lung cancer patients with acquired MET alterations were treated with a combination of lorlatinib and crizotinib and achieved rapid responses to ALK/MET combination therapy, validating that MET was the resistance driver and the combination’s therapeutic potential.77 Although this study confirmed the rationale for exploring ALK/MET combinations in the clinic, in the setting of MET-dependent resistance to ALK TKIs, the optimal combination needs to be evaluated in prospective clinical trials, especially taking into consideration newer generation MET inhibitors’ potency and activities for brain metastasis. This study demonstrated a comparable prevalence of MET amplification in patients relapsing on ALK TKIs to that seen in EGFR-mutant NSCLC, and interestingly, presented similar findings of increased frequency of MET amplification in tumors resistant to the third-generation, broad-spectrum ALK TKI lorlatinib.77

Selpercatinib and pralsetinib are highly selective RET kinase inhibitors that have recently been FDA approved for advanced RET-fusion NSCLC based on impressive efficacy data from the LIBRETTO-001 and ARROW studies, respectively. Molecular mechanisms of acquired resistance to RET inhibitors are not yet fully understood; however, recent data confirm MET amplification as a recurrent mechanism of resistance to targeted therapy in NSCLC patients treated with selpercatinib. Lin et al.82 recently performed a multi-institutional analysis of repeat tumor or plasma biopsies from a cohort of patients with RET-fusion NSCLC following treatment with selpercatinib and pralsetinib, to systematically characterize acquired resistance mechanisms to these inhibitors (patients received pralsetinib or selpercatinib in clinical trials).

A strikingly similar prevalence was noted, comparable to EGFR-/ALK-resistance cases, as three resistant cases (15%) harbored acquired MET amplification without concurrent RET-resistance mutations82; acquired MET mutations were identified in two cases (10%) and KRAS amplification in one case. A recently published work confirmed these data, and provided further preclinical evidence that that MET amplification is sufficient to cause selpercatinib resistance in in vitro models.80 Rosen et al.80 identified that patients treated with selpercatinib have MET amplification associated with resistance to selpercatinib, and proposed a dual targeting strategy to overcome MET-dependent resistance to RET-directed therapy, piloting a combination strategy using selpercatinib and crizotinib to rescue the phenotype.

Rosen and investigators80 demonstrated that this combination strategy with selpercatinib and crizotinib overcame MET-dependent resistance to selective RET inhibition in patients with RET-fusion lung cancer (one case of clinical activity and tolerability, with response lasting 10 months), and that this strategy was tolerable and feasible. The numbers in this report are admittedly small (n = 4) and further prospective work is needed, as our collective clinical experience with RET-fusion NSCLC is increased. Interestingly, while the level of MET gene amplification was shown to clearly increase during selpercatinib monotherapy, in three of four cases, some degree of MET gain was already present before exposure to selpercatinib: this is reminiscent of EGFR-mutant NSCLC, in which rare clones with high-level MET amplification may be detected at baseline, before EGFR inhibitor therapy.32,66

ROS1-fusion-positive lung cancer

Genetic rearrangements of the ROS1 gene account for 1%-2% of NSCLC. ROS1 can be targeted by TKIs such as crizotinib, entrectinib, and lorlatinib, which results in dramatic responses58,83,84; however, ROS1-independent resistance mechanisms remain poorly characterized. Recent evidence suggests a role for MET amplification.85

Lin et al. recently analyzed repeat tumor biopsies derived from advanced ROS1-fusion-positive NSCLC patients progressing on lorlatinib using NGS (n = 17) or whole-exome sequencing (n = 1) to detect potential drivers of
resistance. While on-target ROS1 kinase domain mutations featured prominently as a mechanism of resistance, 38.9% harbored a ROS1-resistance mutation. NGS analyses also identified MET copy number gain in a lorlatinib-resistant case, validated by FISH as high-level focal MET amplification without a concomitant ROS1-resistance mutation. There are no published data investigating combination strategies in MET-amplified ROS1-positive lung cancer. Thus there is a clear need to further elucidate ROS1-independent resistance mechanisms and develop strategies to tackle resistance.

**NTRK-fusion-positive lung cancer**

Similar to ALK- and ROS1-fusion-positive lung cancers, neurotrophic tropomyosin-related kinase (NTRK)-fusion-positive cancers can develop on- and off-target resistance to TKI therapy. Recently, published data suggest that resistance to TKR inhibition is mediated by genomic alterations that converge to activate the mitogen-activated protein kinase (MAPK) pathway, and MET amplification has been identified as a mediator of resistance, together with BRAF V600E mutation or hotspot mutations involving KRAS. To date, there are a paucity of published reports regarding NTRK-fusion-positive lung cancer resistance after TKI therapy; a recent combination of a TRK and MET inhibitor achieved a confirmed response to therapy in a patient with a NTRK-fusion-positive cholangiocarcinoma with MET amplification-dependent resistance to a first-generation TRK inhibitor, accompanied by the disappearance of detectable NTRK fusion and MET amplification in circulating free DNA.

**BRAF-mutant-positive lung cancer**

BRAF gene is mutated in up to 5% of lung adenocarcinomas and represents another actionable target in lung cancer. Sca¢t evidence has been available concerning the mechanisms of resistance to BRAF/MEK inhibitors in BRAF V600E NSCLC. Recently, circulating tumor DNA genomics have demonstrated that mutations in effectors of the MAPK and PI3K pathways may play a role in resistance. Onco- genic mutations in KRAS, which encode immediate upstream regulators of the RAF kinases have also been suggested. MET amplification has not been identified as a driver of resistance; however, complete molecular analyses were available for only seven patients.

**KRAS G12C-mutant NSCLC**

The KRAS G12C mutation occurs in ~13%-34% of NSCLC and is emerging as the newest actionable target in lung cancer. While previously KRAS has proven to be an elusive target, Hong and colleagues recently demonstrated that a potent and selective small-molecule KRAS G12C inhibitor, sotorasib (AMG 510), can induce impressive, durable responses in KRAS G12C-mutant NSCLCs. The phase II CodeBreak 100 trial has recently further validated these impressive data: a response rate of 37.1%, a disease control rate of 80.6%, and a median PFS of 6.8 months. Therefore understanding the resistance spectrum will become critically important.

Serial biopsy data and serial circulating tumor DNA data have yet to be reported in the CodeBreak study; however, recently published data from Awad et al. have confirmed MET amplification as a mechanism for resistance in patients with KRAS G12C-mutant NSCLC previously treated with the KRAS G12C inhibitor adagrasib. Preclinical models have highlighted the importance of RTK and SHP2 activation in acquired resistance to KRAS inhibitors, and there are published data which show that METex14 and KRAS G12 mutations can co-occur, at a rate of co-occurrence significantly higher than in other major driver-defined lung cancer subsets. In the study by Awad et al., 10 patients with KRAS G12C-mutant NSCLC had samples available for assessment on progression of therapy; furthermore, acquired MET amplification was the only potential genomic mechanism of adagrasib resistance, which was identified in two of these patients (20%). This is again a frequency rate similar to other oncogene-driven NSCLCs, and suggests that MET amplification may also be a driver of resistance to selective small-molecule KRAS G12C inhibitors.

**Conclusions**

MET amplification is a well-defined mechanism of resistance in EGFR-mutant NSCLCs, and in this review, we highlight the increasing number of reports which have underscored that MET amplification plays a role in acquired resistance in a number of other oncogene-driven NSCLCs, including ALK-, RET-, ROS-fusion-positive and more recently, KRAS G12C-mutant lung cancers. The presence and strikingly similar prevalence of MET amplification as a driver of resistance in ~15% of the TKI-treated population across various oncogene-driven NSCLCs is remarkable (Figure 2). In the more recently defined rare molecular subsets of NSCLCs, such as TRK fusion, BRAF mutant, the relative frequency of off-target resistance, such as MET amplification, has yet to be elucidated. Recent data have proved that in KRAS G12C-mutant NSCLCs following adagrasib therapy, MET amplification is a consistent mechanism of resistance. We eagerly await the serial biopsy data and serial circulating tumor DNA data from the seminal sotorasib KRAS G12C study, which will likely confirm adagrasib findings.

As our collective understanding of the molecular mechanisms underpinning TKI resistance in oncogene-driven NSCLCs continues to mature, the development of rationale combination strategies will be crucial in overcoming acquired resistance. For combination therapy, the EGFR story provides the highest level of evidence and proof of concept, where combining potent and selective MET inhibitor with EGFR inhibitor in patients with EGFR-mutant MET-amplified resistant tumors has produced clinically meaningful responses and tolerable safety profiles. MET amplification-dependent TKI resistance therefore demands attention from the field because of the need to prospectively identify and treat these patients with efficacious and safe combinations.
together, these data highlight that 

dependent, including 
de novo METex14 and high MET amplification. EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer.

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