**MET Exon 14 Skipping Mutations in Non–Small-Cell Lung Cancer: An Overview of Biology, Clinical Outcomes, and Testing Considerations**

Mark A. Socinski, MD\(^1\); Nathan A. Pennell, MD, PhD\(^2\); and Kurtis D. Davies, PhD\(^3\)

**INTRODUCTION**

In the United States, lung cancer is the second most frequently diagnosed type of cancer and the leading cause of cancer deaths.\(^1\) Non–small-cell lung cancer (NSCLC), which accounts for approximately 85% of lung cancer diagnoses, is a heterogeneous disease consisting of numerous histologies and many known driver mutations (Fig 1).\(^2,4\)

Today, approved targeted therapies are available for patients with NSCLC who are positive for oncogenic drivers such as *EGFR*, *ALK*, *BRAF* V600E, *ROS1*, *NTRK1/2/3*, *RET*, and *MET* exon 14 skipping mutations (METex14).\(^3,8\) Given the number of distinct actionable oncogenic drivers, it is important to use broad molecular profiling at the diagnosis of locally advanced or metastatic lung cancer to identify key genetic alterations and ensure that appropriate therapies are selected.\(^9-13\) Importantly, patients with an oncogenic driver mutation who receive the appropriate targeted therapy have improved outcomes.\(^9,13-18\)

In NSCLC, METex14 is observed in approximately 3%-4% of cases and typically occurs in the absence of other driver mutations.\(^3,19-22\) This incidence rate is on par with or greater than those of other actionable oncogenic drivers in NSCLC, such as *ROS1* (approximately 1%-2%), *NTRK1/2/3* (< 1%), *RET* (approximately 1%-2%), *BRAF* (approximately 1%-5%), and *ALK* (approximately 5%-7%).\(^2,9,23,24\)

With the recent approvals of capmatinib and tepotinib for patients with metastatic METex14 NSCLC, METex14 is now an actionable biomarker in metastatic NSCLC.\(^6,12,23\) However, the underlying genomic events leading to MET exon 14 skipping are complex and diverse, necessitating careful consideration of the testing platform used for identification. This review will discuss the complex genomic events leading to MET exon 14 skipping, clinical data supporting targeted intervention for this oncogenic driver, and the types of molecular testing for reliably detecting METex14.

**BIOLOGY OF METex14**

The *MET* gene encodes for a receptor tyrosine kinase that activates signaling pathways involved in cell proliferation, survival, and growth and plays a role in embryonic development, wound healing, and tissue regeneration.\(^26\) Mutations (eg, alterations leading to exon 14 skipping), gene amplification, and protein overexpression may all lead to oncogenic activation of MET-mediated signaling.\(^3,26-28\) Mutations leading to MET exon 14 skipping are the most commonly reported oncogenic MET mutations,\(^28\) and as with many other oncogenic drivers, coexistence of METex14 with other oncogenic drivers is rare.\(^3,20\) METex14 may be associated with MET amplification, with a co-occurrence rate between 0% and 40.5%.\(^21,28,30-37\) MET amplification is caused by an increase in the copy number of the *MET* gene\(^3,30\) and has been identified as a resistance mechanism in *EGFR* mutation–positive NSCLC.\(^38-40\) Several agents are being investigated in patients with NSCLC with either de novo MET amplification\(^41,42\) or *EGFR* mutation–positive disease\(^43-46\); however, these discussions are outside the scope of this review. Importantly, both METex14 and MET amplifications are associated with poor prognosis in patients with NSCLC.\(^28,47-52\)

Exon 14 encodes the 47-amino acid juxtamembrane domain of the MET receptor, a key regulatory region that prevents MET oversignaling.\(^53-55\) In METex14–altered cancers, the proper transcription process of the *MET* gene is disrupted by underlying alterations in the intronic regions surrounding exon 14, alterations within exon 14 itself, or complete genomic deletion of exon 14. These events result in mature mRNA in which exon 13 is fused with exon 15 (Fig 2A).\(^53,54\) Point mutations within exon 14, such as Y1003X or D1010X, may also mimic the loss of this region.\(^19-21\) The mechanisms behind the oncogenesis are incompletely explored, and multiple mechanisms may be involved; however, it is believed that loss of this region—or mutations that mimic the loss of this region—results in impairment of proper receptor degradation, leading to overactive MET-mediated signaling and thus cell proliferation and tumor growth.\(^20,21,31,56\)

Hundreds of distinct genetic alterations leading to MET exon 14 skipping have been reported (Fig 2B), including base substitutions and insertions or deletions (indels) at the splice acceptor site, at the splice donor site, and in intronic noncoding regions immediately adjacent to the splice acceptor site, as well as whole exon deletions.\(^3,20,53\)
We review the considerations for detecting \textit{MET} exon 14 skipping mutation (\textit{MET}ex14) in non–small-cell lung cancer (NSCLC) using next-generation sequencing (NGS).

**Knowledge Generated**

Clinical data support targeting \textit{MET}ex14 in NSCLC; however, the ability of NGS assays to identify the diverse set of genetic alterations leading to \textit{MET}ex14 varies. Hybrid capture–based NGS has proven to be a more reliable method for identifying \textit{MET}ex14 compared with amplicon-based methods when using DNA as the input material. RNA-based testing overcomes some limitations of DNA-based analysis but is associated with additional technical considerations.

**Relevance**

The approval of capmatinib and tepotinib for metastatic \textit{MET}ex14 NSCLC has made \textit{MET}ex14 an additional actionable oncogenic driver in NSCLC, making it an important biomarker for screening to identify patients who may be eligible for a targeted therapy. It is important for clinicians to carefully consider limitations of the sequencing assays they use to guide treatment decisions.

**CLINICAL DATA IN METex14 NSCLC**

\textit{MET}ex14 incidence varies by histology: approximately 2% in adenocarcinoma, approximately 1% in squamous cell carcinoma, approximately 6% in adenosquamous cell carcinoma, and approximately 13% in pulmonary sarcomatoid carcinoma (PSC). Patients with \textit{MET}ex14 are generally older (median age, 65-76 years), more often female, and less likely to have a history of smoking compared with those without \textit{MET}ex14. These patients are also significantly older than patients with other oncogenic drivers (\textit{EGFR}, \textit{KRAS}, or \textit{ALK}).

Furthermore, in a retrospective review of 148 patients with \textit{MET}ex14 NSCLC, of the 71 patients who developed metastases, the most common sites were lymph nodes (67%), lung (53%), pleural/pericardial metastases or malignant effusions (51%), bone (49%), and brain (37%).

Numerous agents have been investigated for the treatment of \textit{MET}ex14 NSCLC in both clinical trials and off-label use. Below, we provide an overview of the key \textit{MET} tyrosine kinase inhibitors (TKIs) that have been investigated in \textit{MET}ex14 NSCLC. Importantly, with \textit{MET} TKIs, peripheral edema is a common adverse event (AE). Patients may require additional supportive care because peripheral edema is a leading cause of dose reductions or interruptions and discontinuation with many agents.

**Crizotinib**

Historically, some patients with \textit{MET}ex14 NSCLC have been treated with off-label crizotinib, a multikinase inhibitor approved for \textit{ALK}- or \textit{ROS1}-rearranged advanced NSCLC that also has activity against \textit{MET} kinase. The NCCN guidelines note that crizotinib is a therapy that may be useful in certain circumstances for patients with metastatic \textit{MET}ex14 NSCLC. The PROFILE 1001 trial (NCT00585195) investigated the use of crizotinib in patients with a number of genetic alterations, including \textit{MET}ex14 NSCLC. \textit{MET}ex14 was primarily identified by local DNA- or RNA-based next-generation sequencing (NGS).

Among response-evaluable patients with \textit{MET}ex14 NSCLC (N = 65) who were either treatment naive or previously treated, the ORR was 32% (95% CI, 21 to 45; Fig 3) and the median duration of response (mDOR) was 9.1 months (95% CI, 6.4 to 12.7 months). A subgroup analysis showed ORRs of 25% (95% CI, 10 to 47) in treatment-naive patients (n = 24) and 37% (95% CI, 22 to 53) in previously treated patients (n = 41). The most common treatment-related AEs in this trial (≥20%) were edema, vision disorder, nausea, diarrhea, vomiting, fatigue, and constipation.

**Tepotinib**

Tepotinib is an oral \textit{MET} kinase inhibitor that has been approved for use in Japan and the United States. The VISION trial (NCT02864992) was a prospective, non-randomized, open-label phase II study investigating the use of tepotinib in patients with \textit{MET}ex14 or \textit{MET}-amplified NSCLC. \textit{MET}ex14 was mainly identified centrally either by cell-free DNA from liquid biopsy with the Guardant360 NGS panel or by RNA from tissue biopsy with the Oncomine Focus Assay. Treatment-naive \textit{MET}ex14 patients (n = 69) had an ORR of 43% (95% CI, 32 to 56) and an mDOR of 10.8 months (95% CI, 6.9 months to not estimable) per blinded independent review committee (BIRC). Previously treated \textit{MET}ex14 patients receiving tepotinib in the second- or later-line setting (n = 83) had an ORR of 43% (95% CI, 33 to 55) and an mDOR of 11.1 months (95% CI, 9.5 to 18.5 months) per BIRC. Responses were consistent across the liquid and tissue biopsy groups.

Tepotinib has shown some clinical evidence of intracranial activity through a case report published from the VISION trial. Intracranial response rates have not been reported.

Among patients with \textit{MET}ex14 NSCLC treated with tepotinib (N = 255), the most common adverse reactions or AEs
Capmatinib is an oral kinase inhibitor that targets MET protein, including the mutant variant produced by MET ex14. It was the first US Food and Drug Administration–approved targeted therapy for METex14 metastatic NSCLC and is also approved in Japan; approval was based on the results from the GEOMETRY mono-1 trial (NCT02414139). The GEOMETRY mono-1 trial was a prospective, non-randomized, open-label phase II study that enrolled patients with advanced or metastatic NSCLC into multiple study cohorts based on their prior treatment and MET dysregulation status (METex14 and/or MET amplification). METex14 was identified centrally from tissue samples by reverse transcriptase-polymerase chain reaction (RT-PCR); a retrospective analysis validated the use of the FoundationOne CDx NGS assay for METex14 detection, showing a concordance rate of 99% (72 of 73 patient samples) with the RT-PCR clinical trial assay. The additional patient had a noncanonical mutation leading to MET exon 14 skipping. Treatment-naive METex14 patients (N = 28) had an ORR of 68% (95% CI, 48 to 84) and an mDOR of 12.6 months (95% CI, 5.6 months to not estimable) per BIRC. Previously treated METex14 patients receiving capmatinib in the second- or third-line setting (N = 69) had an ORR of 41% (95% CI, 29 to 53) and an mDOR of 9.7 months (95% CI, 5.6 to 13.0 months) per BIRC. An expansion cohort of previously treated METex14 patients receiving capmatinib in the second-line setting (N = 31) showed consistent results, with an ORR of 48% (95% CI, 30 to 67) per BIRC. The difference in responses between treatment-naive and previously treated patients is not yet understood and is distinct from other MET TKIs, but it may be attributable to small sample sizes or to longer durations of disease in previously treated patients, which could have allowed for the evolution of resistant clones during first-line therapy.

Capmatinib has also shown clinical evidence of intracranial activity. In the GEOMETRY mono-1 trial, among 13 patients who had data evaluable by an independent neuroradiologic review committee, 92% had intracranial disease control and 54% had an intracranial response (including 31% with complete response). Among all patients treated with capmatinib (N = 364), the most common AEs (any cause; ≥ 20%) were peripheral edema, nausea, vomiting, increased blood creatinine, dyspnea, fatigue, and decreased appetite. Savolitinib is a selective oral MET TKI currently under clinical development. Among 70 patients treated with savolitinib in a single-arm phase II study (NCT02897479) in patients with METex14 PSC or other NSCLC histologies, 57% had adenocarcinoma and 36% had PSC; 60% of patients had been previously treated. METex14 was centrally confirmed with Sanger sequencing or NGS (Geneseeq Tetradecan panel). In treatment-naive patients (n = 24), the interim ORR was 54.2% (95% CI, 32.8 to 74.5) and the interim mDOR was 6.8 months (95% CI, 3.8 months to not reached) per independent review committee in the efficacy analysis set. In previously treated patients (n = 37), the interim ORR was 46.0% (95% CI, 29.5 to 63.1) and the interim mDOR was not reached (95% CI, 6.9 months to not reached) per independent review committee in the efficacy analysis set. The most common treatment-related AEs (≥ 20%) were peripheral edema, nausea, vomiting, increased blood creatinine, dyspnea, fatigue, and decreased appetite. Savolitinib has also shown clinical evidence of intracranial activity. In the GEOMETRY mono-1 trial, among 13 patients who had data evaluable by an independent neuroradiologic review committee, 92% had intracranial disease control and 54% had an intracranial response (including 31% with complete response). Among all patients treated with capmatinib (N = 364), the most common AEs (any cause; ≥ 20%) were peripheral edema, nausea, vomiting, increased blood creatinine, dyspnea, fatigue, and decreased appetite.

Mechanisms of Resistance to MET TKIs
MET TKI resistance can be broadly grouped into two categories: MET dependent (on target) and bypass (off target). The most common AEs (any cause; ≥ 20%) were peripheral edema, nausea, vomiting, increased blood creatinine, dyspnea, fatigue, and decreased appetite.
on-target resistance to type Ia (crizotinib) and Ib (capmatinib, tepotinib, and savolitinib) TKIs may remain sensitive to type II (cabozantinib, merestinib, and glesatinib) TKIs and vice versa, which may support switching MET TKIs when acquired resistance mutations arise.69 Off-target mechanisms of resistance may involve gene amplification of EGFR, HER3, and MAPK pathway genes (KRAS/BRAF) or KRAS mutations. These off-target mechanisms may support the use of combination therapy.68

According to the available data, it may be possible to select subsequent therapy based on specific acquired mutations detected at the time of progression and the properties of clinically available MET inhibitors.68,69

Rationale for Testing for METex14

Retrospective Real-World Analyses of MET Inhibitors in METex14 NSCLC

In addition to the clinical trial data supporting the use of MET inhibitors in patients with metastatic METex14 NSCLC, multiple studies have shown that patients with METex14 NSCLC have better outcomes when receiving a targeted therapy.48,49,70

A retrospective review of 61 patients with stage IV METex14 NSCLC showed an association between longer survival and receiving a MET TKI (crizotinib, glesatinib, or capmatinib). The median overall survival (mOS) was 24.6 months (95% CI, 12.1 months to not reached) for patients who received a MET TKI (n = 27) compared with 8.1 months (95% CI, 5.3 months to not reached) for patients who did not receive a MET TKI (n = 34). It is important to note that some patients in the group that did not receive a MET TKI might not have received one because of a lack of recognition of an actionable genomic alteration or the inability of the patients to access MET TKIs; this was a study limitation in the retrospective analysis, and it further highlights the need to test patients for oncogenic drivers at diagnosis of advanced NSCLC.68

A real-world analysis of patients with METex14 NSCLC (N = 87) also saw an association between mOS and receiving a MET inhibitor (inhibitor not specified). Among patients who received a MET inhibitor (n = 36), the mOS from first diagnosis of metastatic NSCLC was 25.3 months (95% CI, 18.8 to 40.9 months), compared with 10.9 months (95% CI, 7.4 to 16.9 months) for patients who did not receive a MET inhibitor (n = 51).49
Another real-world analysis compared treatment-naive METex14 patients from GEOMETRY mono-1 with a matched cohort of real-world treatment-naive patients with advanced METex14 NSCLC, who were treated with first-line antineoplastic therapies, excluding MET inhibitors. Median progression-free survival was longer with first-line capmatinib than with first-line chemotherapy and/or immunotherapy (12.0 months vs 6.2 months, after weighting). The benefits of MET inhibitor therapy are not limited to newly diagnosed METex14 NSCLC, further highlighting the...
need for molecular testing in all patients with advanced or metastatic NSCLC. A review of data from the Sarah Cannon Research Institute found that patients with METex14 were responsive to MET inhibitor therapy even after receiving standard-of-care therapy (eg, chemotherapy, immunoncology, and/or radiation).71

**Immunotherapy in Patients With METex14**

The NCCN guidelines for NSCLC note that the presence of an oncogenic driver may be a contraindication for the use of immunotherapy in metastatic NSCLC because these patients, even those with high programmed death ligand-1 (PD-L1) levels, do not respond to immunotherapy.12 Based on clinical data for MET TKIs in patients with METex14, the limited data for the use of immunotherapy, and current guidelines recommending upfront broad molecular profiling, we recommend that patients with METex14-positive metastatic NSCLC receive first-line targeted therapy with a MET TKI.

To date, few studies have investigated the use of immunotherapy in patients with METex14 NSCLC. The available evidence supporting the use of immunotherapy in patients with METex14 NSCLC is not definitive, and reported response rates are mixed.72-75 In a small study of patients with METex14 NSCLC (N = 25), of whom 13 received an immune checkpoint inhibitor in the second-line setting, six patients had prolonged progression-free survival (> 18 months). Of these six patients, five showed responses within the first 4 months of treatment; four patients had a partial response, and two had a complete response. PD-L1 levels were ≥ 20% for four of six patients (data not available for one patient); however, these data must be interpreted carefully, because the outcomes for the other seven patients are not described.73 In contrast, three case studies reported progressive disease as the best response with pembrolizumab in patients with METex14 NSCLC with high PD-L1 expression.74,76 Overall, these case studies are consistent with a retrospective review of response-evaluable patients with METex14 NSCLC (N = 24) treated with pembrolizumab, nivolumab, durvalumab, atezolizumab, or ipilimumab plus nivolumab, in which an ORR of 17% (95% CI, 6.0 to 36.0) was reported. For patients with available data (n = 21), the median progression-free survival was 1.9 months (95% CI, 1.7 to 2.7 months). Responses were not enriched in tumors with high PD-L1 expression (≥ 50%).72 This ORR was similar to the ORR of 14% observed in the OAK trial with atezolizumab, which had an unselected, previously treated patient population (N = 425).72,76

**TESTING FOR METex14**

**Next-Generation Sequencing**

Historically, a number of different tests to identify METex14 have been used, including single-gene tests, using technologies such as RT-PCR and Sanger sequencing.83,77-79 With an incidence of approximately 3%-4% for METex14 in NSCLC and given the total number of actionable biomarkers that should be tested for, single-gene testing is now generally considered impractical.18,22,79-82 This is particularly true in NSCLC, where biopsies tend to be small or have minimal tumor content, meaning that employing multiple tests on a single sample is not possible.18,80-82 To complement tissue biopsy, liquid biopsy may be used to test for circulating tumor DNA. Liquid biopsies are recommended when tumor tissue is scarce or unavailable or when a significant delay in obtaining tissue (> 2 weeks) is anticipated. A positive result by circulating tumor DNA testing could trigger treatment with targeted agents. However, a negative result does not rule out an oncogenic driver, because some tumors do not shed sufficient amounts of DNA to be detected by liquid biopsies. Negative results should be followed up with a secondary test using a tissue-based method.82 NGS is a rational choice as a testing platform because it can detect other oncogenic drivers concurrently using one test performed on a single sample.2,80,81

In clinical oncology diagnostics, whole-genome or whole-exome sequencing is rarely used, for two primary reasons. First, most of the genome or exome is currently not clinically informative for oncology, meaning that most of the data derived from these approaches are clinically useless. Second, to ensure detection of low-variant allele frequency variants, sequencing depth needs to be high; thus, sequencing needs to be focused on actionable targets. Therefore, nearly all clinical oncology diagnostic NGS assays employ some degree of target enrichment.11,83,84 To accomplish this, there are two main types of library preparation approaches: amplicon and hybrid capture.84 Given the diversity of alterations leading to MET exon 14 skipping, different approaches to target enrichment for NGS vary dramatically in their ability to detect these events.3,33,76,85-86

The amplicon-based method uses primers that flank the regions of interest for sequencing (Fig 4). This approach has a number of disadvantages. Primary among these is that allele dropout may occur if there is a single-nucleotide variant or short indel in the primer region, because the primer will be mismatched and not bind. Additionally, if the entirety of a genomic region is deleted, the primer binding sites will also be missing.84 The diversity in position and size of alterations leading to MET exon 14 skipping can lead to allele dropout and provide false negatives.78 In routine clinical practice, many targeted NGS assays that use amplicon-based library preparation techniques have not been properly optimized to detect mutations leading to MET exon 14 skipping, resulting in low detection rates.76,82 An evaluation of seven DNA-based amplicon NGS assays revealed that, based on primer design, none of the assessed assays would detect more than 63% of known METex14 in an in silico analysis.78

At one institution, a laboratory-developed amplicon-based NGS assay built on the Ion AmpliSeq Colon and Lung Cancer Research Panel v2 detected MET exon 14 skipping in 0.3%
of 1,514 NSCLC samples.\textsuperscript{83} Previous in silico analysis found that the Ion AmpliSeq Colon and Lung Cancer Research Panel v2 would identify only up to 24\% of alterations leading to \textit{MET} exon 14 skipping.\textsuperscript{78} Optimization of the assay by incorporating fragment analysis and including three additional amplicons to cover exon 14 and its surrounding introns increased the detection rate of \textit{MET}ex14 to 2.2\% of 365 additional NSCLC samples analyzed.\textsuperscript{83}

Furthermore, comparisons of DNA-based amplicon-mediated methods with RNA-based methods continue to highlight the rates of false negatives in detecting \textit{MET}ex14.\textsuperscript{85,86} Relative to DNA-based amplicon-mediated methods, \textit{MET}ex14 detection with RNA-based methods has been demonstrated to be superior, as shown in recent publications.\textsuperscript{85,86} In the work of Davies et al, a direct comparison of the ArcherDX FusionPlex Solid Tumor assay (RNA-based, anchored multiplex PCR–mediated) and the Illumina TruSight Tumor 26 assay (DNA-based, amplicon-mediated) showed that \textit{MET}exon 14 skipping was detected in 4.2\% (17 of 404) of RNA-based NGS samples, compared with 1.3\% (11 of 856) of DNA-based NGS samples. Among 286 samples tested with both assays, 10 cases of \textit{MET}ex14 were identified with the RNA-based assay, compared with only four cases with the DNA-based assay.\textsuperscript{85} Consistent with this work, Jurkiewicz et al reported a \textit{MET}ex14 detection rate of 2.5\% (16 of 644 lung cancer tumors analyzed) using an amplicon-mediated, targeted, DNA-based NGS panel. Supplemental testing using an RNA-based panel increased \textit{MET}ex14 detection to 3.9\% (25 of 644 samples).\textsuperscript{85}

The hybrid capture library preparation method uses a different approach to target enrichment. Briefly, tumor DNA is fragmented and subsequently mixed with sequence-specific probes to isolate the regions of interest. These probes hybridize to long pieces of the target genome, enabling sequencing of regions surrounding the area of interest. The hybridization probes are significantly longer than PCR primers, making them more tolerant to the presence of mismatches in the binding site. This largely circumvents the issue of allele dropout. One downside to the hybrid capture–based approach is that the longer pieces of the target genome may increase off-target sequencing, reducing the sequencing coverage in the regions of interest.\textsuperscript{54}

Given the diversity of alterations that may lead to \textit{MET} exon 14 skipping and the potential location of these alterations in the \textit{MET} gene, hybrid capture is a preferred approach to avoid the allele dropout commonly observed with amplicon-mediated methods.\textsuperscript{3,19,78,84,85} However, in addition to the right library preparation method, the platform of choice must also have bioinformatic tools optimized to detect these events.\textsuperscript{94} Several available platforms use the hybrid capture approach with optimized bioinformatic analyses. Among them, both MSK-IMPACT and FoundationOne CDx (Foundation Medicine Inc, Cambridge, MA) reliably detect a wide array of alterations leading to \textit{MET} exon 14 skipping, without the need for supplemental RNA-based testing.\textsuperscript{5,20,67,72}

**RNA-Based Testing**

RNA-based testing may be used to augment DNA-based sequencing to provide more robust assessment of the state of several oncogenic drivers. RNA sequencing need only detect the direct result of alterations leading to \textit{MET} exon 14 skipping: fusion of exons 13 and 15.\textsuperscript{53,78,85} Importantly, this method may be useful for identifying \textit{MET}ex14 when patients have noncanonical intronic mutations that affect splicing.\textsuperscript{87} Some institutions and commercial platforms have implemented parallel or sequential RNA-based testing to maximize the chance of identifying an actionable oncogenic driver.\textsuperscript{78,79,87,88} However, there are technical
challenges to consider with the adoption of routine RNA sequencing in clinical practice. RNA is substantially more vulnerable to degradation than DNA, which leads to a reduction in the quality of RNA acquired in clinical cases, particularly for formalin-fixed, paraffin-embedded samples. Clinical assays that use RNA as input material must incorporate quality control metrics that alert the user when RNA quality in a sample is too poor to allow confident interpretation of negative results. RNA detection is further complicated by low basal rates of alternative splicing (potentially low-level splicing errors made by the cells), which may lead to false positives. It has been reported that low levels of mRNA with fused exons 13 and 15 may be detected even when underlying alterations leading to MET exon 14 skipping are not present. It should be noted that there is no strong evidence to suggest that pathogenic levels of MET exon 14 skipping can occur in the absence of an underlying genomic event.

**FUTURE OF MOLECULAR TESTING FOR METex14**

In the future, interrogation of MET protein levels in tumor tissue may also be incorporated to select patients who may be responsive to MET inhibitors. In a small study, Guo et al measured MET levels by quantitative mass spectrometry or immunohistochemistry (IHC) in patients with advanced METex14 NSCLC. Patients with detectable levels of MET by mass spectrometry had an ORR of 60% (6 of 10 patients) with a MET TKI, whereas the response rate was 0% (zero of five patients) with a MET TKI in patients with undetectable levels of MET. Likewise, patients with detectable levels of MET with an IHC H-score ≥ 200 had an ORR of 62% (8 of 13 patients), whereas the ORRs in patients with H-scores of 150-199 and 1-149 were 25% (one of four patients) and 33% (one of three patients), respectively. The one patient without MET protein expression by IHC did not have a response. However, MET protein detection should not be considered a stand-alone testing regimen and has been shown to be an unreliable screen for identifying METex14-positive patients.

It is important for clinicians to recognize that assays including MET in their list of covered genes may not detect all alterations that lead to MET exon 14 skipping. In addition to testing for METex14, some assays may also report on MET amplification and MET positivity. These are distinct conditions that are currently being evaluated in ongoing clinical trials. When selecting the most appropriate assay for broad molecular testing, carefully consider each assay's limitations.

**AFFILIATIONS**

1AdventHealth, Orlando, FL
2Department of Hematology and Medical Oncology, Cleveland Clinic, Cleveland, OH
3Department of Pathology, University of Colorado Anschutz Medical Campus, Aurora, CO

**CORRESPONDING AUTHOR**

Mark A. Socinski, MD, AdventHealth, Cancer Institute, 2501 N. Orange Ave, Orlando, FL 32804; e-mail: Mark.Socinski.MD@AdventHealth.com.

**DISCLAIMER**

The sponsor had no role in the writing of the report and in the decision to submit the article for publication.

**SUPPORT**

Supported by Novartis Pharmaceuticals Corporation, East Hanover, NJ. Employees of the company were involved in medical accuracy review.

**AUTHOR CONTRIBUTIONS**

Conception and design: Mark A. Socinski, Nathan A. Pennell
Collection and assembly of data: Mark A. Socinski, Kurtis D. Davies
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/po/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Mark A. Socinski
Speakers’ Bureau: AstraZeneca, Bristol-Myers Squibb, Celgene, Genentech, Merck, Novartis
Research Funding: AstraZeneca, Bristol-Myers Squibb, Genentech, Merck, Novartis, Takeda

Nathan A. Pennell
Consulting or Advisory Role: Amgen, AstraZeneca, Bristol-Myers Squibb, Cota, Eli Lilly, Genentech, Invivta, Merck, Pfizer
Open Payments Link: https://openpaymentsdata.cms.gov/physician/204570/summary

Kurtis D. Davies
Consulting or Advisory Role: Novartis
Travel, Accommodations, Expenses: Archer

No other potential conflicts of interest were reported.

**ACKNOWLEDGMENT**

The authors thank James Banigan, PhD, of Chameleon Communications International, New York, NY, for providing medical writing assistance, which was funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ, in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).
66. Recondo G, Bahcall M, Spurr LF, et al: MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science 316:1039-1043, 2007
67. FoundationOne CDx. Technical Information. Cambridge, MA, Foundation Medicine, 2021
65. Mazieres J, Veillon R, Felip E, et al: Activity of tepotinib in brain metastases: Preclinical models and clinical data from patients with MET exon 14-mutant non-small-cell Lung cancer (NSCLC) patients with MET amplification/exon 14 deletion (MET/AmpEx14Δ). J Clin Oncol 38:9510, 2020
66. Recondo G, Bahcall M, Spurr LF, et al: MET inhibitor capmatinib plus EGFR tyrosine kinase inhibitor naxitnib for EGFR-mutant non-small-cell lung cancer. Ann Oncol 31:S829-S830, 2020
69. Fujino T, Kobayashi Y, Suda K, et al: Sensitivity and resistance of MET exon 14 mutations in lung cancer to eight MET tyrosine kinase inhibitors in vitro. J Thorac Oncol 14:1753-1765, 2019
70. Wolf J, Neal J, Mansfield A, et al: Comparison of clinical outcomes of patients with METΔex14 NSCLC treated with first-line capmatinib in the GEOMETRY mono-1 trial. Presented at the 2020 World Conference on Lung Cancer Singapore, January 28-31, 2021
71. McGiheary S, Mazieres J, Veillon R, et al: Activity of tepotinib in brain metastases: Preclinical models and clinical data from patients with MET exon 14 skipping mutations (METEx14Δ). J Clin Oncol 38:9613, 2020
72. Sadari JK, Leonardi GC, Shu CA, et al: PD-L1 expression, tumor mutational burden, and response to immunotherapy in patients with MET exon 14 altered lung cancers. Ann Oncol 29:2085-2091, 2018
73. Mayenga M, Assil JB, Monnet I, et al: Durable responses to immunotherapy of non-small-cell lung cancers harboring MET exon-14 skipping mutations. A series of 6 cases. Lung Cancer 150:21-25, 2020
74. Baba K, Tanaka H, Sakamoto H, et al: Efficacy of pembrolizumab for patients with both high PD-L1 expression and an MET exon 14 skipping mutation: A case report. Thorac Cancer 10:369-372, 2019
75. Reis H, Metzenmacher M, Goetz M, et al: MET expression in advanced non-small-cell lung cancer: Effect on clinical outcomes of chemotherapy, targeted therapy, and immunotherapy. Clin Lung Cancer 19:e441-e463, 2018
76. Rittmeyer A, Barlesi F, Waterkamp D, et al: Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): A phase 3, open-label, multicentre randomised controlled trial. Lancet 389:255-265, 2017
77. Heist RS, Garon EB, Tan DSW, et al: Accurate detection of METex14 mutations in non-small cell lung cancer (NSCLC) with comprehensive genomic sequencing: Results from the GEOMETRY mono-1 study (abstract B11). J Thorac Oncol 15:S30-S31, 2020
78. Point B, Doucet L, Benhenda S, et al: MET exon 14 alterations and new resistance mutations to tyrosine kinase inhibitors: Risk of inadequate detection with current amplicon-based NGS panels. J Thorac Oncol 12:1582-1587, 2017
79. Kim EK, Kim KA, Lee CY, et al: Molecular diagnostic assays and clinicopathologic implications of MET exon 14 skipping mutation in non-small-cell lung cancer. Clin Lung Cancer 20:e123-e132, 2019
80. Drikos A, Wang L, Arcila ME, et al: Broad, hybrid capture-based next-generation sequencing identifies actionable genomic alterations in lung adenocarcinomas otherwise negative for such alterations by other genomic testing approaches. Clin Cancer Res 21:3631-3639, 2015
81. Pennell NA, Mutebi A, Zhou Z-Y, et al: Economic impact of next-generation sequencing versus single-gene testing to detect genomic alterations in metastatic non-small-cell lung cancer using a decision analytic model. JCO Precis Oncol 3:1-9, 2019
82. Yu TM, Morrison C, Gold EJ, et al: Multiple biomarker testing tissue consumption and completion rates with single-gene tests and investigational use of Oncomine Dx Target Test for advanced non-small-cell lung cancer: A single-center analysis. Clin Lung Cancer 20:20-29.e8, 2019
83. Descarpentries C, Leprêtre F, Escande F, et al: Optimization of routine testing for MET exon 14 splice site mutations in NSCLC patients. J Thorac Oncol 13:1873-1883, 2018
84. Jennings LJ, Arcila ME, Corless C, et al: Guidelines for validation of next-generation sequencing-based oncology panels: A joint consensus recommendation of the Association for Molecular Pathology and College of American Pathologists. J Mol Diagn 19:341-365, 2017
85. Davies KD, Lomboy A, Lawrence CA, et al: DNA-based versus RNA-based detection of MET exon 14 skipping events in lung cancer. J Thorac Oncol 14:737-741, 2019
86. Jankiewicz M, Szać A, Mansukhani MM, et al: Efficacy of DNA versus RNA NGS-based methods in MET exon 14 skipping mutation detection. J Clin Oncol 38:9036, 2020
87. Benayed R, Offin M, Mullaney K, et al: High yield of RNA sequencing for targetable kinase fusions in lung adenocarcinomas with no mitogenic driver alteration detected by DNA sequencing and low tumor burden. Clin Cancer Res 25:4712-4722, 2019
88. An Approach for Establishing Oncomine Focus Assay Performance. White Paper. Waltham, MA, ThermoFisher Scientific, 2016
89. Penland SK, Keku TO, Torrice C, et al: RNA expression analysis of formalin-fixed paraffin-embedded tumors. Lab Invest 87:383-391, 2007
90. von Ahlfen S, Missel A, Bendrat K, et al: Determinants of RNA quality from FFPE samples. PLoS One 2:e1261, 2007
91. Davies KD, Le AT, Sheren J, et al: Comparison of molecular testing modalities for detection of ROS1 rearrangements in a cohort of positive patient samples. J Thorac Oncol 13:1474-1482, 2018
92. Manthei D, Weigelin H, Kleyman-Smith Y, et al: Improved detection of MET exon 14 skipping mutations in lung adenocarcinoma with combined DNA/RNA testing and refined analysis methods (ST009). Presented at the Association for Molecular Pathology Annual Meeting and Expo, Baltimore, MD, November 5-9, 2019
93. Guo R, Offin M, Brannon AR, et al: MET exon 14-altered lung cancers and MET inhibitor resistance. Clin Cancer Res 27:799-806, 2021
94. Guo R, Berry LD, Asner DL, et al: MET IHC is a poor screen for MET amplification or MET exon 14 mutations in lung adenocarcinomas: Data from a tri-institutional cohort of the Lung Cancer Mutation Consortium. J Thorac Oncol 14:1666-1671, 2019
95. Liang H, Wang M: MET oncogene in non-small cell lung cancer: Mechanism of MET dysregulation and agents targeting the HGF/c-Met axis. Onco Targets Ther 13:2491-2510, 2020
96. Vansteenkiste JF, Van De Kerkhove C, Wauters E, et al: Capmatinib for the treatment of non-small cell lung cancer. Expert Rev Anticancer Ther 19:669-671, 2019
97. Paik PK, Sakai H, Filip E, et al: Tepotinib in patients with MET exon 14 (METex14) skipping advanced NSCLC: Updated efficacy results from VISION Cohort A. Presented at the 2020 World Conference on Lung Cancer Singapore, January 28-31, 2021