review articles

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

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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 (*MET*ex14).[5-8] 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, *MET*ex14 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 *MET*ex14 NSCLC, *MET*ex14 is now an actionable biomarker in metastatic NSCLC.[6,12,25] 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 *MET*ex14.

BIOLOGY OF *MET*EX14

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,[29] and as with many other oncogenic drivers, coexistence of *MET*ex14 with other oncogenic drivers is rare.[3,20] *MET*ex14 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[35,41,42] or *EGFR* mutation–positive disease[43-46]; however, these discussions are outside the scope of this review. Importantly, both *MET*ex14 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 *MET*ex14-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]

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CONTEXT

Key Objective

We review the considerations for detecting *MET* exon 14 skipping mutation (*MET*ex14) in non–small-cell lung cancer (NSCLC) using next-generation sequencing (NGS).

Knowledge Generated

Clinical data support targeting *MET*ex14 in NSCLC; however, the ability of NGS assays to identify the diverse set of genetic alterations leading to *MET*ex14 varies. Hybrid capture–based NGS has proven to be a more reliable method for identifying *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 *MET*ex14 NSCLC has made *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 *MET*EX14 NSCLC

*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 *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 *MET*ex14. These patients are also significantly older than patients with other oncogenic drivers (*EGFR*, *KRAS*, or *ALK*).[22] Furthermore, in a retrospective review of 148 patients with *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%).[48]

Numerous agents have been investigated for the treatment of *MET*ex14 NSCLC in both clinical trials and off-label use.[35,41,48,57-59] Below, we provide an overview of the key MET tyrosine kinase inhibitors (TKIs) that have been investigated in *MET*ex14 NSCLC. Importantly, with 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.[6,25,35,41,57,60-63]

Crizotinib

Historically, some patients with *MET*ex14 NSCLC have been treated with off-label crizotinib, a multikinase inhibitor approved for *ALK*- or *ROS1*-rearranged advanced NSCLC that also has activity against MET kinase.[48,57] The NCCN guidelines note that crizotinib is a therapy that may be useful in certain circumstances for patients with metastatic *MET*ex14 NSCLC.[12] The PROFILE 1001 trial (NCT00585195) investigated the use of crizotinib in patients with a number of genetic alterations, including *MET*ex14 NSCLC.[57] *MET*ex14 was primarily identified by local DNA- or RNA-based next-generation sequencing (NGS).[57] Among response-evaluable patients with *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.[57]

Tepotinib

Tepotinib is an oral MET kinase inhibitor that has been approved for use in Japan and the United States.[25,41] The VISION trial (NCT02864992) was a prospective, nonrandomized, open-label phase II study investigating the use of tepotinib in patients with *MET*ex14 or *MET*-amplified NSCLC.[41] *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.[41] Treatment-naive *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 *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.[25] Responses were consistent across the liquid and tissue biopsy groups.[41]

Tepotinib has shown some clinical evidence of intracranial activity through a case report published from the VISION trial.[64,65] Intracranial response rates have not been reported.[41,64,65]

Among patients with *MET*ex14 NSCLC treated with tepotinib (N = 255), the most common adverse reactions or AEs

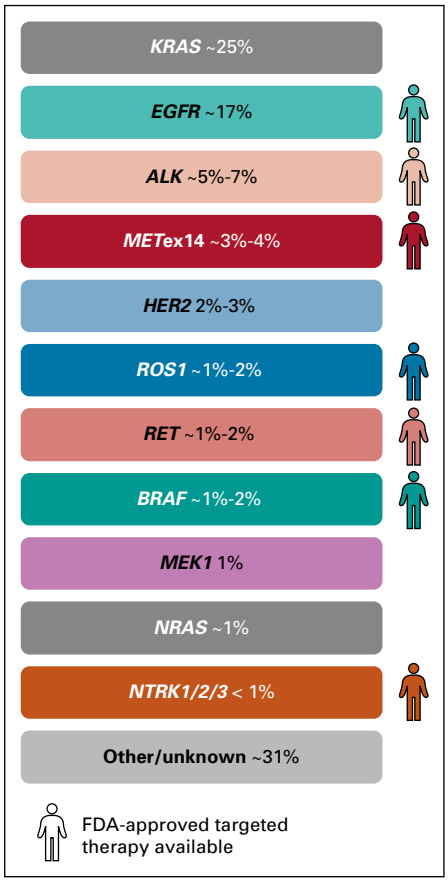

FIG 1. Driver mutations involved in NSCLC. Adenocarcinoma, the most common NSCLC histology, can be further characterized by various oncogenic drivers. Many of these oncogenic drivers have an FDA-approved targeted therapy available.[2,8,22,24] FDA, US Food and Drug Administration; NSCLC, non–small-cell lung cancer.

(any cause; ≥ 20%) were edema, fatigue, nausea, diarrhea, increased blood creatinine, musculoskeletal pain, and dyspnea.[25,63]

Capmatinib

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 *MET*ex14 metastatic NSCLC and is also approved in Japan; approval was based on the results from the GEOMETRY mono-1 trial (NCT02414139).[6,66]

The GEOMETRY mono-1 trial was a prospective, nonrandomized, 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 (*MET*ex14 and/or *MET* amplification). *MET*ex14 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 *MET*ex14 detection, showing a concordance rate of 99% (72 of 73 patient samples) with the RT-PCR clinical trial assay.[35,67] The additional patient had a noncanonical mutation leading to *MET* exon 14 skipping.[35] Treatment-naive *MET*ex14 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 *MET*ex14 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 *MET*ex14 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.[6,35] 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.[35]

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).[35]

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.[6,35]

Savolitinib

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 *MET*ex14 PSC or other NSCLC histologies, 57% had adenocarcinoma and 36% had PSC; 60% of patients had been previously treated. *MET*ex14 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, increased AST/ALT, vomiting, and hypoalbuminemia.[58]

Mechanisms of Resistance to MET TKIs

MET TKI resistance can be broadly grouped into two categories: MET dependent (on target) and bypass (off target).[68] Preclinical work has shown that clones with

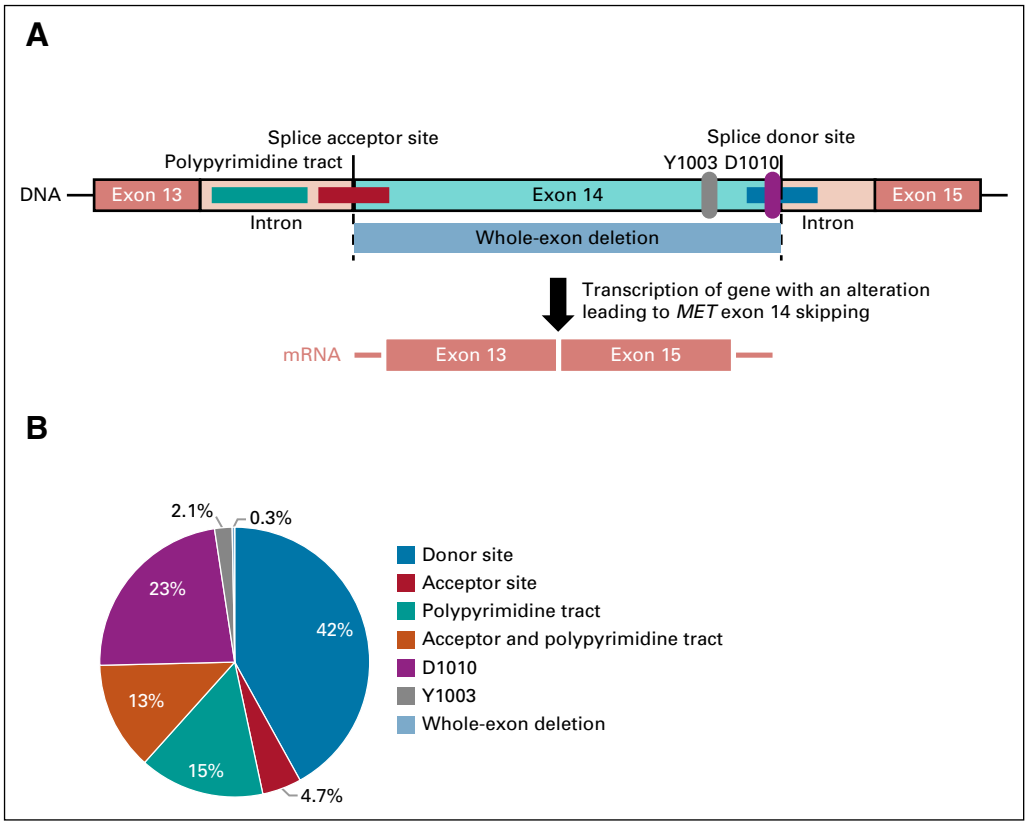

FIG 2. *MET* exon 14 skipping alterations by site and regions of interest for sequencing. (A) To detect these potential alterations, it is important to sequence both exon 14 and its surrounding regions. The regions where known alterations leading to exon 14 skipping can occur are mapped onto the schematic of the *MET* gene. *MET* exon 14 skipping alterations in any of these regions will result in an mRNA where exons 13 and 15 are fused.[3,20,53,85] (B) An analysis of 1,387 samples found that a plurality of *MET* exon 14 skipping events occur at the donor site; however, events are spread across and around exon 14.[20]

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 *MET*EX14

Retrospective Real-World Analyses of MET Inhibitors in *MET*ex14 NSCLC

In addition to the clinical trial data supporting the use of MET inhibitors in patients with metastatic *MET*ex14 NSCLC, multiple studies have shown that patients with *MET*ex14 NSCLC have better outcomes when receiving a targeted therapy.[48,49,70]

A retrospective review of 61 patients with stage IV *MET*ex14 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.[48]

A real-world analysis of patients with *MET*ex14 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]

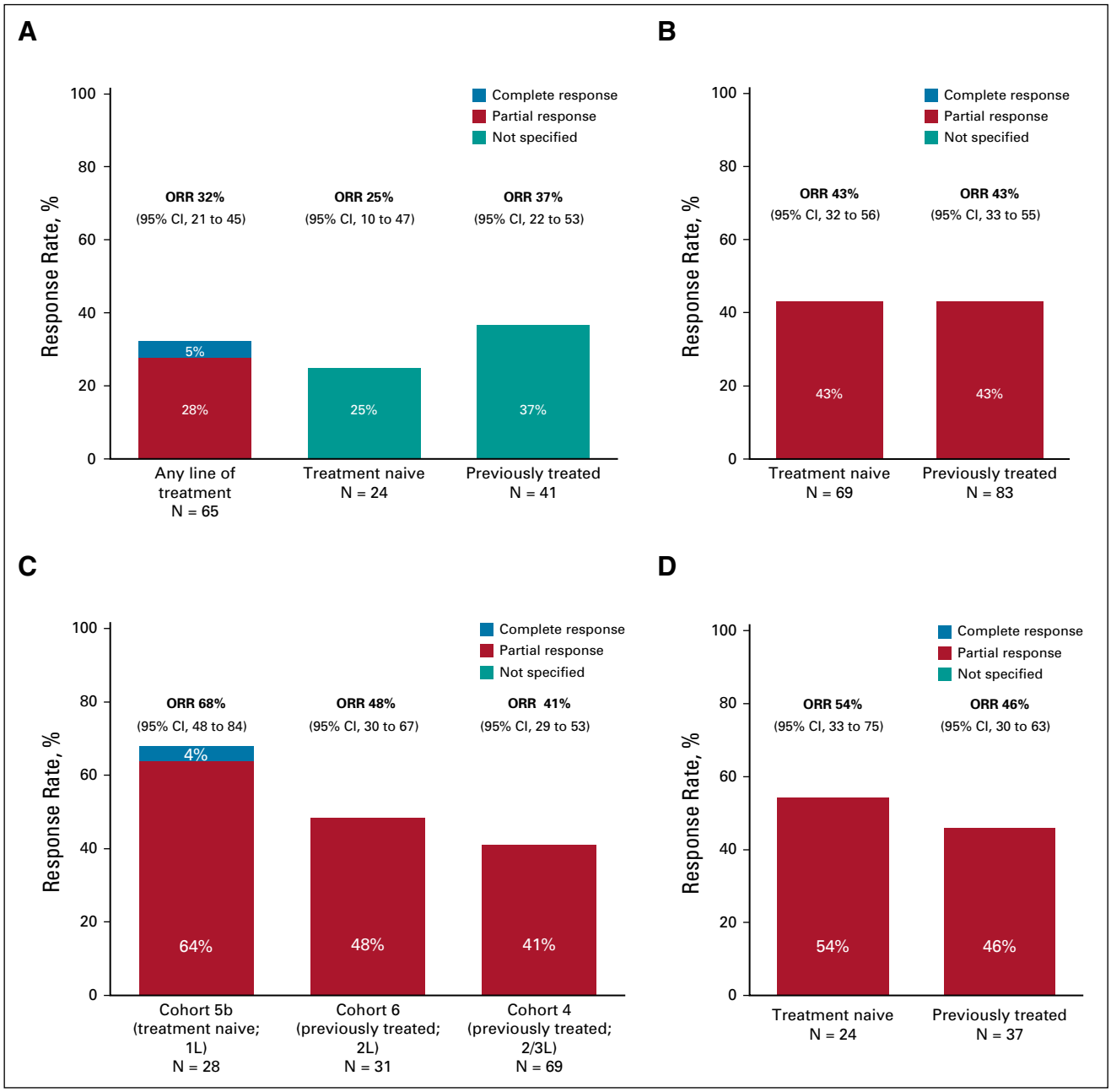

FIG 3. Treatment responses in clinical trials with MET inhibitors. (A) Best overall response in patients with advanced *MET*ex14 NSCLC who were treated with crizotinib in the PROFILE 1001 trial. Patients in this trial were a mix of treatment naive and previously treated.[57] (B) Best overall response per BIRC in patients with advanced *MET*ex14 NSCLC who were treated with tepotinib in the VISION trial. Patients in this trial were a mix of treatment naive and previously treated; data are shown from the analysis by line of treatment.[25,41,97] (C) Best overall response per BIRC in patients with advanced *MET*ex14 NSCLC who were treated with capmatinib in the GEOMETRY mono-1 trial. Patients in cohort 5b were treatment naive and received capmatinib in the first-line setting. Patients in cohorts 6 and 4 were previously treated and received capmatinib in the second-line setting and the second- or third-line setting, respectively.[35] (D) Best overall response in patients with advanced *MET*ex14 NSCLC who were treated with savolitinib in trial NCT02897479. Patients in this trial were a mix of treatment naive and previously treated; data are shown from the analysis by line of treatment.[58] 1/2/3L, first-/second-/third-line; BIRC, blinded independent review committee; *MET*ex14, *MET* exon 14 skipping mutation; NSCLC, non–small-cell lung cancer.

Another real-world analysis compared treatment-naive *MET*ex14 patients from GEOMETRY mono-1 with a matched cohort of real-world treatment-naive patients with advanced *MET*ex14 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 *v* 6.2 months, after weighting).[70]

The benefits of MET inhibitor therapy are not limited to newly diagnosed *MET*ex14 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 *MET*ex14 were responsive to MET inhibitor therapy even after receiving standard-of-care therapy (eg, chemotherapy, immuno-oncology, and/or radiation).[71]

Immunotherapy in Patients With *MET*ex14

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 *MET*ex14, the limited data for the use of immunotherapy, and current guidelines recommending upfront broad molecular profiling, we recommend that patients with *MET*ex14-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 *MET*ex14 NSCLC. The available evidence supporting the use of immunotherapy in patients with *MET*ex14 NSCLC is not definitive, and reported response rates are mixed.[72-75] In a small study of patients with *MET*ex14 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 *MET*ex14 NSCLC with high PD-L1 expression.[74,75] Overall, these case studies are consistent with a retrospective review of response-evaluable patients with *MET*ex14 NSCLC (N = 24) treated with pembrolizumab, nivolumab, durvalumab, atezolizumab, or ipilimumab plus nivolumab, in which an ORR of 17% (95% CI, 6 to 36) 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 *MET*ex14

Next-Generation Sequencing

Historically, a number of different tests to identify *MET*ex14 have been used, including single-gene tests, using technologies such as RT-PCR and Sanger sequencing.[33,77-79] With an incidence of approximately 3%-4% for *MET*ex14 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.[10] 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.[3,33,78,83,85,86]

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.[78,83] 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 *MET*ex14 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%

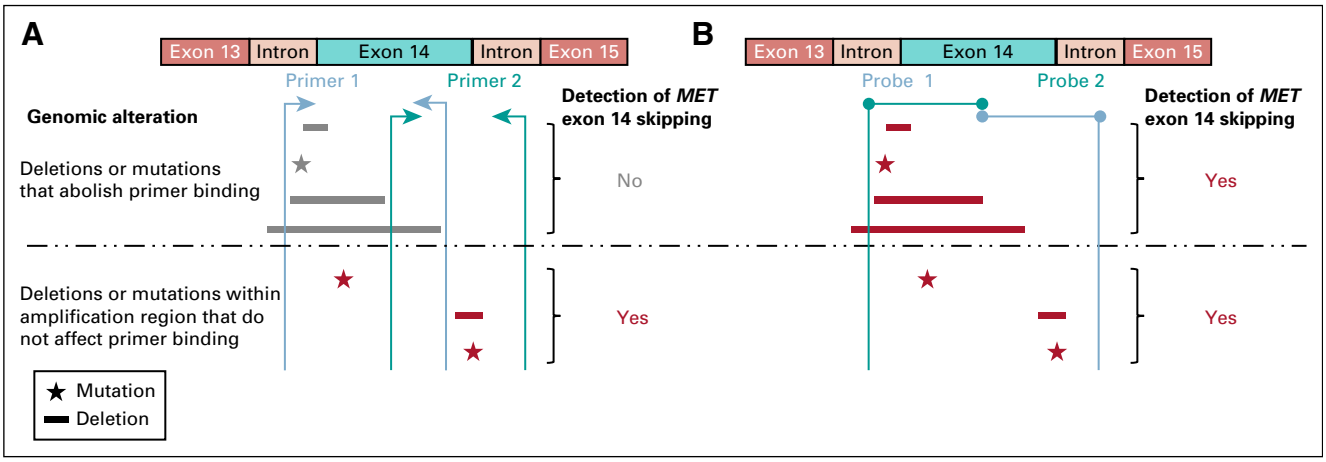

FIG 4. Overview of the (A) amplicon-based and (B) hybrid capture–based DNA NGS methods for targeted sequencing of MET. Amplicon-based NGS methods use polymerase chain reaction primers to amplify the regions of interest. Some alterations that lead to *MET* exon 14 skipping may prevent these primers from binding, leading to false negatives. Hybrid capture–based NGS methods use longer probes to pull down regions of interest, preventing the problem of allele dropout observed in the amplicon-based method and reducing false negatives.[3,19,78,84,85] NGS, next-generation sequencing.

of 1,514 NSCLC samples.[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 *MET* exon 14 skipping.[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 *MET*ex14 to 2.2% of 365 additional NSCLC samples analyzed.[83]

Furthermore, comparisons of DNA-based amplicon-mediated methods with RNA-based methods continue to highlight the rates of false negatives in detecting *MET*ex14.[85,86] Relative to DNA-based amplicon-mediated methods, *MET*ex14 detection with RNA-based methods has been demonstrated to be superior, as shown in recent publications.[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 *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 *MET*ex14 were identified with the RNA-based assay, compared with only four cases with the DNA-based assay.[85] Consistent with this work, Jurkiewicz et al reported a *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 *MET*ex14 detection to 3.9% (25 of 644 samples).[86]

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.[84]

Given the diversity of alterations that may lead to *MET* exon 14 skipping and the potential location of these alterations in the *MET* gene, hybrid capture is a preferred approach to avoid the allele dropout commonly observed with amplicon-based methods.[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.[84] 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 *MET* exon 14 skipping, without the need for supplemental RNA-based testing.[3,20,67,72]

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 *MET* exon 14 skipping: fusion of exons 13 and 15.[53,78,85] Importantly, this method may be useful for identifying *MET*ex14 when patients have noncanonical intronic mutations that affect splicing.[87] Some institutions and commercial platforms have implemented parallel or sequential RNA-based testing to maximize the chance of identifying an actionable oncogenic driver.[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.[85,89,90] 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.[91] 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.[92] 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.[83,87,92]

FUTURE OF MOLECULAR TESTING FOR *MET*EX14

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.[56] In a small study, Guo et al measured MET levels by quantitative mass spectrometry or immunohistochemistry (IHC) in patients with advanced *MET*ex14 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.[93] However, MET protein detection should not be considered a stand-alone testing regimen and has been shown to be an unreliable screen for identifying *MET*ex14-positive patients.[31,94]

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.[78,85] In addition to testing for *MET*ex14, some assays may also report on *MET* amplification and MET positivity. These are distinct conditions that are currently being evaluated in ongoing clinical trials.[31,32,41,42,52,94-96] When selecting the most appropriate assay for broad molecular testing, carefully consider each assay's limitations.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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