

Uncommon Mutations in Non-Small Cell Lung Cancer (NSCLC): A Focus On *MET*

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KEY TAKEAWAYS

- ▶ The *MET* exon 14 skipping mutation (*METex14*) is an actionable biomarker in metastatic non-small cell lung cancer (mNSCLC). Several *MET* kinase inhibitors, including capmatinib and tepotinib, recently were approved to treat patients with mNSCLC with *METex14*.^{1,2}
- ▶ Biomarker testing is critical in identifying appropriate targeted therapies for NSCLC with *MET* alterations and other uncommon mutations. However, variable testing uptake and barriers (eg, insufficient tissue samples, long turnaround times, poor communication, reimbursement challenges) continue to impede testing in practice.^{3,4}
- ▶ When possible, broad molecular profiling using next-generation sequencing (NGS) is recommended to identify rare driver mutations and gene fusions with minimal tissue requirements to help guide treatment decision-making.⁵
- ▶ Improved provider education surrounding uncommon mutations in NSCLC and associated biomarker testing is needed to optimize treatment selection and enhance patient care.
- ▶ Future research using large, prospective trials and real-world studies is needed to provide greater insight into and allow appropriate selection and sequencing of treatments for NSCLC that harbors *MET* alterations and other uncommon mutations.

Introduction

ON NOVEMBER 10, 2022, the OncLive® Scientific Interchange: Uncommon Mutations in Non-Small Cell Lung Cancer (NSCLC): A Focus on *MET* featured a panel of thoracic oncology experts. **Nicholas Rohs, MD**, assistant professor of medicine, hematology and medical oncology, at the Icahn School of Medicine at Mount Sinai in New York City, New York, moderated. Experts discussed uncommon mutations in NSCLC, including the current treatment landscape, associated molecular testing, unmet treatment needs, novel treatment approaches, and new therapeutic strategies for NSCLC with *METex14*. Ahead is a summary of key discussion points and stakeholder insights.

MET-Altered NSCLC

First identified in 1994, *METex14* is the most frequently reported *MET* alteration; it often occurs in the absence of other driver mutations of NSCLC.^{6,7} In the United States, *METex14* occurs in approximately 3% of NSCLC cases, with varying incidence according to histological subtype (adenocarcinoma, 2%; squamous cell carcinoma, 1%; adenosquamous cell carcinoma 6%; pulmonary sarcomatoid carcinoma, 13%).⁸ Aberrant *MET* signaling contributes to tumor progression, angiogenesis, tumor invasiveness, and metastatic tumor activity; this subtype is associated with therapeutic resistance and poor prognosis.⁸⁻¹⁰

Biomarker Testing in NSCLC

Experts emphasized the importance of biomarker testing, noting study data showing improved outcomes for patients with identified actionable mutations who receive appropriate targeted therapy.¹¹ With recent approvals of the *MET* kinase inhibitors capmatinib and tepotinib for patients with metastatic NSCLC (mNSCLC) with *METex14*, this mutation is now an actionable biomarker in this disease.^{1,2} Treatment with *MET* kinase inhibitors can significantly prolong overall survival (OS) (HR, 0.11; $P = .04$) in patients with NSCLC with *METex14*, which strongly suggests the need for *METex14* testing for patients with NSCLC.¹²

Molecular becomes increasingly important as the treatment of NSCLC continues to advance with more biomarker-driven therapy approaches.³ However, faculty noted that biomarker testing uptake and practices vary among practice sites, and further education is needed to emphasize the importance of testing to guide treatment. Up to 25% of tumor biopsies have inadequate tissue necessary to perform appropriate biomarker testing.⁴ Compared with other testing methods (eg, polymerase chain



reaction [PCR] and fluorescence in situ hybridization [FISH]) that provide results within 3 to 4 days, NGS results can take 7 days to several weeks.³ The panel noted that other barriers to biomarker testing include poor communication, a lack of reflex testing, testing reimbursement, and different practice sites for biopsy and treatment.^{3,4}

Guidelines for Biomarker Testing in Nonsquamous NSCLC

For all eligible patients with mNSCLC, updated National Comprehensive Cancer Network guidelines recommend molecular testing that assesses, at minimum, *ALK*, *EGFR*, *BRAF*, *HER2*, *KRAS*, *MET*14, *NTRK1*, *NTRK2*, *NTRK3*, *RET*, and *ROS1*, as well as immunohistochemistry (IHC) for PD-L1.⁵ Broad molecular profiling using NGS is recommended for improved patient care, as it allows for identification of rare driver mutations with minimal tissue requirements and reduced sample wastage.⁵ RNA-based NGS should be considered for patients without an identifiable driver oncogene to maximize detection of fusion events.⁵

Experts noted that when inadequate tissue is available for biomarker testing, biopsy and/or plasma testing is recommended. If alternative testing is not feasible, treatment decisions should be guided by available results. When results are unavailable or unknown, treatment is initiated according to the absence of any driver oncogenes.⁵

STAKEHOLDER INSIGHTS

Overall testing practices varied among panelists. Some sites rely on outside companies for NGS testing; others offer in-house testing that involve smaller gene panels. Due to a more rapid turnaround time (3-5 days), initial *EGFR* and *ALK* status generally are determined through methods such as rapid PCR and IHC. According to the experts, NGS testing generally is used to identify *MET*14. Large, comprehensive NGS testing often analyzes RNA, which allows identification of gene fusions; however, such RNA analysis typically requires 3 to 6 weeks for results. Some sites use FoundationOne, a broad panel NGS platform with several FDA-approved companion diagnostic indications, including *MET*14 testing for capmatinib.^{13,14} Reflexive testing often is conducted for early-stage disease. Some institutions have well-maintained reflex testing for lung cancer subtypes and stages.

Therapies For Advanced NSCLC with *MET*14

Several *MET* kinase inhibitors have been evaluated in patients with NSCLC with *MET*14. The **Table** summarizes efficacy and safety data from key trials of these agents.¹⁵⁻²¹

Tepotinib

Tepotinib is a highly selective (type 1b) *MET* kinase inhibitor that inhibits both hepatocyte growth factor-dependent and -independent *MET* phosphorylation, thereby suppressing *MET*-mediated downstream signaling.^{2,15} Following safety and efficacy findings reported in the pivotal VISION trial (NCT02864992), tepotinib was granted accelerated FDA approval on February 3, 2021, with indications for mNSCLC with *MET*14.^{2,22}

VISION

The multicenter, open-label, phase 2 VISION trial evaluated the safety and efficacy of tepotinib in patients with advanced NSCLC with *MET* alterations, including *MET*14.^{15,22} Among the 99 patients with NSCLC with *MET*14 who were eligible for analysis, the reported objective response rate (ORR) by an independent review committee was 46% (95% CI, 36%-57%).¹⁵ The median progression-free survival (mPFS) was 8.5 months, and the median OS (mOS) was 17.1 months.¹⁵ Treatment-related adverse events (TRAEs) of any grade were reported in 89% of patients. TRAEs of grade 3 or greater were observed in 28% of patients (most frequently, peripheral edema [7%]).¹⁵

INSIGHT 2

The ongoing, phase 2 INSIGHT-2 study (NCT03940703) is investigating the safety and efficacy of tepotinib plus osimertinib in patients with mNSCLC with activating *EGFR* mutations and *MET* amplification who have disease progression after first-line treatment with osimertinib.¹⁶ Initial findings reported at the 2022 European Society for Molecular Oncology Congress showed that after at least 9 months of follow-up, the ORR was 54.5% among patients (n = 22) with FISH-detected *MET* amplification who had received tepotinib plus osimertinib. With a follow-up of at least 6 months, the ORR was 8.3% among those (n = 12) with FISH-detected *MET* amplification who were treated with tepotinib monotherapy.

Any-grade AEs occurred in 73.9% of patients; the most commonly reported were diarrhea (40.9%), peripheral edema (23.9%), and paronychia (17.1%). AEs of grade 3 or greater

Table. Key Trial Data for MET Kinase Inhibitors in NSCLC¹⁵⁻²¹

MET kinase inhibitor	Trial (NCT number)	Patient population	Phase	Efficacy	Safety (TRAEs, AG/≥ G3)
Tepotinib	VISION (NCT02864992)	NSCLC with <i>MET</i> ex14 (cohort A)	Phase 2 (N = 99)	ORR by IRC, 46% mDOR, 11.1 mo mPFS, 8.5 mo mOS, 17.1 mo	Peripheral edema, 63%/7% Nausea, 26%/1% Diarrhea, 22%/1%
	INSIGHT 2 (NCT03940703)	<i>EGFR</i> m NSCLC with <i>MET</i> amplification	Phase 2 (N = 100)	ORR: ≥ 9 mo FU, 54.5% ≥ 3 mo FU, 45.8%	Peripheral edema, 23.9%/4.5% Diarrhea, 40.9%/0% Paronychia, 17.0%/1.1%
Capmatinib	GEOMETRY mono-1 (NCT02414139)	NSCLC with <i>MET</i> ex14 or <i>MET</i> amplification	Phase 2 (n = 97 ^a)	Previously treated: ORR, 41% mPFS, 5.4 mo Treatment-naive: ORR, 68% mPFS, 12.4 mo	Peripheral edema, 51%/9% Nausea, 45%/2% Vomiting, 28%/2%
	(NCT02897479)	mPSC with <i>MET</i> ex14 or other NSCLCs without <i>EGFR</i> , <i>ALK</i> , or <i>ROS1</i> mutations	Phase 2 (N = 70)	ORR, 47.1% mPFS, 6.9 mo mOS, 12.5 mo	Peripheral edema, 56%/9% Nausea, 46%/0% ALT elevation, 39%/10% AST elevation, 37%/13%
Savolitinib	SAVANNAH (NCT03778229)	<i>EGFR</i> m NSCLC with <i>MET</i> overexpression and/or amplification	Phase 2 (N = 193)	With IHC90+/FISH10+: ORR, 49% mDOR, 9.3 mo mPFS, 7.1 mo Without IHC90+/FISH10+: ORR, 9% mDOR, 6.9 mo mPFS, 2.8 mo	NR
	SAFFRON (NCT05261399)	<i>EGFR</i> m NSCLC with <i>MET</i> overexpression and/or amplification	Phase 3 (N ≈ 324)	PE: PFS by BICR SE: OS, ORR, DOR, PK	NR

AG, any grade; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BICR, blinded independent central review; DOR, duration of response; *EGFR*m, *EGFR* mutant; FU, follow-up; G3, grade 3; IHC90+/FISH10+, MET immunohistochemistry overexpression (3+) staining ≥ 90% tumor cells and/or fluorescence in situ *MET* copy number ≥ 10; IRC, independent review committee; mDOR, median duration of response; *MET*ex14, *MET* exon 14 skipping mutation; mo, month(s); mOS, median overall survival; mPFS, median progression-free survival; mPSC, metastatic pulmonary sarcomatoid carcinoma; NR, not reported; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PE, primary end point; PFS, progression-free survival; PK, pharmacokinetics; SE, secondary end point; TRAE, treatment-related adverse events.

^aIndicates the number of patients with *MET*ex14 across cohorts 1-5; efficacy reported for NSCLC with *MET*ex14, and safety reported for all cohorts.

were observed in 23.9% of patients (diarrhea, 0%; peripheral edema, 4.5%; paronychia, 1.1%).¹⁷

Capmatinib

Capmatinib is a potent, selective MET kinase inhibitor that blocks downstream MET-dependent signaling and tumor cell survival.^{1,18} On May 6, 2020, findings reported in the GEOMETRY mono-1 trial led to accelerated approval for capmatinib use in patients with mNSCLC with *MET*ex14; subsequent regular approval for the same indication was granted on August 10, 2022.^{1,23}

GEOMETRY MONO-1

The open-label, phase 2 GEOMETRY mono-1 trial (NCT02414139) assessed the safety and efficacy of capmatinib in patients with advanced NSCLC with *MET*ex14 or *MET* amplification. Among patients with NSCLC with *MET*ex14 NSCLC, the reported ORR was 41% among previously treated patients and 68% among treatment-naive patients; mPFS was 5.4 months and 12.4 months, respectively.¹⁸

AEs of grade 3 or greater were reported in 67% of patients, with peripheral edema (9%) most frequently reported. »

TRAEs occurred in 13% of patients, leading to treatment discontinuation in 11% of patients.¹⁸

Savolitinib

Savolitinib is a potent, highly selective MET kinase inhibitor designed to interrupt the MET signaling pathway.²⁴ Associated antitumor activity and reduced MET signaling resulting from savolitinib that were shown in early patient-derived xenograft models were confirmed by results of the phase 1 TATTON study (NCT02143466).²⁵⁻²⁷ Savolitinib was granted conditional approval in China for the treatment of patients with NSCLC with *MET*_{ex14} and progression after prior systemic therapy and who are ineligible for chemotherapy; it is currently under clinical investigation in the United States for MET-overexpressed or -amplified mNSCLC.^{18,21,28}

SAVANNAH

The single-arm, phase 2 SAVANNAH trial (NCT03778229) assessed the safety and efficacy of savolitinib in combination with osimertinib in patients with *EGFR*-mutant NSCLC with *MET* overexpression or amplification and disease progression following osimertinib therapy. *MET* overexpression was determined via IHC (IHC 3+ in $\geq 50\%$ of tumor cells [IHC50+]; IHC3+ in $\geq 90\%$ of tumor cells [IHC90+]).²⁰ *MET* amplification was determined via FISH (*MET* copy number ≥ 5 and/or *MET:CEP7* signal ratio ≥ 2 [FISH5+]; *MET* copy number ≥ 10 [FISH10+]). Among the 108 patients in the IHC90+ and FISH10+ subgroup, the ORR was 49%, with a median duration of response (mDOR) of 9.3 months and an mPFS of 7.1 months. Comparatively, reported efficacy was lower among patients with IHC50+ or FISH5+ (ORR, 32%; mDOR, 8.3 months; mPFS, 5.3 months) and those without IHC90+ or FISH10+ (ORR, 9%; mDOR, 6.9 months; mPFS, 2.8 months).²⁰

SAFFRON

The ongoing, global, open-label, phase 3 SAFFRON trial (NCT05261399) is evaluating the safety and efficacy of savolitinib in combination with osimertinib vs platinum-based chemotherapy (carboplatin or cisplatin plus pemetrexed) in patients with *EGFR*-mutant, *MET*-overexpressed or -amplified mNSCLC.²¹ Eligible patients must have documented disease progression after their most recent use of osimertinib in the first- or second-line setting; no prior chemotherapy in the metastatic setting is allowed. PFS by blinded independent central review is the primary study end point.

Secondary end points include OS, ORR, DOR, safety, and pharmacokinetics.²¹

STAKEHOLDER INSIGHTS

Faculty noted that targeted therapy with MET kinase inhibitors generally is used in the frontline setting for patients with NSCLC with *MET*_{ex14}. However, in patients with PD-L1–positive disease, some experts opt for immunotherapy prior to treatment with MET kinase inhibitors. In patients who test negative for *MET*_{ex14} but have *MET* amplification, treatment approaches typically include standard chemotherapy or immunotherapy. Faculty expressed a preference for initiating MET kinase inhibitors at low dosages followed by slow upward titration to improve tolerability. Experts noted that, in practice, capmatinib is used more frequently. However, some faculty have shifted to using tepotinib due to the incidence of pneumonitis in patients given capmatinib.

Experts agreed that peripheral edema can be a challenging AE for patients receiving treatment with MET kinase inhibitors. Although edema may improve over time in some patients, implementation of symptom management strategies or dose delays is often required. Frontline strategies to manage edema include elevation and use of compression stockings. When possible, treatment with diuretics (eg, furosemide) is avoided due to the potential for hypotension and acute renal failure; however, faculty may use these agents in some cases.

Looking Ahead

Faculty agreed that improved provider education regarding uncommon mutations in NSCLC and the appropriate testing to identify these alterations is needed. Long turnaround times for NGS-based biomarker testing and challenges related to interpretation of results remain barriers to its widespread use in practice. Improved clinical data from large, prospective trials and real-world studies are needed to help guide treatment selection and determine appropriate therapeutic sequencing for NSCLC that harbors uncommon mutations. Collaborative research between individual institutions, consortiums, and research foundations is needed to generate larger pooled data sets for these patient subgroups. ■

References are available on [OncLive.com](https://www.onclive.com).