Finding the target in *METex14* skipping NSCLC

Optimizing patient benefit through best practice

A virtual expert consensus touchROUNDTABLE meeting held on 05 February, 2025

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Online activity details

This resource has been downloaded from a touchROUNDTABLE, hosted on touchONCOLOGY. The full activity, which includes video resources, can be accessed at:

www. https://touchoncology.com/lung-cancer/learning-zone/finding-the-target-in-metex14-skipping-nsclc-optimizing-patient-benefit-through-best-practice/

This content is for healthcare professionals only.

Learning objectives

After watching the touchROUNDTABLE activity, you should should be better able to:

- ✓ Discuss the complex landscape of biomarker testing for NSCLC in the advanced setting
- ✓ Describe the recently-published near-global consensus statements on diagnostic best practice in *METex14* skipping NSCLC
- ✓ Discuss how optimizing testing and diagnosis can aid treatment decisions, improve patient selection, and benefit patients through early initiation of targeted therapy
- ✓ Provide an overview of the current treatment landscape in *METex14* skipping NSCLC, and discuss the challenges oncologists and pathologists face in its diagnosis and management

Expert panel

Prof. Christian Rolfo

The Ohio State Comprehensive Cancer Center, The James, Columbus, OH, USA

Dr Mervat Mahrous

Prince Sultan Military Medical City, Riyadh, KSA & Minia University, Egypt

Dr Umberto Malapelle

University of Naples Federico II, Naples, Italy

Dr Yasushi Yatabe

National Cancer Center Hospital, Tokyo, Japan

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Agenda

	Discussion opening and faculty introductions	**3 mins**	**Christian Rolfo**
1	**Introduction:** The importance of oncogenic driver mutations	**5 mins**	**Christian Rolfo**
2	**Current best practice for *METex14* skipping NSCLC diagnostic testing:** Review of recent ATORG, MEAR and EU/US consensus recommendations	**20 mins**	**Yasushi Yatabe (APAC)** **Mervat Mahrous (MEAR)** **Umberto Malapelle (EU/US)**
3	Current treatment options for *MET*ex14 skipping NSCLC	**5 mins**	**Christian Rolfo**
4	**DISCUSSION:** Challenges / considerations with *METex14* skipping testing, current best practice, impact of consensus recommendations, future directions	**25 mins**	**All faculty**
	Close	**2 mins**	**Christian Rolfo**

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What are oncogenic driver mutations in NSCLC?

- NSCLC is a heterogeneous disease that can be broadly categorized by the presence or absence of specific oncogenic driver mutations[1]
- These are present in ~60% of lung adenocarcinoma cases, and define several molecular subtypes of NSCLC[1]
- Key drivers include KRAS, EGFR, ALK, and *MET*[2,3]
- Specifically, NSCLC with a *METex14* skipping mutation is considered an extremely aggressive subtype with a poor prognosis[2]

Incidence of oncogenic drivers in NSCLC[3–5]*

	Global	Asian population
KRAS	29%	11%
EGFR	19%	50%
MET	3%	2%
BRAF	5%	
ALK	3%	
HER2	3%	

*Blue values represent global estimates, purple values (where presented and where data are available) represent estimates for an Asian population.

ALK, Anaplastic lymphoma kinase; BRAF, v-raf murine sarcoma viral oncogene homolog B; EGFR, Epidermal growth factor receptor; HER2, Human epidermal growth factor 2; KRAS, Kirsten rat sarcoma; *MET*, mesenchymal epithelial transition gene; NSCLC, non-small cell lung cancer.

1. Malapelle U, et al. *Br J Cancer.* 2024;131:212–219; 2. Mahrous M, et al. *Cureus.* 2023;15:e41992; 3. Chevallier M, et al. *World J Clin Oncol.* 2021; 12:217–237; 4. Ahn M-J, et al. *Clin Lung Cancer.* 2022;23:670–685; 5. Friedlander A, et al. *Biomarker Res.* 2024;12: https://doi.org/10.1186/s40364-024-00566-0.

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Why is it important to identify them?

- Targeted therapies matched to their oncogenic drivers are associated with improved survival and quality of life, and are recommended by various clinical guidelines including ESMO, ASCO, and NCCN[1]
    - Specifically, targeted *METex14* skipping treatments (TKIs) have shown response rates of 25–68%, with up to three-fold improvements in median OS[2]
- However, while NGS enables many driver mutations to be tested simultaneously, there still remain challenges to implementation and reporting of molecular testing[1]

ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing.

1. Malapelle U, et al. *Br J Cancer.* 2024;131:212–219; 2. Chevallier M, et al. *World J Clin Oncol.* 2021; 12:217–237.

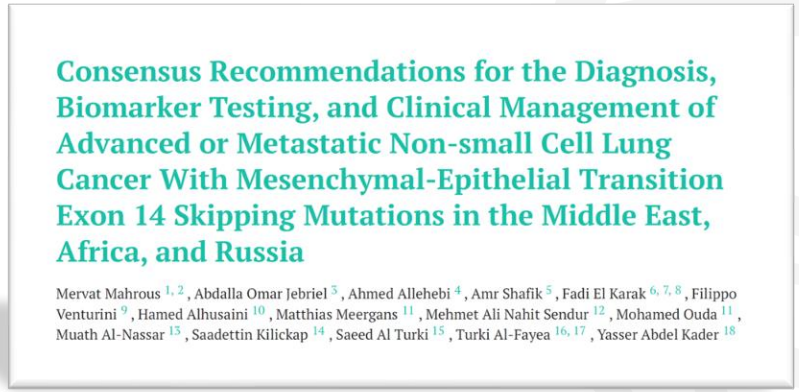
Current best practice for *MET*ex14 skipping NSCLC diagnostic testing

- Recently, three publications have provided near-global consensus/expert panel recommendations for *METex14* skipping NSCLC diagnostic approaches[1-3]


Asian Thoracic Oncology Research Group (ATORG) Expert Consensus Statement on *MET* Alterations in NSCLC: Diagnostic and Therapeutic Considerations

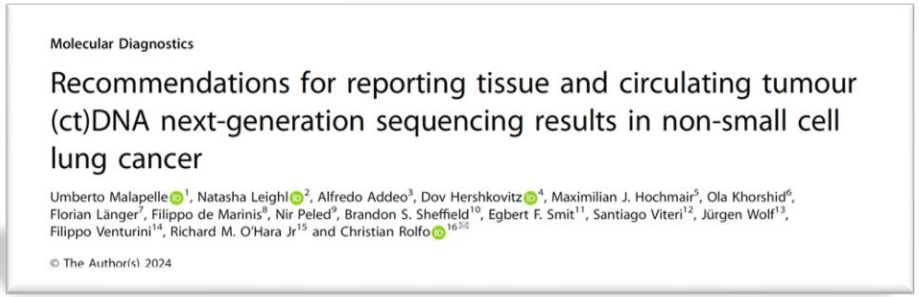
Myung-Ju Ahn,[1] Marvin Jonne L. Mendoza,[2] Nick Pavlakis,[3] Terufumi Kato,[4] Ross A. Soo,[5] Dong-Wan Kim,[6] Chong Kin Liam,[7] Te-Chun Hsia,[8] Chee Khoon Lee,[9] Thanyanan Reungwetwattana,[10] Sarayut Geater,[11] Oscar Siu Hong Chan,[12] Naiyarat Prasongsook,[13] Benjamin J. Solomon,[14] Thi Thai Hoa Nguyen,[15] Toshiyuki Kozuki,[16] James Chih-Hsin Yang,[17] Yi-Long Wu,[18] Tony Shu Kam Mok,[19] Daniel Shao-Weng Tan,[20] Yasushi Yatabe[21]

Ahn M-J, et al. *Clin Lung Cancer.* **2022**;23:670–685


Consensus Recommendations for the Diagnosis, Biomarker Testing, and Clinical Management of Advanced or Metastatic Non-small Cell Lung Cancer With Mesenchymal-Epithelial Transition Exon 14 Skipping Mutations in the Middle East, Africa, and Russia

Mervat Mahrous [1, 2], Abdalla Omar Jebriel [3], Ahmed Allehebi [4], Amr Shafik [5], Fadi El Karak [6, 7, 8], Filippo Venturini [9], Hamed Alhusaini [10], Matthias Meergans [11], Mehmet Ali Nahit Sendur [12], Mohamed Ouda [11], Muath Al-Nassar [13], Saadettin Kilickap [14], Saeed Al Turki [15], Turki Al-Fayea [16, 17], Yasser Abdel Kader [18]

Mahrous M, et al. *Cureus.* **2023**;15:e41992


Molecular Diagnostics

Recommendations for reporting tissue and circulating tumour (ct)DNA next-generation sequencing results in non-small cell lung cancer

Umberto Malapelle[1], Natasha Leighl[2], Alfredo Addeo[3], Dov Hershkovitz[4], Maximilian J. Hochmair[5], Ola Khorshid[6], Florian Länger[7], Filippo de Marinis[8], Nir Peled[9], Brandon S. Sheffield[10], Egbert F. Smit[11], Santiago Viteri[12], Jürgen Wolf[13], Filippo Venturini[14], Richard M. O'Hara Jr[15] and Christian Rolfo[16]✉

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Malapelle U, et al. *Br J Cancer.* **2024**;131:212–219

1. Ahn M-J, et al. *Clin Lung Cancer.* 2022;23:670–685; 2. Mahrous M, et al. *Cureus.* 2023;15:e41992; 3. Malapelle U, et al. *Br J Cancer.* 2024;131:212–219.

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ATORG: *MET*-specific Expert Consensus Statements (2022)

Testing for *METex14* skipping is preferred within multi-gene panels for detecting targetable driver mutations in NSCLC

Testing for *METex14* skipping with advanced NSCLC is recommended. Currently, optimal testing methods are not prescribed and should be based on availability, disease status, and patient characteristics

Diagnostic challenges associated with *MET* testing include the lack of standardization, no national funded programs, and choice of tests based on local test availability

Tepotinib and capmatinib (+ savolitinib in China) can be considered 1L or 2L treatment in metastatic NSCLC with *METex14* skipping mutations

Given the reported clinical benefits of *MET* inhibitors in patients with NSCLC and *METex14* skipping**, improving awareness and access to these targeted treatments is warranted** in the APAC region

1L, first line; 2L, second line; APAC, Asia-Pacific; ATORG, Asian Thoracic Oncology Research Group.

1. Ahn M-J, et al. *Clin Lung Cancer.* 2022;23:670–685.

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Middle East, Africa, Russia: Consensus Recommendations (2023)

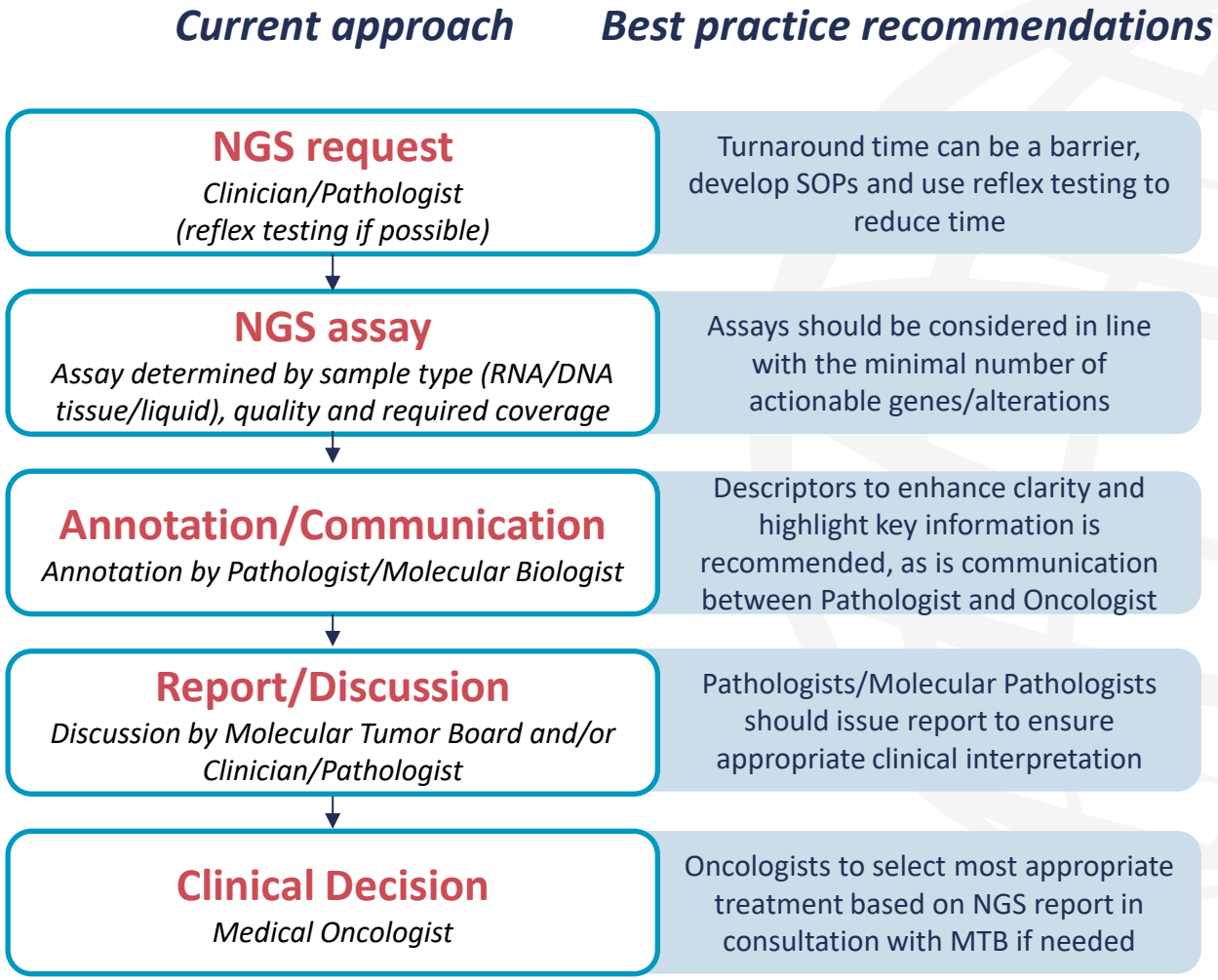
Initial Workup	• All patients with confirmed NSCLC (stage IIIb-IV) should undergo molecular testing before initiating systemic therapy
Molecular Testing	• NGS molecular testing (full panel including KRAS, EGFR, PD-L1, *MET*ex14 skipping) is recommended for all patients with adenocarcinoma, large cell carcinoma, NSCLC not otherwise specified, and select SCC • Relative preference is for RNA-based testing vs DNA-based testing • Tissue-based NGS is recommended for all patients with an adequate biopsy, whereas liquid biopsy is recommended only when this is not available (and should be performed prior to treatment)
Treatment	• Patients with *METex14* skipping mutations and ECOG PS ≤2 should receive 1L oral *MET*-specific TKI therapy (tepotinib, capmatinib); crizotinib or platinum chemotherapy may be an alternative if these are unavailable • 2L treatment options for patients with adenocarcinoma, large-cell carcinoma, and NSCLC (not otherwise specified) are pembrolizumab or pemetrexed (+ platinum-based therapy) • Best supportive care is only recommended for patients with ECOG PS 3–4, multiple comorbidities, and decompensated organ function

ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD-L1, programmed death-ligand 1; SCC, squamous cell carcinoma; TKI, tyrosine kinase inhibitor

1. Mahrous M, et al. *Cureus.* 2023;15:e41992.

Europe/US: NGS Reporting Consensus Recommendations (2024)

- Focussed on best practice recommendations for NGS reporting in NSCLC – one of the key barriers to successful implementation of molecular testing
- These complement existing guidelines / recommendations on the use of NGS and appropriately-targeted NSCLC therapies (e.g., ESMO, ASCO, NCCN)
- ***Overall aim:*** to ensure the most appropriate treatment options are selected based on robust molecular profiles in well-defined reports



Adapted with permission from Malapelle U, et al. Br J Cancer. 2024;131:212–219

DNA, deoxyribonucleic acid; MTB, molecular tumor board; RNA, ribonucleic acid; SOP, standard operating procedure.

1. Malapelle U, et al. *Br J Cancer.* 2024;131:212–219.

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What treatments are available for *METex14* skipping NSCLC?[1,2*]

Capmatinib[1]

----------INDICATIONS AND USAGE----------

Capmatinib is a kinase inhibitor indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping as detected by an FDA-approved test. (1)

ORR[1]
68% (treatment-naïve)
44% (previously treated)

GEOMETRY mono-1 study

Tepotinib[2]

----------INDICATIONS AND USAGE----------

Tepotinib is a kinase inhibitor indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (*MET*) exon 14 skipping alterations. (1)

ORR[2]
57% (treatment-naïve)
45% (previously treated)

VISION study

ORR, overall response rate
*Savolitinib is also available in China/Hong Kong.[3]
1. Capmatinib. Highlights of prescribing information. Available at https://www.novartis.com/us-en/sites/novartis_us/files/tabrecta.pdf; 2. Tepotinib. Highlights of prescribing information. Available at https://www.emdserono.com/us-en/pi/tepmetko-pi.pdf; 3. Ahn M-J, et al. *Clin Lung Cancer.* 2022;23:670–685.

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GROUP DISCUSSION

Key considerations for METex14 skipping NSCLC testing

What are the differences between liquid and tissue biopsies?

Both are recommended for testing, though tissues tests (i.e., RNA) are preferred if available, and ctDNA liquid NGS tests if not

What are key considerations for NGS?

Multiplex gene panel testing is important, to identify different mutations and isolate the driving mutation

Equally, covering the appropriate range of mutations for a single-gene test is important, as there can be multiple causes of METex14 skipping

What is the difference between DNA- and RNA-based assays?

RNA testing is preferred over DNA due to better sensitivity/detection rates and ease of interpretation (though DNA can be used if RNA is unavailable or as an external service)

What is meant by a 'complementary approach'?

Testing of both RNA/DNA using both tissue/liquid biopsy samples to provide the most comprehensive molecular picture of the tumor – though reimbursement could be a barrier to this approach

What are the key considerations for testing and treatment sequencing?

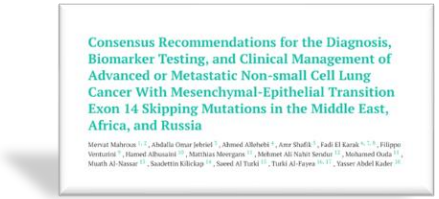
Early testing (reflex, ideally) is recommended

Always recommended to follow national/international testing and treatment guidelines

ctDNA, circulating tumor DNA.

How will standardized consensus recommendations for *METex14* skipping NSCLC impact clinical practice and benefit patients?


Asian Thoracic Oncology Research Group (ATORG) Expert Consensus Statement on *MET* Alterations in NSCLC: Diagnostic and Therapeutic Considerations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Recommendations for reporting tissue and circulating tumour (ct)DNA next-generation sequencing results in non-small cell lung cancer

Consensus Recommendations

Earlier identification of NSCLC

Targeted treatment

Patient benefits

Early initiation of targeted treatment
Treatment targeted to oncogenic drivers
Improved survival and quality of life[1]

1. Malapelle U, et al. *Br J Cancer.* 2024;131:212–219.

GROUP DISCUSSION

Diagnostic challenges for METex14 skipping NSCLC

An accurate/early diagnosis requires good tissue fixing/preservation for comprehensive molecular testing – what if these are not available?

A complementary approach using both tissue (if available) and liquid ctDNA testing would be the preferred strategy, though liquid alone is an option

DNA testing can also be performed on older tissue samples, due to less degradation vs RNA

What are the differences between METex14 skipping, EGFR mutations, and ALK fusions?

METex14 skipping NSCLC is an aggressive form of the disease – with targeted treatments durable responses can be achieved, though targeted treatments with ALK fusion and EGFR can achieve even better survival and response outcomes

In NSCLC, EGFR is the most common oncogenic driver of the three, especially in Asian populations

What is best reporting practice?

Simple and quick reporting is key (e.g., <14 days; highlighting METex14 skipping first, before details on specific mutations)

Report complementary findings (DNA/RNA, tissue/liquid)

Additional important details include relevant treatment class for the mutation, relative dominance (if more than one mutation is identified), type of tissue sample and the genes tested

Reflex testing and quick reporting would be the ideal approach

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GROUP DISCUSSION

How do you see the diagnosis and management of METex14 skipping NSCLC evolving in the future?

What is the future direction of oncogenic driver testing?

Tailoring of treatment to specific oncogenic driver mutations – e.g., METex14 skipping, overexpression, and/or fusion proteins

Adjustment and tailoring of strategies for different resistant mechanisms

How might oncogenic driver testing be integrated in these settings – what would be clear/concise best practice options?

Initiate testing as early as possible, ideally in the adjuvant/neoadjuvant setting

Reflex testing in all patients with NSCLC, using a comprehensive gene panel (NGS), a complementary approach (tissue/liquid) and providing a simple and clear report of the results

"Testing, testing, testing is the key message for the future"

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