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Precision targeting of *MET* in NSCLC: A multidisciplinary approach

Practice aid for NSCLC with *MET* alterations

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Tissue sample collection

General principles[1,2]

- The diagnostic strategy should be individualized depending on:
  - Size and location of the tumour
  - Presence of mediastinal or distant disease
  - Patient characteristics (e.g. comorbidities)
  - Local expertise
- Preferably, a metastatic lesion is biopsied for both diagnostic and staging purposes
- Systematic collaboration between pathologists and interventionalists are encouraged; this may include rapid onsite sample evaluation (ROSE)
- Adequate tissue material for histological diagnosis and molecular testing should be obtained

Commonly used procedures[2–4]

Image-guided transthoracic fine-needle aspiration and/or core biopsy
- Indicated in case of mid to peripheral lesions
- Significant risk of complications (pneumothorax, chest tube drainage, haemorrhage)

Bronchoscopy
- Ideally suited to central lesions
- Used with bronchial washing, brushing or bronchial/transbronchial biopsy

EBUS-guided needle aspiration
- Allows for evaluation of regional lymph nodes
- Minimally invasive technique
- Can yield sufficient tissue for diagnosis, staging and molecular testing

Thoracentesis
- Diagnostic tool and symptomatic treatment for pleural effusion

Considerations for molecular testing[1]

- Tumour testing has been primarily focused on FFPE tissues but can be performed on other cytopathology preparations
- Testing on cell blocks is recommended when it is the only or best material
- With minimally invasive techniques, the yield may be insufficient for molecular, biomarker and histologic testing
- Peripheral blood (plasma ctDNA) can be a surrogate sample

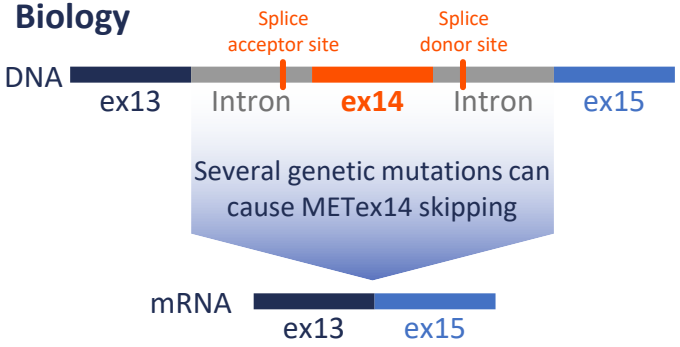
Considerations for liquid biopsy[5]

- A tissue biopsy should be given priority and a liquid biopsy only be performed if the tissue biopsy cannot be done or is not informative due to low yield or poor nucleic quality
- Liquid and tissue biopsy can be systematically and simultaneously performed in thoracic oncology before treatment
- The identification of certain alterations, such as gene fusions and gene amplifications, is less sensitive with a liquid than a tissue biopsy

MET aberrations and molecular testing

*MET*ex14 skipping mutation[6,7]

Biology



Clinical relevance

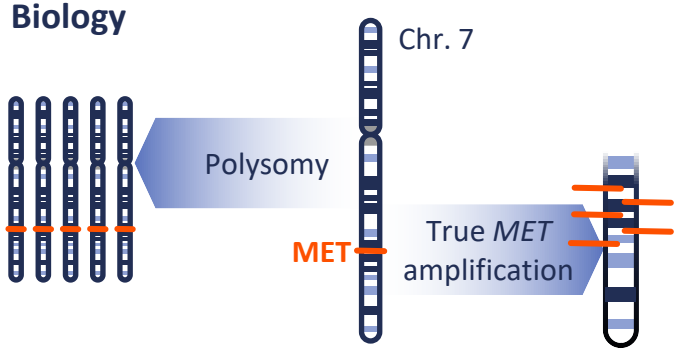
- 2–4% of advanced NSCLC
- Patients tend to be older than with other oncogenic drivers (median age: 70 years)
- Patients frequently have a history of tobacco exposure (up to 50% of patients)

Testing

- To complement tissue biopsy, liquid biopsy may be used to test for ctDNA
  - A positive result on ctDNA could trigger treatment with targeted agents
  - A negative result on ctDNA does not rule out *MET*ex14 skipping mutation
- Higher rates of false negatives with DNA-based vs RNA-based NGS

MET amplification[7]

Biology



Clinical relevance

- True *MET* amplification more likely to lead to oncogene addiction than polysomy
- De novo alteration in 1–5% of untreated NSCLC (strong smoking association)
- Resistance mutation in TKI-treated NSCLC:
  - 4–30% overall
  - 5–22% in EGFR-TKI-treated NSCLC

Testing

- Can be detected with different methods, including FISH, qPCR and NGS, with caveats:
  - Difficult to establish cut-off to define MET-amp
  - Interobserver variability
- Higher rate of co-occurring mutations (*TP53*, *KRAS*, and *KEAP1*) than with *MET*ex14

MET overexpression[7]

Biology

- Dysregulation of c-MET signalling due to receptor overexpression

Clinical relevance

- 35–72% of NSCLC and correlates with poorer outcomes (may co-occur with *MET*ex14 or *MET*-amplification)

Testing

- Immunohistochemistry

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MET-TKIs for advanced or metastatic NSCLC with *MET* alterations

Capmatinib[8,9]

Formulation
- Oral tablets: 150 or 200 mg

Dose and administration
- 400 mg twice daily with or without food

Approvals[8–11]
- Advanced/metastatic NSCLC with *MET*ex14 skipping mutation

Guidelines[1,2]
- Recommended/preferred treatment for NSCLC with *MET*ex14 skipping mutation
- Can be used with osimertinib for *EGFR*-mutant NSCLC that develops high-level MET amplification (>10 copies)

Side effects[8–12,*]
- Most common: **Oedema** (59–82% of patients in RCT, all grades)
  - Usually mild or moderate
  - Conservative management → Compression garments, lymphatic massage and kinesiotherapy
  - Diuretics may be considered (not included as recommendations in clinical trials and PI)
- Other common: Nausea, musculoskeletal pain, fatigue, GI side effects, dyspnoea and decreased appetite

Key warnings and precautions[8–11,*]

Warning	Monitoring	Action on MET-TKI treatment
Interstitial lung disease/pneumonitis	New or worsening pulmonary symptoms	Permanently discontinue
Hepatotoxicity	Liver function	Withhold, dose reduce or permanently discontinue based on severity
Pancreatic toxicity	Amylase and lipase	

Tepotinib[10,11]

Formulation
- Oral tablets: 225 mg

Dose and administration
- 450 mg once daily with food

Crizotinib[13,14]

Not approved for NSCLC with *MET* alterations in Europe nor the USA

Guidelines[1,2]
- *MET*ex14: Useful in certain circumstances
- High-level *MET*-amp: Can be used with osimertinib

Side effects*
Common side effects include vision disorders, GI side effects, oedema, fatigue, decreased appetite, URI and neuropathy

Savolitinib[15]

Approval
- Advanced/metastatic NSCLC with *MET*ex14 skipping mutation

Side effects*
- Most common: Oedema (62% of patients in RCT)

* List of side effects, warnings and precautions is not exhaustive, please refer to Prescribing Information or Summary of Product Characteristics of individual drugs for full details.

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Abbreviations and references

Abbreviations

ctDNA; circulating tumour DNA; EBUS, endobronchial ultrasound; EGFR; epidermal growth factor receptor; FISH, fluorescence in situ hybridization; FFPE, formalin-fixed paraffin-embedded; GI, gastrointestinal; KEAP1, Kelch-like ECH-associated protein 1; KRAS; Kirsten rat sarcoma virus; MET, mesenchymal epithelial transition factor; mRNA, messenger RNA; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; PI, prescribing information; qPCR, quantitative polymerase chain reaction; RCT, randomized controlled trial; SPC, summary of product characteristics; TKI, tyrosine kinase inhibitor; TP53, tumour protein 53.

References

1. NCCN. Non-small cell lung cancer treatment guidelines. Version 10.2024 (accessed 14 October 2024).
2. Hendriks LE et al. *Ann Oncol*. 2023;34:358-376. ESMO Non-Oncogene-Addicted Metastatic Non-Small-Cell Lung Cancer Living Guidelines, v1.1 March 2024.
3. Ghigna MR, et al. *J Thorac Dis*. 2018;10:4653–8.
4. Muriana P, Rossetti F. *Mediastinum*. 2020;4:23.
5. Hofman P. *Transl Oncol*. 2023:35:101735.
6. Socinski MA, et al. *JCO Precis Oncol*. 2021;5:PO.20.00516.
7. Remon J, et al. *J Thorac Oncol*. 2023;18:419–35.
8. EMA. Capmatinib SPC. 2023.
9. FDA. Capmatinib PI. 2024.
10. EMA. Tepotinib SPC. 2024.
11. FDA. Tepotinib PI. 2024.
12. Ahn L, et al. *Clin J Oncol Nurs*. 2022; 26:543–51.
13. EMA. Crizotinib SPC. 2024.
14. FDA. Crizotinib PI. 2023.
15. Yu Y, et al. *Lancet Respir Med*. 2024:S2213-2600(24)00211-X.

All EMA SPCs available at: www.ema.europa.eu/en/medicines.
All FDA Pis available at: www.accessdata.fda.gov/scripts/cder/daf/index.cfm.
All links accessed 23 October 2024.

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