Moving *MET* into the clinic: Latest evidence for MET inhibitors in NSCLC

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MET inhibitor clinical efficacy: Update from ASCO 2021

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How significant is *MET* as a therapeutic target in patients with NSCLC?

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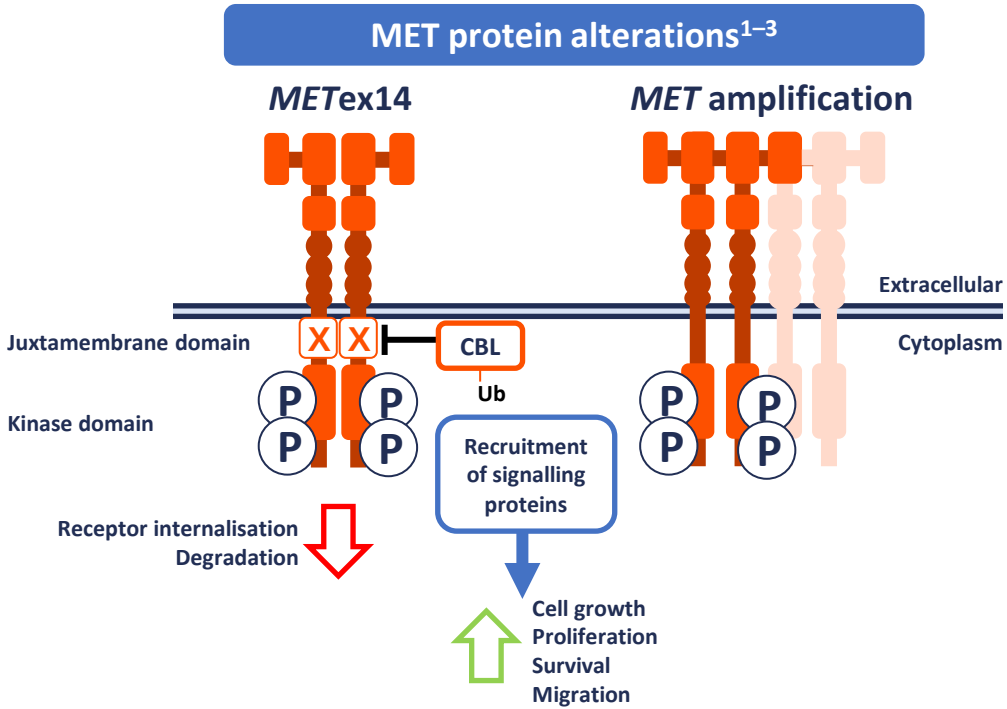
MET mutations in NSCLC



- Patients with advanced or metastatic NSCLC[4]
- Older patients are affected, regardless of sex or smoking status[5]
- Majority of patients have only extrathoracic metastases (67.6%)[5]

- Mutations leading to *MET*ex14 are found in approximately 3–4% of patients with NSCLC[6]
- Patients with *MET*ex14 usually do not have other known molecular drivers of NSCLC[6]
- *MET*ex14 is a biomarker associated with poor prognosis[6]
- *MET* amplifications are found in approximately 1–6% of patients with NSCLC[7]

CBL, casitas B-lineage lymphoma; *MET*, mesenchymal–epithelial transition; *MET*ex14, *MET* exon 14 skipping mutation; NSCLC, non-small cell lung cancer; P, phosphorylated; Ub, ubiquitin.

1. Tan AC, et al. *Lung Cancer (Auckl).* 2021;12:11–20; 2. Safi D, et al. *Transl Lung Cancer Res.* 2021;10:462–74; 3. Salgia R, et al. *Cancer Treat Rev.* 2020;87;
4. Paik PK, et al. *N Engl J* Med. 2020;383:931–43; 5. Digumarthy SR, et al. *Cancers*. 2019;11:2033; 6. Wu YL, et al. *Cancer Treat Rev*. 2021;95;
7. Wolf J, et al. *N Engl J Med*. 2020;383:944–57.

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How do current data support the use of MET-inhibitor therapy in patients with *MET*+ NSCLC?

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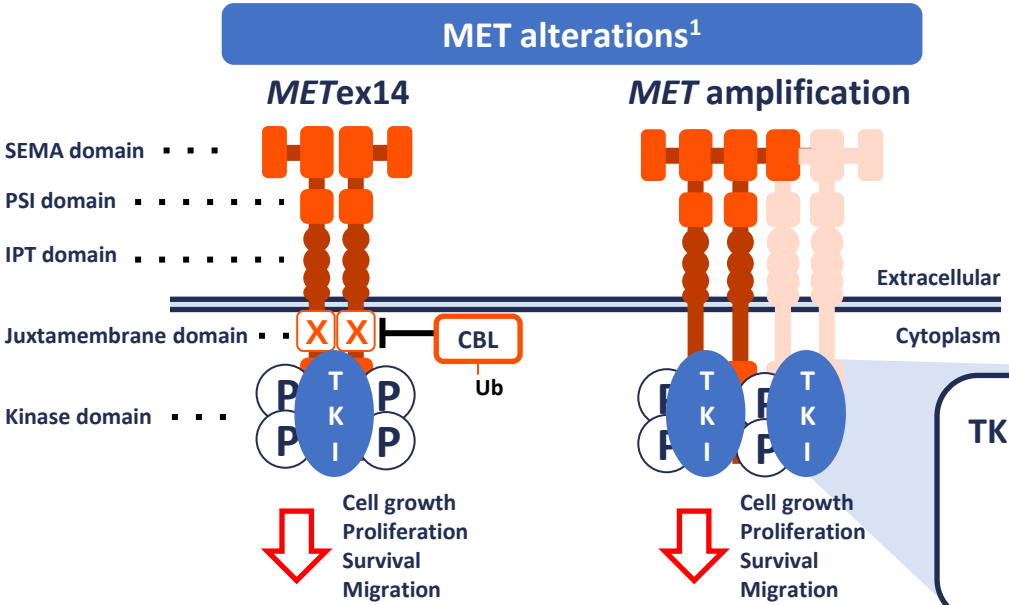
MET inhibitors: Mechanism of action



TKIs capmatinib, tepotinib, savolitinib, and crizotinib block MET kinase domain in NSCLC, which prevents downstream signalling[2–4]

CBL, casitas B-lineage lymphoma; IPT, immunoglobulin-plexins-transcription factors; MET, mesenchymal-epithelial transition; *MET*ex14, *MET* exon 14 skipping mutation; NSCLC, non-small cell lung cancer; P, phosphorylated; PSI, plexins-semaphorins-integrins; SEMA, semaphorins; TKI, tyrosine kinase inhibitor; Ub, ubiquitin.

1. Tan AC, et al. *Lung Cancer (Auckl).* 2021;12:11–20; 2. Vansteenkiste JF, et al *Expert Rev Anticancer Ther.* 2019;19:659–71; 3. Markham A. *Drugs*. 2020;80:829–33; 4. Rehman S, Dy GK. *EMJ Respir*. 2018;6:100–11.

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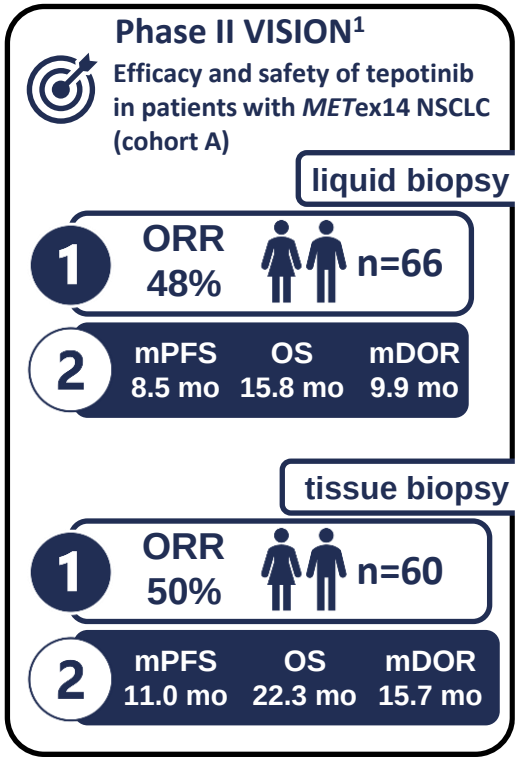
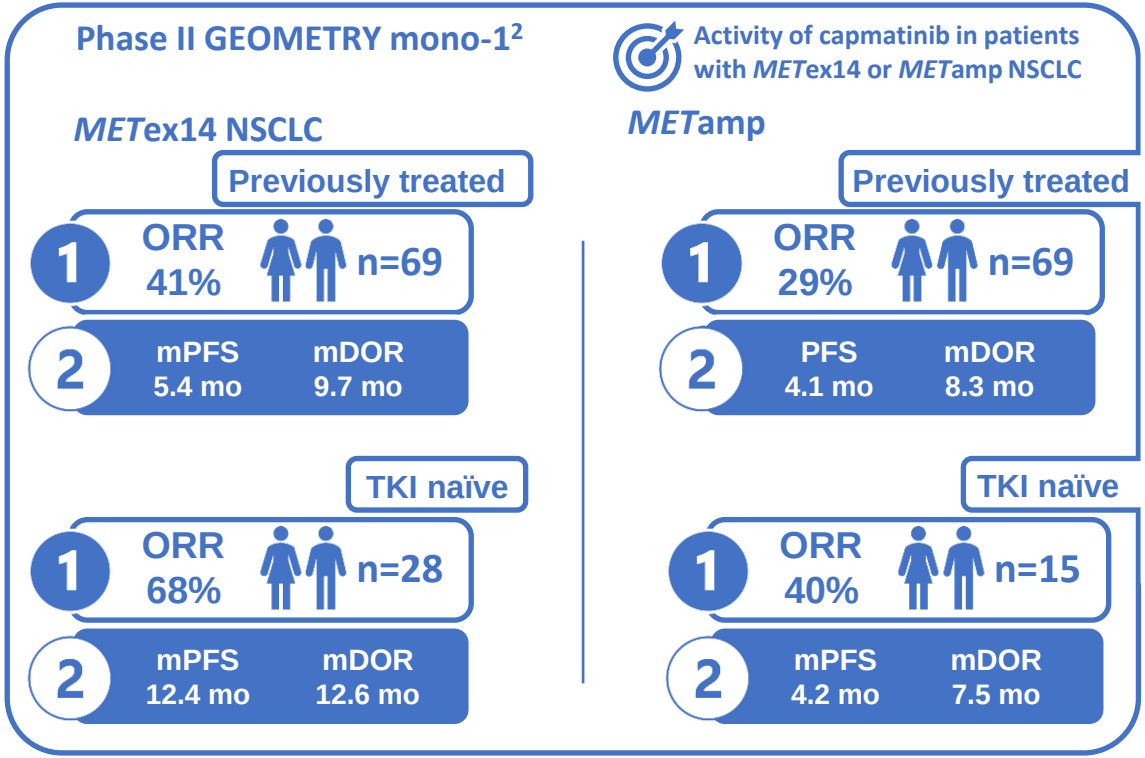
MET inhibitors in NSCLC: Key efficacy outcomes





Data based on independent review results.
mDOR, median duration of response; MET, mesenchymal–epithelial transition; *MET*amp, *MET* amplification; *MET*ex14, *MET* exon 14 skipping mutation; mo, months; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; TKI, tyrosine kinase inhibitor.
1. Paik PK, et al. *N Engl J* Med. 2020;383:931–43; 2. Wolf J, et al. *N Engl J Med*. 2020;383:944–57.

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What were the updated findings at ASCO 2021 for the VISION and GEOMETRY mono-1 studies in patients with *MET*+ NSCLC?

ASCO 2021: MET inhibitors in *MET*+ NSCLC

VISION (Cohort B results)[1]

Cohort A: *MET*ex14
Cohort B: *MET*amp

- **ORR:** 42% overall; 1L 71%; 2L 30%; 3L 29%
- **mDOR:** NE

Cohort B n=24

1L	2L	3L
n=7	n=10	n=7

- **Treatment was ongoing for >1 year in 5 patients (1L, n=2; 2L, n=2; 3L, n=1)**

Tepotinib showed high and clinically meaningful activity, especially in 1L, in NSCLC with *MET*amp

VISION (Intracranial response)[2]

Cohort A: *MET*ex14 with BM (n=23/152 at baseline)

- 15 patients evaluable by RANO-BM
- 12 patients received prior RT

Systemic BOR: PR, n=9; SD, n=3; PD, n=3.
Intracranial BOR: (all 7 patients received prior RT) PR, n=5; SD, n=1; PD, n=1

Of the seven patients with disease control, three had CR of the enhancing non-target lesions.

Systemic activity of tepotinib complemented by intracranial activity in patients with BM

1/2/3L, first-, second-, third-line; ASCO, American Society of Clinical Oncology; BM, brain metastases; BOR, best objective response; CR, complete response; mDOR, median duration of response; MET, mesenchymal-epithelial transition; *MET*amp, *MET* amplification; *MET*ex14, *MET* exon 14 skipping mutation; NE, not estimatable; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; RT, radiotherapy; SD, stable disease.

1. Le X, et al. *J Clin Oncol.*2021;39:suppl 15; abstr 9021; 2. Patel JD, et al. *J Clin Oncol.*2021;39:suppl 15; abstr 9084.

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ASCO 2021: MET inhibitors in *MET*ex14 NSCLC

GEOMETRY mono-1 (Cohort 7 results)[1]

***MET*ex14 NSCLC (n=160)**
Treatment-naïve (Cohort 5b and 7)/ prior 1L or 2L of therapy (expansion Cohort 6 and 4)

- ORR: 67.9% Cohort 5b; 65.6% Cohort 7
- mPFS: 12.4 mo Cohort 5b; 10.8 mo Cohort 7
- mOS: for Cohorts 6 and 7: NR

Capmatinib in 1L treatment reported highest efficacy in patients with *MET*ex14 NSCLC

Systematic review[2]

Review of original studies evaluating the clinical response of capmatinib in *MET*ex14 NSCLC

- Further studies support GEOMETRY mono-1 results
- Higher ORR achieved in treatment-naive patients
- Long-term follow-up trials needed

PROs demonstrated clinically meaningful improvements in cough, delayed time to lung symptom deterioration and preserved QoL[3]

1/2L, first-, second-line; ASCO, American Society of Clinical Oncology; MET, mesenchymal-epithelial transition; *MET*ex14, *MET* exon 14 skipping mutation; mo, months; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; NSCLC, non-small cell lung cancer; ORR, overall response rate; PRO, patient-reported outcome; QoL, quality of life.

1. Wolf J, et al. *J Clin Oncol.*2021;39:suppl 15; abstr 9020; 2. Khan I, et al. *J Clin Oncol.*2021;39:suppl 15; abstr e21150; 3. Wolf J, et al. *J Clin Oncol.*2021;39:suppl 15; abstr 9056.

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What were the key efficacy findings at ASCO 2021 for MET-inhibitor therapy in patients with advanced NSCLC and *MET* amplification?

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ASCO 2021: MET inhibitors in *EGFR*-mutant NSCLC

Combination approaches for *MET*amp following acquired resistance to EGFR-TKI therapy

Tepotinib + osimertinib[1]

INSIGHT 2 (NCT03940703)
Global, open-label, phase II trial tepotinib + osimertinib in patients with advanced *EGFR*-mutant NSCLC

MET-TKI may overcome MET-related osimertinib resistance

1. **ORR (RECIST v1.1) in patients with *MET*amp, centrally confirmed by FISH** — n=~120
2. **ORR by investigator assessment, DOR, disease control, PFS, OS, PK, HRQoL, tolerability and safety**

Capmatinib + gefitinib[2]

Primary findings from the phase Ib/II study (NCT01610336)
Phase Ib/II ORR: 29%
At recommended phase II dose, ORR: 47% in patients with high *MET*amp tumours

Heavily pre-treated patients with *EGFR*-mutated and *MET* dysregulated NSCLC
Median age 60 years; 81.4% Asian

Updated efficacy results
Median follow-up time for OS: 12.2 mo
Median OS: 13.9 mo

Phase Ib n=61
Phase II n=100

ASCO, American Society of Clinical Oncology; DOR, duration of response; *EGFR*, epidermal growth factor receptor; FISH, fluorescent *in situ* hybridization; HRQoL, health-related quality of life; MET, mesenchymal-epithelial transition; *MET*amp, *MET* amplification; mo, months; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumours; TKI, tyrosine kinase inhibitor.

1. Zhu VW, et al. *J Clin Oncol.*2021;39:suppl 15; abstr TPS9136; 2. Wu YL, et al. *J Clin Oncol.*2021;39:suppl 15; abstr 9048.

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How do the latest data affect current use of MET inhibitors in NSCLC and what are the potential future developments?

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Combination EGFR-MET approaches

Small molecule TKIs + MET inhibition[1]

Real-world study (N=70)

Crizotinib ± EGFR-TKI vs MET TKI mono vs CT

- Advanced *EGFR*-mutant NSCLC
- Progressed from prior EGFR-TKI through the acquisition of *MET*amp

Crizotinib + EGFR-TKI:
ORR, 47.5%; DCR, 84.0%; PFS, 5.0 mo; OS, 10.0 mo
Crizotinib:
ORR, 40.0%; DCR, 70.0%; PFS, 2.3 mo; OS, 4.1 mo
CT:
ORR, 18.2%; DCR, 50.0%; PFS, 2.9 mo; OS, 8.5 mo

Simultaneous inhibition of EGFR and MET improves clinical outcomes of patients with *EGFR*-mutant NSCLC and acquired *MET*amp from prior EGFR-TKI therapy

EGFR-MET bispecific antibody[2]

CHRYSALIS (NCT02609776)

Lazertinib ± amivantamab

Updated results

- *EGFR*-mutant NSCLC
- Progression on osimertinib without intervening CT (N=45)

- **36% confirmed response** (1 CR; 15 PR)
- **44% remain on treatment** (8.2 mo median follow up)
- **mDOR:** 9.6 mo
- **mPFS:** 4.9 mo

CR, complete response; CT, chemotherapy; DCR, disease control rate; EGFR, epidermal growth factor receptor; mDOR, median duration of response; MET, mesenchymal-epithelial transition; *MET*amp, *MET* amplification; mo, months; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; TKI, tyrosine kinase inhibitor.

1. Liu L et al. *J Clin Oncol.* 2021;39:suppl 15; abstr 9043. 2. Bauml J, et al. *J Clin Oncol.* 2021;39:suppl 15; abstr 9006.

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ASCO 2021: Immunotherapy in *MET*-positive NSCLC

Multicentre study ICI and MET-TKI sequencing[1]

43 patients with *MET* alterations; *MET*ex14 (n=29)
69% of patients had PD-L1 ≥50%

- **mOS for the entire cohort:** 24.4 mo
- Significantly longer mOS (48.3 vs 13.6 mo) in patients who received initial ICI (n=13) vs those who received initial TKI (n=11), *irrespective of PD-L1 expression and smoking history*
- 100% of patients who progressed after ICI received further treatment
- 50% of patients who progressed after TKI received subsequent therapy

TMB as prognostic biomarker in NSCLC[2]

- *MET*-non-ex14 mutant patients (7/385) had significantly higher TMB than *MET*ex14 (10/385) and *MET* wild-type (368/385) sub-cohorts, respectively
- DCB was more common in patients with *MET*-non-ex14 mutations than *METex14* and *MET* wild-type (66.7% vs 14.3%; 66.7% vs 29.9%, respectively)
- **mPFS was significantly longer in *MET*-non-ex14-mutant subgroup than patients with *METex14* NSCLC (9.1 vs 2.1 mo)**

ASCO, American Society of Clinical Oncology; DCB, durable clinical benefit; ICI, immune checkpoint inhibitor; *MET*, mesenchymal-epithelial transition; *MET*ex14, *MET* exon 14 skipping mutation; mo, months; mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1; TKI, tyrosine kinase inhibitor; TMB, tumour mutational burden.

1. Lau SCM, et al. *J Clin Oncol.*2021;39:suppl 15; abstr e21123; 2. Li X, et al. *J Clin Oncol.*2021;39:suppl 15; abstr e21032.

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Moving *MET*ex14 testing into the clinic

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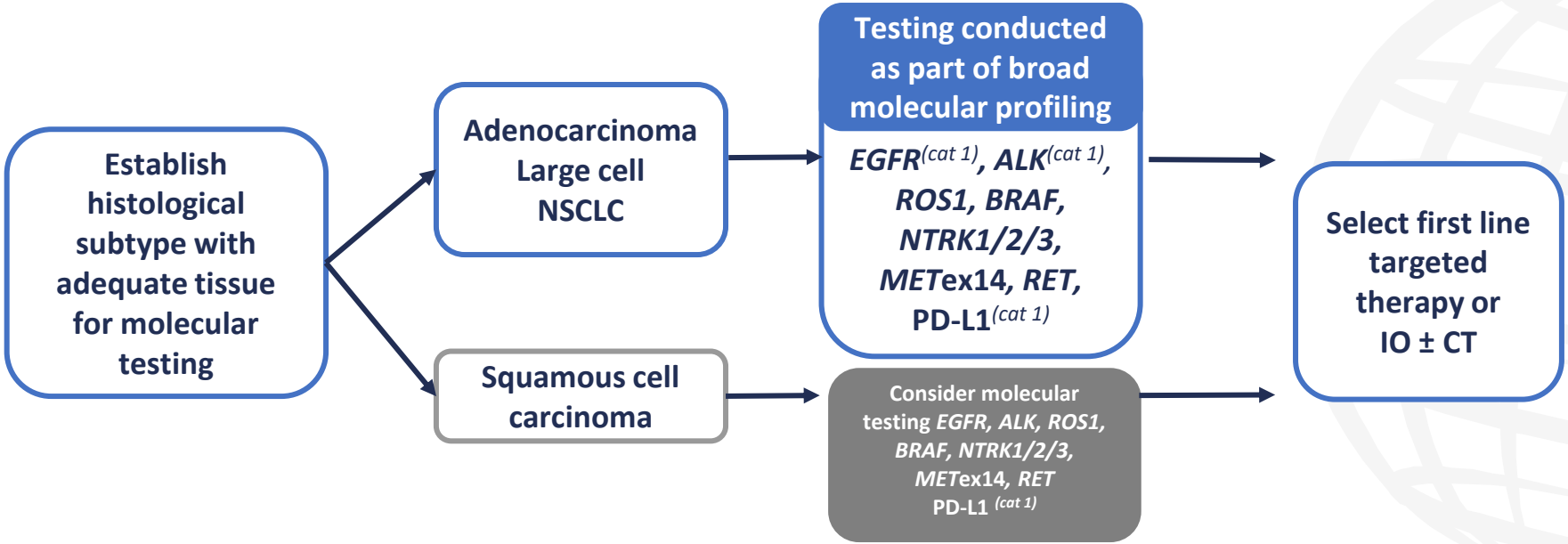
What are the current recommendations for testing *MET*ex14 in patients with NSCLC?

Molecular testing standard of care for NSCLC

NCCN guidelines encourage broad molecular profiling for advanced or metastatic disease



ALK, anaplastic lymphoma kinase; *BRAF*, B-rapidly accelerated fibrosarcoma; cat, category; CT, chemotherapy; *EGFR,* epidermal growth factor receptor; IO, immunotherapy; *MET*, mesenchymal-epithelial transition; *MET*ex14, *MET* exon 14 skipping; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; *NTRK1/2/3,* neurotrophic tyrosine receptor kinase 1/2/3; PD-L1, programmed death ligand 1; *RET,* rearranged during transfection; *ROS1,* reactive oxygen species 1.

NCCN guidelines. 2021. Available at: www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (accessed 19 May 2021).

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What are the challenges for testing and how can next-generation sequencing be used optimally to detect *MET*ex14?

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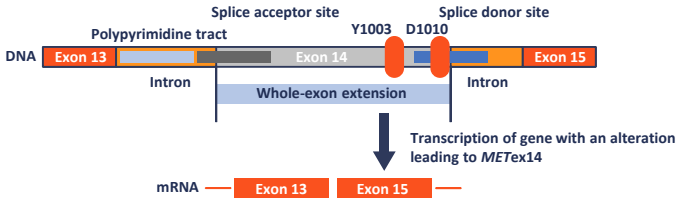
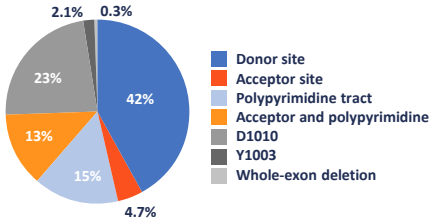
Challenges for *MET*ex14 testing

*MET*ex14 skipping alterations by site and regions of interest for sequencing

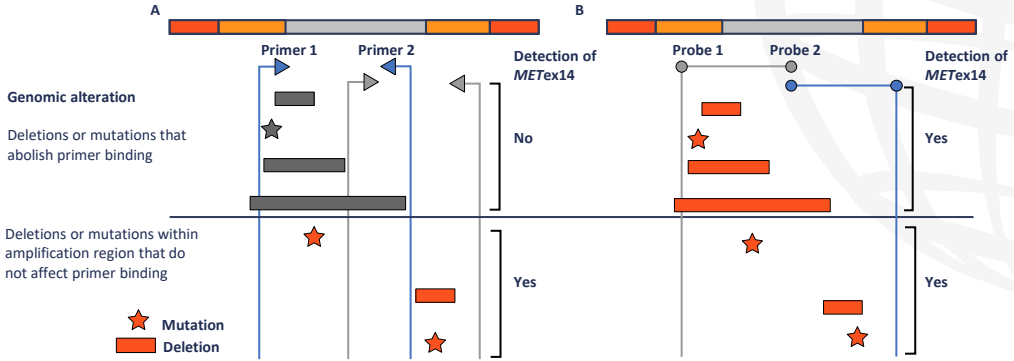


- Underlying genomic events leading to *MET*ex14 are complex and diverse
- NGS assay characteristics and bioinformatics affect ability to detect
- Coexistence of *MET*ex14 with other oncogenic drivers is rare

Plurality of distinct genetic alterations leading to *MET*ex14



A) Amplicon-based and B) hybrid capture-based DNA NGS methods for targeted sequencing of *MET*



MET, mesenchymal-epithelial transition; *MET*ex14, *MET* exon 14 skipping; mRNA, messenger RNA; NGS, next-generation sequencing.

Socinski MA, et al. *Precision Oncology. Epub* April 13, 2021: DOI https://doi.org/10.1200/PO.20.00516. Figures reproduced with permission.

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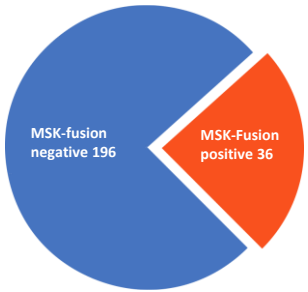
DNA- versus RNA-based NGS testing for MET

RNA-based testing can augment DNA-based testing

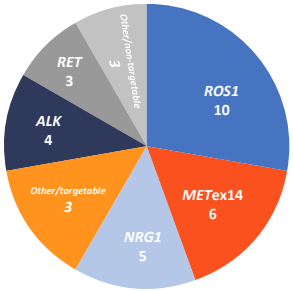
- Targeted DNA-based NGS techniques can reliably detect oncogenic kinase fusions, including *ALK*, *RET*, *ROS1* and *MET*ex14 skipping mutations
- Targeted RNA-based NGS can complement large panel DNA-based NGS testing and increase detection

Incremental benefit of targeted RNA-seq in the identification of gene fusions in patients with DNA-seq driver-negative lung cancers

MSK-IMPACT[a] negative (n=232)



MSK-fusion positive (n=36)



Clinical benefit of matched targeted therapy (n=10)

Rearrangement	Matched therapy	Best response[b]
EML4-ALK	Alectinib	SD
CD74-ROS1	Entrectinib	SD
SQSTM1-NTRK3	Larotrectinib	PR[c]
STRN0-NTRK2	Larotrectinib	SD
CD74-ROS1	Entrectinib	PR[c]
CD74-NRG1	Afatinib	SD
*MET*ex14	Crizotinib	SD
SLC34A2-ROS1	Crizotinib	PD
SLC34A2-ROS1	Crizotinib	SD
SDC4-NRG1	Afatinib	PD

[a]MSK-IMPACT: a large panel, hybrid capture-based NGS assay designed to capture common kinase fusions; [b]Response assessment by RECIST version 1.1.; [c]Confirmed PR.
ALK, anaplastic lymphoma kinase; DNA-seq, DNA sequencing; MET, mesenchymal-epithelial transition; METex14, *MET* exon 14 skipping mutation; MSK-Fusion, Memorial Sloan Kettering RNA-based solid tumour fusion panel; NGS, next-generation sequencing; NRG1, neuregulin 1; PD, progression of disease; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumours; *RET,* rearranged during transfection; RNA-seq, RNA sequencing; *ROS1,* reactive oxygen species 1; SD, stable disease.

Benayed R, et al. *Clin Cancer Res*. 2019;25:4712–22

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Do data presented at ASCO 2021 further support the use of RNA-sequencing for *MET*ex14 testing?

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ASCO 2021: DNA versus RNA sequencing

Targeted RNA-seq identifies gene fusions undetected by DNA-seq

DNA-seq driver-negative adenocarcinomas

Discovery cohort n=219

- 75.8% generated RNA-seq data
- **44 previously undetected alterations** including 40 gene fusions, 1 *MET*ex14 and 3 other alternative splicing variants
- 15 actionable alterations from 14 patients

Actionable alterations

- 4 *ROS1* fusions
- *3 BRAF* fusions
- 2 *NRG1* fusions
- 2 *EGFR* fusions
- 1 *ALK* fusion
- 1 *MET* fusion
- 1 *MET*ex14
- 1 *NTRK* fusion

Validation cohort n=100

- 69.0% generated RNA-seq data
- **22 previously undetected alterations**
- 7 actionable fusions

Actionable fusion

- 3 *ROS1* fusions
- 2 *ALK* fusions
- 1 *EGFR* fusion
- 1 *MET* fusion

To evaluate if RNA-seq can identify DNA-seq undetectable gene alterations in lung adenocarcinomas

Lacking sufficient coverage spanning the rearrangement breakpoint in the DNA-seq panel mainly accounted for the failure of DNA-seq to detect fusions

ALK, anaplastic lymphoma kinase; ASCO, American Society of Clinical Oncology; *BRAF,* B-rapidly accelerated fibrosarcoma; DNA-seq, DNA sequencing; *EGFR*, epidermal growth factor receptor; *MET*, mesenchymal-epithelial transition; *MET*ex14, *MET* exon 14 skipping mutation; *NRG1, neuregulin 1; NTRK1/2/3;* neurotrophic tyrosine receptor kinase 1/2/3; RNA-seq, RNA sequencing; *ROS1,* reactive oxygen species 1.

Zhao R et al. *J Clin Oncol.*2021;39:suppl 15; abstract 3052.

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What are the pros and cons of using tissue versus liquid biopsy for testing?

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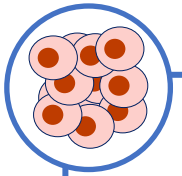
Tissue vs liquid biopsy in clinical practice



Tissue biopsy[1–3]

- Clinically validated gold standard
- Invasive; potential for bleeding and infection
- Difficult to repeat/obtain adequate samples
- Single–tissue site biopsies may not reflect genetic heterogeneity
- Impractical for periodic monitoring of treatment response
- Not all patients suitable for biopsy

Liquid (plasma ctDNA) biopsy[1–3]

- Non-invasive; able to perform in clinic
- An alternative when tissue biopsy is insufficient or unfeasible
- Reflects tumour heterogeneity; assesses DNA from all tumour sites
- Can obtain serial samples at diagnosis and at required resistance of monitoring
- Some tumours may not shed ctDNA
- A negative result will need to be confirmed by tissue biopsy

ctDNA, circulating tumour DNA.

1. Lim M, et al. *Micromachines*. 2018;9:100; 2. Pennell NA, et al. *Am Soc Clin Oncol Educ Book.* 2019;39:531–42; 3. Rolfo C, et al. *J Thorac Oncol.* 2018;13:1248–68.

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How do data presented at ASCO 2021 expand our knowledge on the role of liquid biopsy in *MET*ex14 NSCLC?

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ASCO 2021: Liquid biopsy in *MET*ex14 NSCLC

GEOMETRY mono-1
Comparison of LDx using plasma samples vs patients screened for *MET*ex14 status by RT-PCR clinical trial assay

***MET*ex14-positive**

- **Pre-treated Cohort 4, n=69**
- **Treatment naïve Cohort 5b, n=28**

88 pts had minimum input

***MET*ex14-negative**

- **Cohort 1b, Cohort 2 and Cohort 3, n=126**

+ 21 tissue-matched samples

57 pts LDx positive
26 pt LDx negative
5 invalid sequencing results

PPA 68.7%
NPA 100%[a]

88 pts LDx negative
0 pts LDx positive
9 invalid sequencing results

Pts identified by positive LDx

ORR, 48.8%; mDOR, 9.8 mo; mPFS, 5.4 mo; mOS, 13.6 mo

ORR, 81.3%; mDOR, 20.3 mo; mPFS, 12.4 mo; mOS, 17.9 mo

Clinical findings in *MET*ex14 pts identified by LDx comparable to patients identified by CTA

[a]Excluding LDx invalid results

ASCO, American Society of Clinical Oncology; CTA, clinical trial assay; LDx, liquid biopsy test; mDOR, median duration of response; METex14, MET exon 14 skipping mutation; mo, months; mOS, median overall survival; mPFS, median progression-free survival; NPA, negative percent agreement; NSCLC, non-small cell lung cancer; ORR, overall response rate; PPA, positive percent agreement; pts, patients; RT-PCR, reverse transcriptase-polymerase chain reaction.

Heist RS, et al. *J Clin Oncol.* 2021;39:suppl 15; abstract 9111.

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ASCO 2021: Serial liquid biopsy in *MET*ex14 NSCLC

VISION[1]
Use of serial LBx to monitor treatment response/non-response in *MET*exon14 skipping NSCLC

***MET*ex14-positive (Cohort A)**

Pre-treated n=35

Treatment naïve n=30

LBx samples taken at baseline, Weeks 6 and 12, and end of treatment*

ctDNA depletion in *MET*ex14-VAF associated with improved clinical response to tepotinib

Confirmed molecular status	Molecular response	Molecular progression
N (all patients)	46	5
ORR, n (%)	35 (76)	0
mDOR, mo	14	n/a
DCR, n (%)	42 (91)	3 (60)
mPFS, mo	11	5.5

*Analyzed using Guardant360® CDx (73 genes).
ASCO, American Society of Clinical Oncology; ctDNA, circulating tumour DNA; DCR, disease control rate; LBx, liquid biopsy; mDOR, median duration of response; METex14, MET exon 14 skipping mutation; mo, months; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; ORR, overall response rate; VAF, variant allele frequency.
Paik P, et al. *J Clin Oncol*. 2021;39:suppl 15; abstract 9012.

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What are the key takeaways from ASCO 2021 for NSCLC testing?

Adverse event management and implementation of MET inhibitor therapy

Dr Takashi Seto

Medical Oncologist
National Kyushu Cancer Center
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What are common adverse events associated with MET inhibitors in patients with *MET*ex14 NSCLC?

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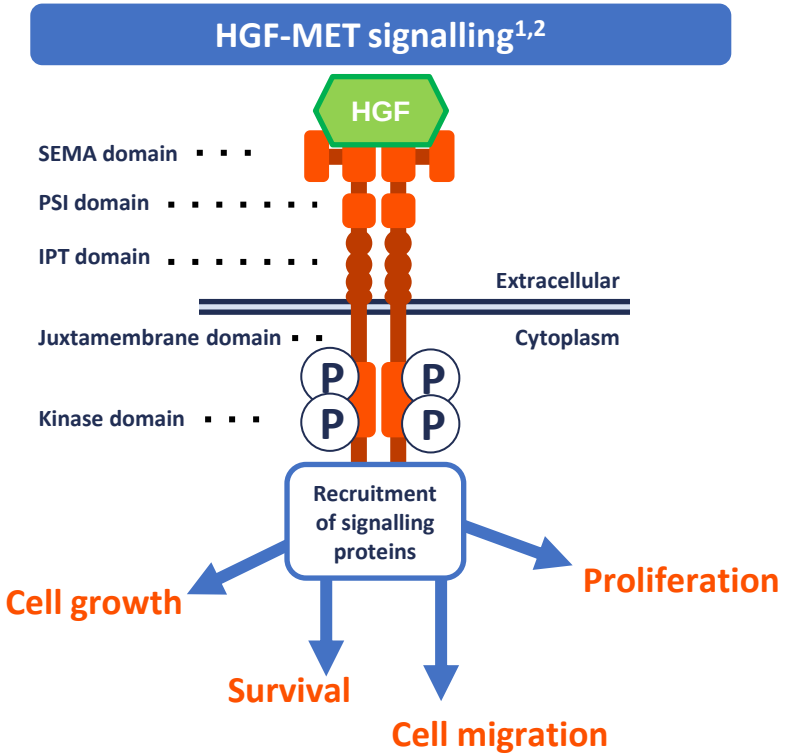
Targeting the HGF-MET signalling pathway



AEs caused by MET inhibition may be associated with the biological functions of MET[3]

- **HGF and MET are broadly expressed in epithelial cells of many organs, playing essential physiological roles**
- **HGF-MET is responsible for the defensive physiological response to tissue damage and has cytoprotective activity**
- **MET targeted therapy may block these important physiological functions, causing increased patient susceptibility to tissue damage**

AE, adverse event; HGF, hepatocyte growth factor; IPT, immunoglobulin-plexins-transcription factors; MET, mesenchymal-epithelial transition; P, phosphorylated; PSI, plexins-semaphorins-integrins; SEMA, semaphorins.

1. Lee D, et al. *ImmunoTargets Ther*. 2015;4:35; 2. Tan AC, et al. *Lung Cancer (Auckl)*. 2021;12:11–20; 3. Hu CT, et al. *Cancers*. 2017;9:58.

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Common AEs associated with approved MET inhibitors

Tepotinib VISION[1,2]

General disorders
- Peripheral oedema
- Fatigue/decreased appetite
- Pain

GI disorders
- Nausea/vomiting
- Diarrhoea

Respiratory disorders
- Pleural effusion
- ILD (2.2%)

Kidney function
- Creatinine increase

Liver function
- AST/ALT increase (13.0%)

AEs led to permanent discontinuation in 11.0% patients[1]

Capmatinib GEOMETRY mono-1[3,4]

General disorders
- Peripheral oedema
- Fatigue
- Decreased appetite

GI disorders
- Nausea/vomiting

Respiratory disorders
- Dyspnoea, cough
- ILD (4.5%)

Kidney function
- Creatinine increase

Liver function
- AST/ALT increase (13.0%)

AEs led to permanent discontinuation in 11.0% patients[3]

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GI, gastrointestinal; ILD, interstitial lung disease; MET, mesenchymal-epithelial transition; PI, prescribing information.

1. Paik PK, et al. *N Engl J Med*. 2020;383:931–43; 2. Tepotinib PI 2020. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/214096s000lbl.pdf (accessed 5 May 2021); 3. Wolf J, et al. *N Engl J Med.* 2020;383:944–57; 4. Capmatinib PI. 2020. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2020/213591s000lbl.pdf (accessed 5 May 2021).

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How are adverse events associated with MET inhibitors managed in clinical practice?

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AE management with approved MET inhibitors

Prophylactic and supportive measures based on experiences from clinical trials[1–4]

Peripheral oedema[1,2]

Monitor regularly: early detection is key
Patients advised to increase movement, elevate limbs (consider compression stockings) and diuretics. Consider dose reduction

GI symptoms[1,2]

Ensure adequate hydration and monitor for dehydration
Consider standard antiemetics and anti-diarrhoeals or treatment interruption. Consider premedication with 5-HT3 antagonist

ILD[2]

Monitor for ILD symptoms (e.g. dyspnoea, cough, fever)
Interrupt treatment if ILD suspected/discontinue if confirmed

Pleural effusion[2]

Perform thoracentesis to rule out malignant cause

Creatinine increase[2]

Monitor levels during first 2 months of therapy
If creatinine increase grade ≥3, reduce dose or interrupt treatment

Liver enzyme increase[2–4]

Monitor ALT/AST prior to start and every 2 weeks during first 3 months, then once a month
If symptoms continue, consider dose reduction or interruption

Increasing severity

DOSE MODIFICATION AND INTERRUPTION
Reduce dose, withhold or permanently discontinue

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GI, gastrointestinal; ILD, interstitial lung disease; MET, mesenchymal-epithelial transition.

1. Goodwin K, et al. *J Thorac Oncol*. 2021;16:S16–7; 2. Alexander T, et al. InONS 46th Annual Congress 2021 Mar 1. ONS;
3. Tepotinib PI 2020. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/214096s000lbl.pdf (accessed 5 May 2021);
4. Capmatinib PI. 2020. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2020/213591s000lbl.pdf (accessed 5 May 2021).

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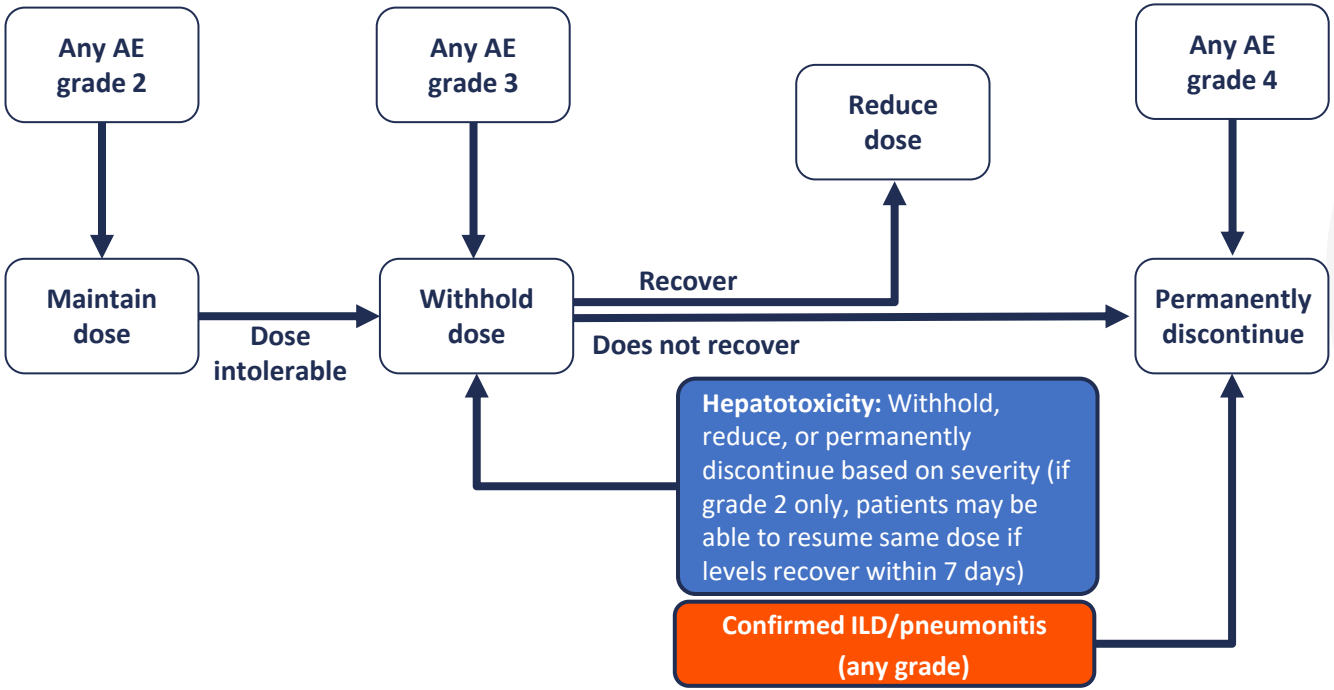
Recommended dose modifications

MET inhibitor safety recommendations: Capmatinib and tepotinib[1,2]



AE, adverse event; ILD, interstitial lung disease; MET, mesenchymal-epithelial transition.

1. Tepotinib Prescribing Information. 2020. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2021/214096s000lbl.pdf (accessed 5 May 2021);
2. Capmatinib Prescribing Information. 2020. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2020/213591s000lbl.pdf (accessed 5 May 2021).

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What were the key safety data updates for MET inhibitors at ASCO 2021, either as monotherapy or in combination with an EGFR inhibitor?

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ASCO 2021: Safety of MET inhibitors in NSCLC

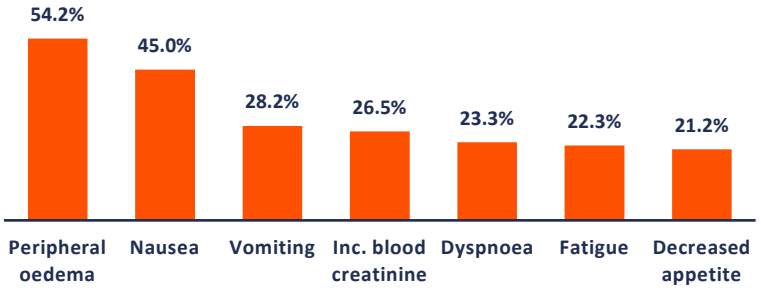
Capmatinib monotherapy and in combination with EGFR-TKI

GEOMETRY mono-1 Updated results[1]

***MET*ex14 NSCLC (n=373)**

Updated safety: All cohorts

- 98.4% of patients reported AEs (grade 3/4, 68.6%)
- 16.1% reported AEs leading to discontinuation
- Most common AEs (any grade; ≥20%):



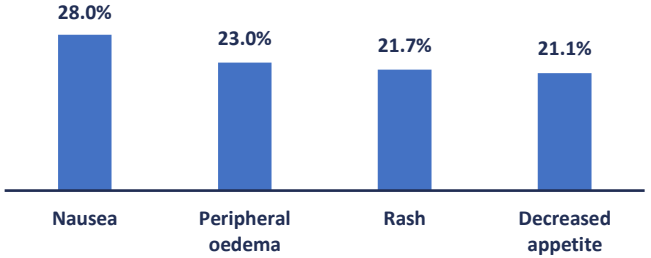
Capmatinib + gefitinib (NCT01610336)[2]

***EGFR*-mutant and *MET*-dysregulated NSCLC (n=161)**

Primary findings from the phase Ib/II study

98.8% of patients reported AEs (87.0% TEAEs)

- Grade 3/4 TEAEs: 31.7% of patients across both phases
  Most frequent reported (≥5%): increased amylase (6.2%), increased lipase (6.2%) and peripheral oedema (5.0%)
- Most common TEAEs (any grade; ≥20%):



AE, adverse event; ASCO, American Society of Clinical Oncology; EGFR, epidermal growth factor; Inc., increased; MET, mesenchymal-epithelial transition; *MET*ex14, *MET* exon 14 skipping; NSCLC, non-small cell lung cancer; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor.

1. Wolf J, et al. *J Clin Oncol.* 2021;39:suppl 15; abstr 9020; 2. Wu YL, et al. *J Clin Oncol*. 2021;39:suppl 15; abstr 9048.

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ASCO 2021: Safety of MET inhibitors in NSCLC

Tepotinib monotherapy and in combination with EGFR-TKI

VISION[1]

Cohort B n=24

1L	2L	3L
n=7	n=10	n=7

Patients with advanced NSCLC and *MET*amp

TEAEs, 66.7%
Grade 3/4, 29.2%

Peripheral oedema, 37.5%
Grade 3/4, 8.3%
Generalized oedema, 16.7%
Grade 3/4, 8.3%

Constipation, 16.7%
Grade 3/4, 0%

Tepotinib monotherapy was generally well tolerated in patients with NSCLC with *MET*amp

INSIGHT 2[2] (NCT03940703)

Global, open-label, phase II trial assessing tepotinib + osimertinib in patients with advanced *EGFR*-mutant NSCLC

MET-TKI may overcome MET-related osimertinib resistance

Secondary endpoints include tolerability and safety

n=~120

1/2/3L, first-, second-, third-line; ASCO, American Society of Clinical Oncology; MET, mesenchymal-epithelial transition; *MET*amp, *MET* amplification; NSCLC, non-small cell lung cancer; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor.

1. Le X, et al. *J Clin Oncol.* 2021;39:suppl 15; abstr 9021; 2. Zhu VW, et al. *J Clin Oncol.* 2021;39:suppl 15; abstr TPS9136.

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Is the risk:benefit profile for the use of immunotherapy acceptable in *MET*ex14 NSCLC?

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ASCO 2021: Immunotherapy in MET-positive NSCLC

Relationship between *MET*ex14 NSCLC and ICI therapy

Multicentre study: ICI and MET-TKI sequencing[1]

43 patients with *MET* alterations; *MET*ex14 (n=29)
69% of patients had PD-L1 ≥50%

- 85.7% patients experienced a grade ≥3 AE, resulting in permanent discontinuation of TKI in half of patients
- **Increased toxicity when a TKI is used after ICI; careful monitoring is necessary**

Identifying which patients may benefit most from ICI[2]

N=385 ICI-treated NSCLC patients:

- *MET* mutations, 4.4%
- *MET*ex14, 2.6%
- *MET*-non-ex14, 1.8%

MET-non-ex14 mutations associated with higher TMB and improved DCB rate

TMB potential prognostic biomarker in patients with NSCLC treated with ICIs[2]

AE, adverse event; ASCO, American Society of Clinical Oncology; DCB, durable clinical benefit; ICI, immune checkpoint inhibitor; MET, mesenchymal-epithelial transition; METex14, MET exon 14 skipping mutation; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1; TKI, tyrosine kinase inhibitor; TMB, tumour mutational burden.

1. Lau SCM, et al. *J Clin Oncol.* 2021;39:suppl 15; abstr e21123; 2. Li X, et al. *J Clin Oncol.* 2021;39:suppl 15; abstr e21032.

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