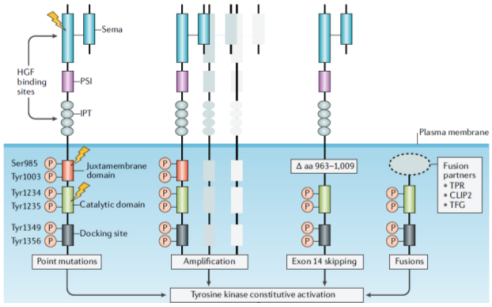
HAVE We *MET* in NSCLC ?

WHAT is *MET* ?

The ***MET* (mesenchymal-to-epithelial transition factor)** proto-oncogene plays crucial roles in cell growth and proliferation, survival and apoptosis, epithelial-mesenchymal transition (EMT) and invasion. [1,2]

The hepatocyte growth factor (HGF) receptor (MET) alterations (point mutations, amplification, protein overexpression, and fusions) in another receptor tyrosine kinase (RTK) have been identified in NSCLC. [3]

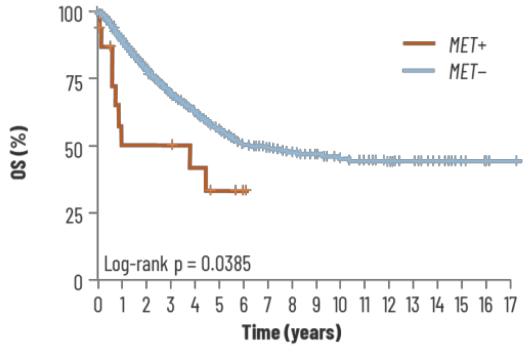


***MET* structural alterations and oncogene addiction.** [4]

The main structural domains and aminoacidic residues involved in *MET* functional regulation through phosphorylation (P) are indicated. The hepatocyte growth factor (HGF) binding site is complex. Structural analysis identified the semaphorin (sema) domain, and ligand- binding and functional studies revealed the presence of additional sites in the immunoglobulin- like, plexins, transcription factors (IPT) domains. Point mutations (blizzard symbol) are concentrated in domains critical for ligand binding (sema) or receptor signalling (juxtamembrane and catalytic). Newly discovered *MET* gene alterations include mutations in exon 14 splicing sites, which cause exon skipping and deletion of the entire juxtamembrane amino acid sequence (Δ aa 963–1,009) as well as oncogenic fusions. Among the latter, the prototype is translocated promoter region *(TPR)-MET*. This construct and the recently discovered CAP- Gly domain- containing linker protein 2 *(CLIP2)-MET* (1,235 amino acids) and TRK- fused gene *(TFG)-MET* (574 amino acids) constructs contain *MET* exons 15–21, that is, the entire sequence downstream of the juxtamembrane domain. This is fused at its amino terminus either with exons 1–12 from *CLIP2* or with exons 1–4 from *TFG*. Other fusion proteins featuring the entire *MET* sequence fused at its amino terminus with various fragments of the protein- tyrosine phosphatase receptor type Z polypeptide 1 (PTPRZ1) protein are not shown. PSI, plexin–semaphorin–integrin domain.

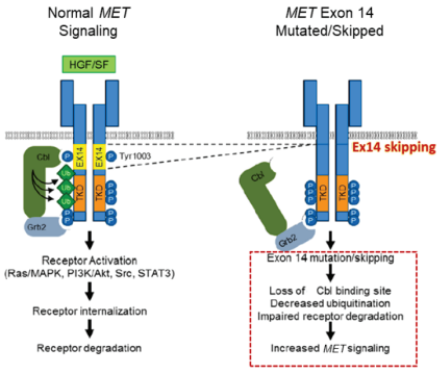
METex14 is associated with **shorter OS** in patients with NSCLC

Overall survival in NSCLC according to presence of *METex14*



A study of 687 **treatment-naive patients with resected NSCLC demonstrated that patients with *METex14* had worse survival compared with patients without *MET* mutations** (median follow-up time was 31.6 months [range 0.5-207.8 months]), Multivariable analysis of NSCLC patients with *METex14* mutation (HR, 2.156; 95% CI, 1.096–4.242; P=0.026). [6]

WHY test *METex14* ?



***MET* exon 14 skipping results in impaired *MET* receptor degradation.** [5]

(Left) Normally, the bindingof hepatocyte growth factor, also called scatter factor (HGF/SF), inducesdimerization of the *MET* receptor, phosphorylation of multiple intracellular residues, and activation of several downstream signaling pathways. Cbl, an E3 ubiquitin ligase, binds to tyrosine 1003 in the *MET* juxtamembrane domain, encoded inpart by *MET* exon 14. After ligand binding, the *MET* receptor is internalized into endosomes, and, if ubiquitinated, it isdegraded by means of the lysosomal pathway. (Right) In NSCLC , various somatic point mutations and deletions have been identified in *MET* that cause exon 14 skipping during pre-mRNA splicing, generating a mutant form of the *MET* receptor that deletes the Cbl binding site in the juxtamembrane domain. This leads to decreased *MET* ubiquitination, impaired receptor degradation, increased receptor recycling to the cell surface, and likely ligand-independent aberrant *MET* signaling.

MET, mesenchymal-epithelial transition; Grb2, Growth factor receptor-bound protein 2; Ras/MAPK, rat sarcoma-mitogen-activated protein kinase; PI3K/AKT ,Phosphatidylinositol 3-kinase/protein kinase Bsignaling pathway; Src, Proto-oncogene tyrosine-protein kinase Src; STAT3, signal transducer and activator of transcription 3; P, phosphoryl group; TKD, tyrosine kinase domain; Ub, ubiquitin.

METex14: *MET* exon 14 skipping mutation, NSCLC: non-small-cell lung cancer, OS: overall survival.

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References:
1. Schrock AB, et al. J Thorac Oncol2016;11(9):1493-1502.
2. Pilotto S, et al. Ann Transl Med. 2017;5(1):2.
3. Reungwetwattana T, et al. Lung Cancer 103;2017:27–37.
4. Comoglio, et al. Nature Review Cancer 2018;18:341-58
5. Awad MM, et al. J Clin Oncol. 2016;34:879-81.
6. Tong JH, et al. Clin Cancer Res. 2016;22:3048-56.
7. H.G. Vuong et al. Lung Cancer 123;2018:76–82.
8. NCCN guidelines Non-Small Cell Lung Cancer. Version 4. 2021.
9. Pennell NA, et al. Am Soc Clin Oncol Educ Book. 2019;39:531-42.
10. Wolf J, et al. New Engl J Med. 2020; 383:944-57.
11. Clinical Trial Protocol CINC280A2201, Version 6 (EudraCT 2014-003850-15). Data on file. Novartis Pharmaceuticals Corporation; February 28, 2019.
12. Heist RS, et al. Mol Cancer Ther. 2019;18(12 Suppl):abstract A029.

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HAVE We MET in NSCLC ?

***MET* exon 14 skipping mutation** is reported

~3-4% of patients with NSCLC. [3-5]

***MET* exon 14 mutation,** recently emerged as a new potential oncogenic driver and **mutually exclusive** with other frequently occurring genomic alterations in lung cancer. [2]

WHOM to test *METex14* ?

The mutation is more likely to occur in [7,8]

Female

Older

Non- smoker

Current treatment guideline strongly advises broader molecular profiling to identify rare driver mutations. [8]

HOW to test *METex14* ?

Recommended Biomarker Tests for Patients With Newly Diagnosed NSCLC. [8,9]

Biomarker testing	Non-squamous histology	Squamous histology
Minimum necessary	*EGFR (category1), ALK (category1), PD-L1 IHC (category1), ROS1, BRAF*	*PD-L1 IHC (category1)*
Recommended*	*RET, **METex14,** HER2, KRAS, NTRK*	

*These should be added if testing is done as part of a broad NGS-based panel.

NGS and RT-PCR assays
can be used to detect *METex14* mutation. [8]

NGS-based testing is the primary method for detection of *METex14*. [8]

In the GEOMETRY mono-1 study, *METex14* status was determined using an **RT-PCR test.** [10-12]

The high concordance of detection of *METex14* by both RT-PCR and NGS testing.

In GEOMETRY mono-1 trial, 72 of 73 (99%) *METex14* samples previously identified by RT-PCR assay were also identified by NGS testing and none of the RT-PCR negative patients were reported positive by NGS. [10]

MET: mesenchymal-epithelial transition factor, METex14: MET exon 14 skipping mutation, NSCLC: non-small-cell lung cancer, NGS: next-generation sequencing, RT-PCR: reverse transcriptase polymerase chain reaction.

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1. Schrock AB, et al. J Thorac Oncol2016;11(9):1493-1502.
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