107P - Systemic characterization of *MET* activating mutations in non-small cell lung cancer

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Background

- The Mesenchymal epithelial transition factor (*MET*) gene encodes a receptor tyrosine kinase with pleiotropic functions in cancer.
- *MET* exon 14 skipping alterations (METex14) and high-level *MET* amplification (METamp) are oncogenic alterations targetable in patients with non-small-cell lung cancer (NSCLC) 【1】.
- In *METex14*-altered NSCLC patients, *MET* tyrosine kinase domain (TKD) mutations, such as D1228N/H and Y1230H/C, could mediate acquired resistance (AR) to crizotinib, a type I MET-tyrosine kinase inhibitor (TKI) 【2】.
- Mutations in the TKD of MET, including those within codons V1092, H1094 and L1195, which lead to ligand-independent activation of the pathway, have not been reported as primary oncogenic drivers in NSCLC. In addition, very little is known about whether *MET* TKD mutations mediate AR to EGFR-TKIs in baseline *EGFR*-mutated NSCLC patients.

Methods

- Baseline *MET* TKD mutation-positive NSCLC patients (N=25) and paired samples before and after various TKI treatments (EGFR-TKI, ALK-TKI, or MET-TKI) were analyzed by targeted next-generation sequencing (Fig. 1).

Key Findings

- *MET* TKD mutations were identified in 25 treatment-naïve NSCLC patients at an extremely low frequency (~0.03%), including H1094Y/D, L1195F/V, D1228N/Y, and Y1230C (Fig. 2a). The variant allele frequency (VAF) of *MET* TKD mutations in baseline patients was significantly lower than that of *EGFR* activating mutations (Fig. 3a).
- In EGFR-TKI-resistant samples, a higher prevalence of H1094Y and L1195F was observed compared to patients at resistant to MET-TKIs (Fig. 2b, c). AR to ALK-TKI resulted in a novel large fragment insertion in the *MET* TKD (*MET*-KDD). In addition, the VAF of *MET* TKD mutations after EGFR-TKI treatment was significantly higher than in pretreatment samples ($P<0.05$, Fig. 3b).
- *MET* H1094D was present in treatment-naïve NSCLC patients, but not in patients at resistant to TKIs (Fig. 2).

Results

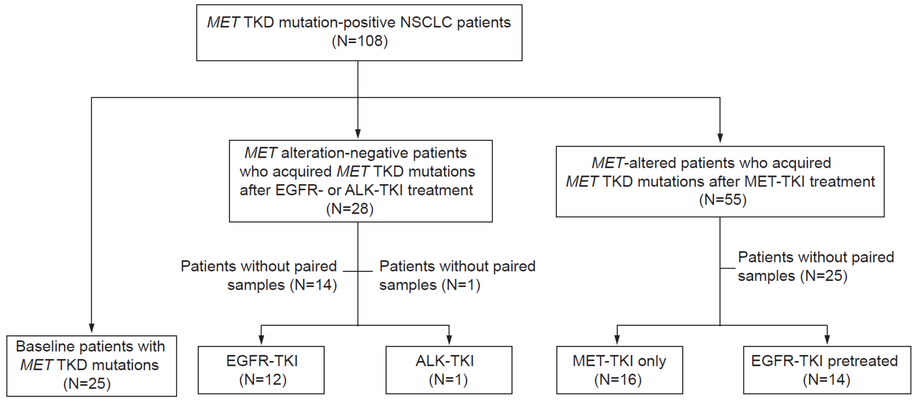

Figure 1. Patient overview

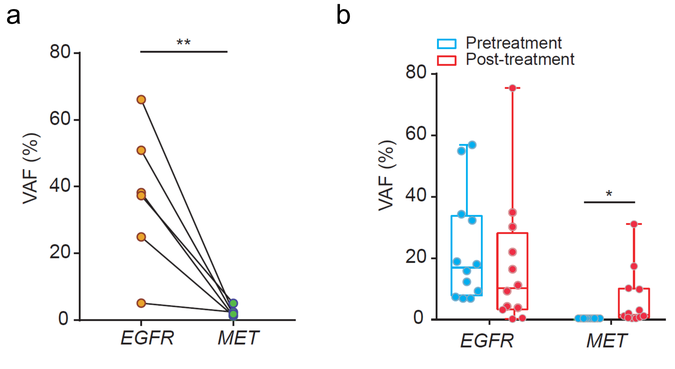

Figure 3. Variant allele frequency (VAF) in baseline and EGFR-TKI-resistant patients

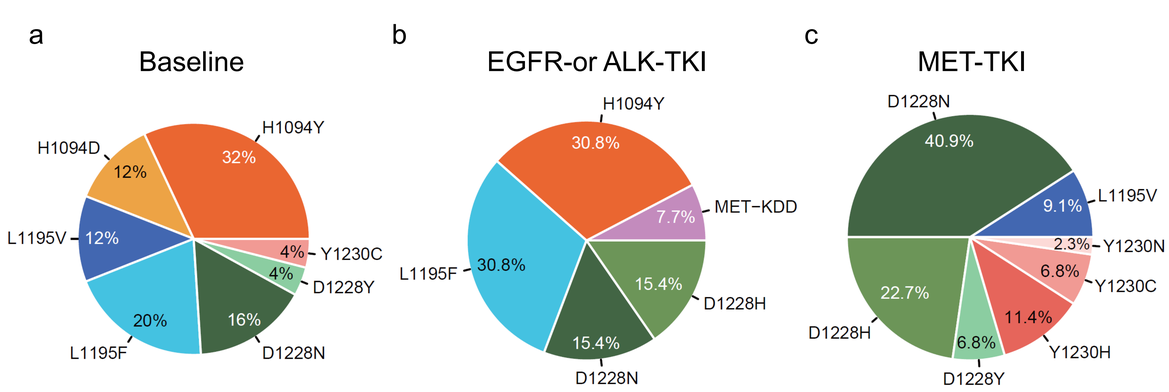

Figure 2. Distribution of *MET* TKD mutations at resistant to TKIs

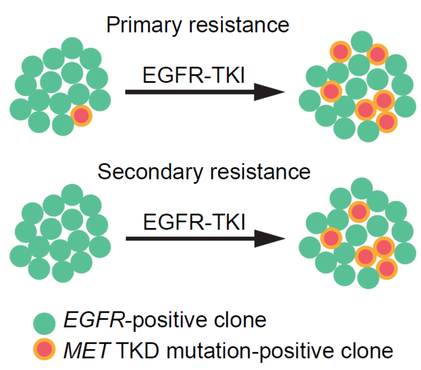

Figure 4. Schematic demonstration of potential AR in *EGFR*-TKI-resistant patients

Conclusions

- Our findings suggest that *MET* TKD mutations, such as H1094Y, L1195F, and *MET*-KDD, might represent a novel AR mechanism to EGFR-TKIs.
- Acquired resistance to EGFR-TKIs might be associated with hereditary mutations at baseline or bypass mutations induced by drug resistance (Fig. 4).
- *EGFR*-mutated NSCLC patients may benefit from combinatorial therapy targeting EGFR and MET.

References

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2. Heist, R.S., L.V. Sequist, D. Borger, J.F. Gainor, R.S. Arellano, L.P. Le, D. Dias-Santagata, J.W. Clark, J.A. Engelman, A.T. Shaw, and A.J. Iafrate, Acquired Resistance to Crizotinib in NSCLC with MET Exon 14 Skipping. J Thorac Oncol, 2016. 11(8): p. 1242-1245.