

Impact of common resistance mechanisms on real-world overall survival for patients receiving osimertinib

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Key Takeaways

Identification of a common resistance mechanism is strongly linked to worse survival; patients with identified resistance had an approximately 2–3 times higher risk of death versus those without detected resistance, with risk remaining elevated across all landmarks

Survival impact was consistent across *EGFR/MET*-dependent and -independent mechanisms, highlighting multiple biological pathways contributing to treatment failure

Conclusions

For patients receiving 1L osimertinib as their first EGFR TKI, commonly observed resistance mechanisms were associated with worse outcomes

Considering that targeted therapies can drive evolving tumor biology, use of 1L therapies that limit the emergence of key resistance mechanisms may improve long-term survival

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The authors report that generative AI was not used in the preparation of this presentation.

- Background**
 - Nearly all patients who receive an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) will eventually experience disease progression,^{1,2} but the impact of common resistance mechanisms (eg, *EGFR* C797S, *MET* amplification) on real-world overall survival (rwOS) remains poorly understood
 - In this study, we evaluated the impact of identified resistance alterations on rwOS among patients receiving osimertinib compared with patients with no identified resistance alterations
- Methods**

Study design

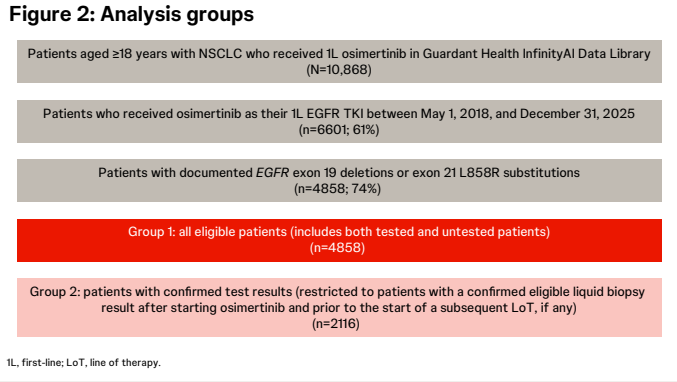
 - This was a retrospective cohort study that used the Guardant Health InfinityAI Data Library, integrating claims and Guardant360 genomic testing data
 - Exploratory validation analysis was performed using the Flatiron Health–Foundation Medicine Clinico-Genomic Database (CGDB)

Study population

 - Patients with metastatic non-small cell lung cancer (NSCLC) receiving osimertinib as the first-line (1L) therapy and the 1L EGFR TKI were included

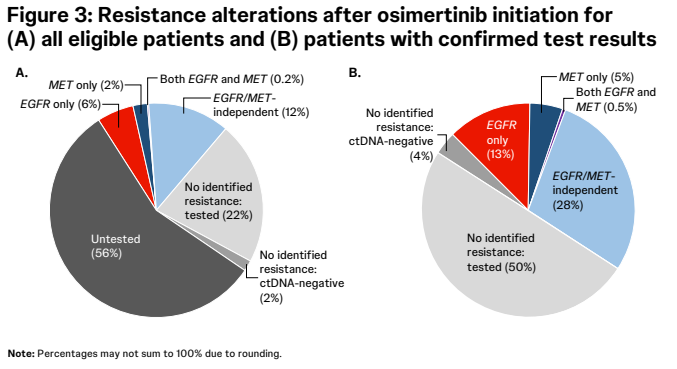
Results From the Guardant Health InfinityAI Cohort

- Two study groups were analyzed: (1) all eligible patients and (2) patients with confirmed test results (**Figure 2**)

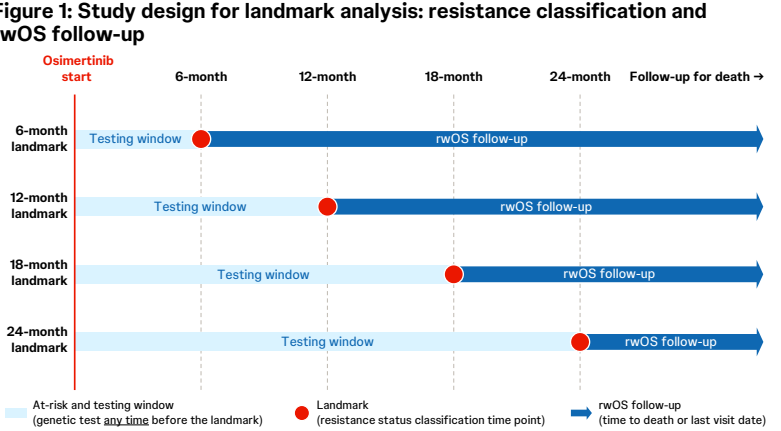


- Resistance definitions for the various groups are shown in **Table 1**
- Among resistance alterations identified after 1L osimertinib, *EGFR/MET*-independent resistance alterations were the most prevalent (**Figure 3**)

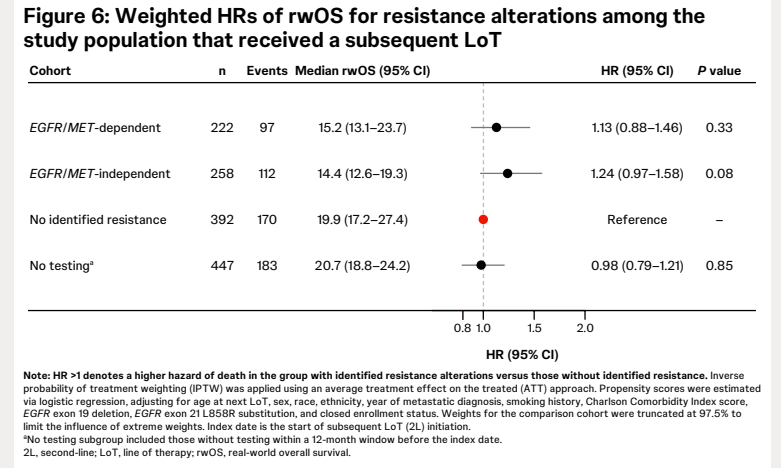
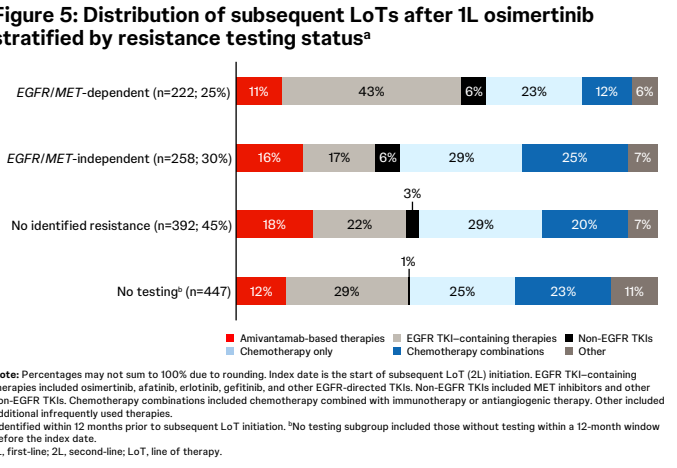
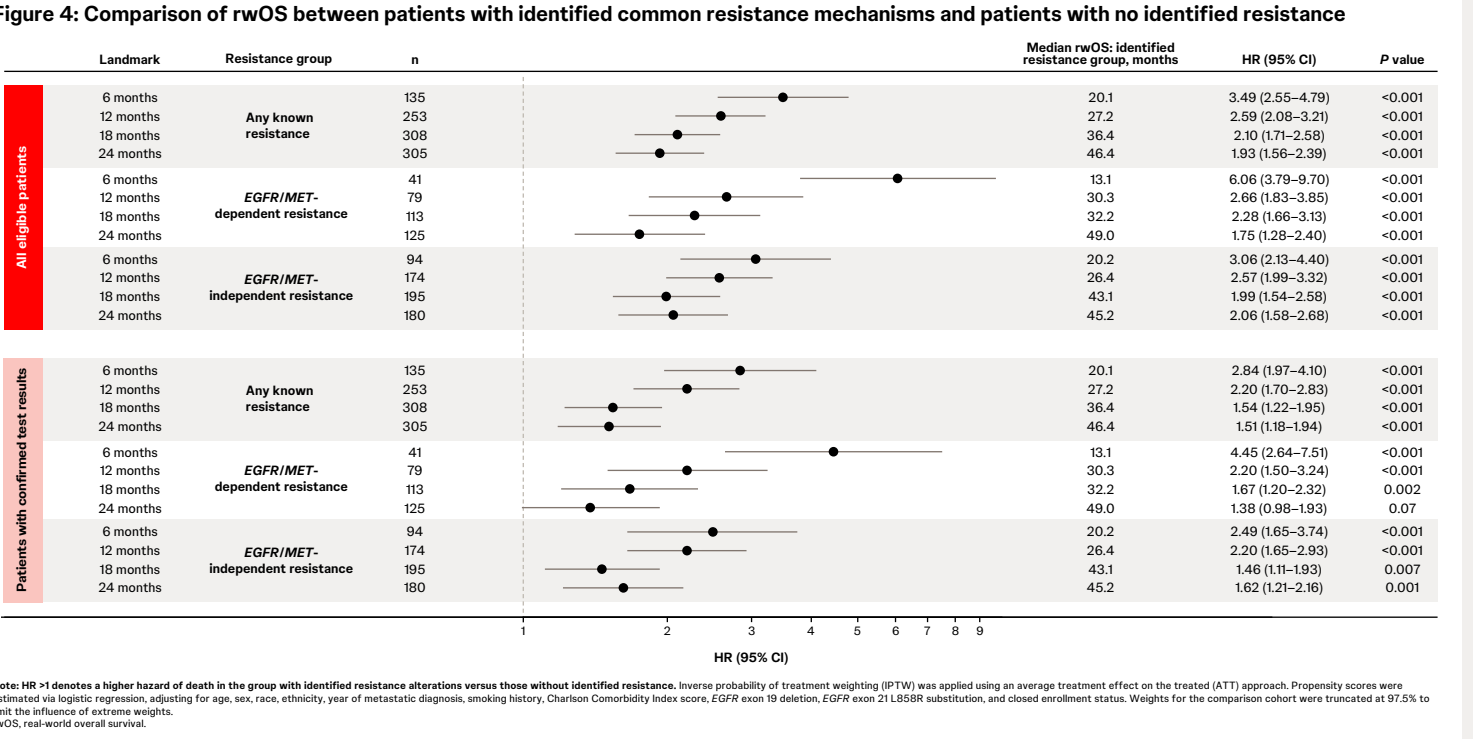
Resistance group	Definition
<i>EGFR/MET</i>-dependent resistance (n=385)	<i>EGFR</i> and/or <i>MET</i> resistance
<i>EGFR</i> (n=280)	<i>EGFR</i> resistance (C797S, L718X, G724X, L892X, G796X)
<i>MET</i> (n=115)	<i>MET</i> resistance (amplification, exon 14 skipping)
<i>EGFR/MET</i>-independent resistance (n=602)	≥1 of the listed gene alterations (eg, <i>HER2</i> amplification, <i>PIK3CA</i> , <i>RAS/RAF</i> , cell cycle, <i>TP53/RB1</i> loss of function) without concurrent <i>EGFR/MET</i> alteration. Pathogenic alterations were defined as activating alterations in oncogenes or loss-of-function alterations in tumor suppressor genes
Any identified resistance alteration (n=987)	≥1 of the listed gene alterations, including <i>EGFR</i> , <i>MET</i> , or any gene included in the <i>EGFR/MET</i> -independent list
No identified resistance (tested, n=1129; untested, n=2742)	No identified resistance alterations listed above



- Resistance classification**
- Testing of resistance alterations identified from Guardant360 was performed after osimertinib initiation and before the start of a subsequent line of therapy (LoT) or prespecified landmark time
 - Resistance mechanisms were categorized as (1) *EGFR/MET*-dependent, (2) *EGFR/MET*-independent, or (3) no identified resistance
 - Landmark analyses were conducted at 6, 12, 18, and 24 months after osimertinib initiation; eligible patients were alive, were uncensored at the landmark, and had ≥1 genomic test prior to the landmark (**Figure 1**)
 - Inverse probability–weighted Cox regression was used to estimate hazard ratios (HRs) for rwOS among the study population and the subgroup that received a subsequent LoT



- Across landmark analyses, patients with identified resistance mechanisms (*EGFR/MET*-dependent or -independent) had a consistently higher hazard of death (HR >1) compared with those without identified resistance in both the Guardant Health InfinityAI dataset (**Figure 4**) and the CGDB dataset (analyzed but not shown)
- Patients with *EGFR/MET*-dependent resistance were substantially more likely to receive EGFR TKI–containing regimens in a subsequent LoT (**Figure 5**)
- Despite greater use of EGFR-targeted therapies in the subsequent LoT (index date), patients with *EGFR/MET*-dependent resistance did not experience better survival outcomes, highlighting the persistent unmet need associated with acquired resistance (**Figure 6**)



References
1. Chmielecki J, et al. *Nat Commun*. 2023;14(1):1070. 2. Leonetti A, et al. *Br J Cancer*. 2019;121(9):725–737.

