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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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Disclosures

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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)

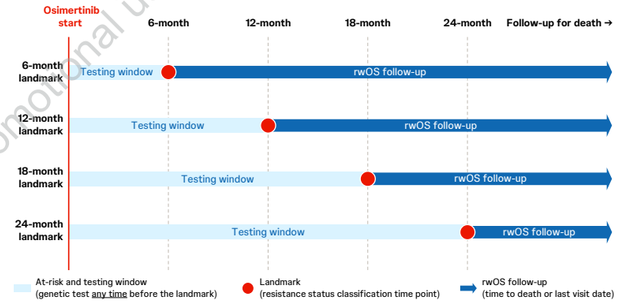
Study population

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

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

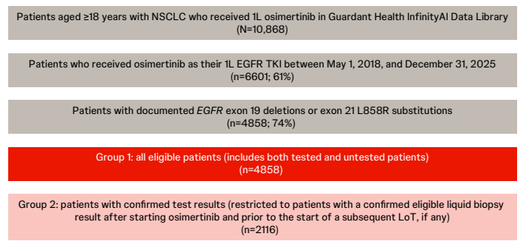
Figure 1: Study design for landmark analysis: resistance classification and rwOS follow-up



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**)

Figure 2: Analysis groups



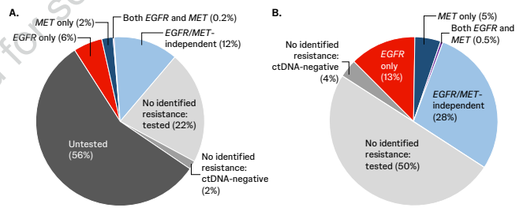
1L, first-line; LoT, line of therapy.

- 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**)

Table 1: Resistance definitions and comparison groups

Resistance group	Definition
***EGFR*/*MET*-dependent resistance (n=385)**	*EGFR* and/or *MET* resistance
EGFR (n=280)	*EGFR* resistance (C797S, L718X, G724X, L892X, G796X)
MET (n=115)	*MET* resistance (amplification, exon 14 skipping)
***EGFR*/*MET*-independent resistance (n=602)**	≥1 of the listed gene alterations (eg, *HER2* amplification, *PIK3CA*, *RAS*/*RAF*, cell cycle, *TP53*/*RB1* loss of function) without concurrent *EGFR*/*MET* 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 *EGFR*, *MET*, or any gene included in the *EGFR*/*MET*-independent list
No identified resistance (tested, n=1129; untested, n=2742)	No identified resistance alterations listed above

Figure 3: Resistance alterations after osimertinib initiation for (A) all eligible patients and (B) patients with confirmed test results

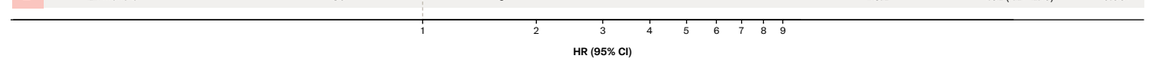


Note: Percentages may not sum to 100% due to rounding.

- 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**)

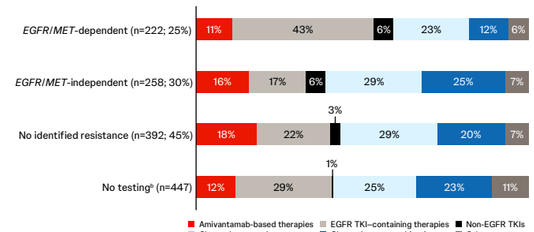
Figure 4: Comparison of rwOS between patients with identified common resistance mechanisms and patients with no identified resistance

	Landmark	Resistance group	n	Median rwOS: identified resistance group, months	HR (95% CI)	*P* value
All eligible patients	6 months	Any known resistance	135	20.1	3.49 (2.55–4.79)	<0.001
	12 months		253	27.2	2.59 (2.08–3.21)	<0.001
	18 months		308	36.4	2.10 (1.71–2.58)	<0.001
	24 months		305	46.4	1.93 (1.56–2.39)	<0.001
	6 months	*EGFR*/*MET*-dependent resistance	41	13.1	6.06 (3.79–9.70)	<0.001
	12 months		79	30.3	2.66 (1.83–3.85)	<0.001
	18 months		113	32.2	2.28 (1.66–3.13)	<0.001
	24 months		125	49.0	1.75 (1.28–2.40)	<0.001
	6 months	*EGFR*/*MET*-independent resistance	94	20.2	3.06 (2.13–4.40)	<0.001
	12 months		174	26.4	2.57 (1.99–3.32)	<0.001
	18 months		195	43.1	1.99 (1.54–2.58)	<0.001
	24 months		180	45.2	2.06 (1.58–2.68)	<0.001
Patients with confirmed test results	6 months	Any known resistance	135	20.1	2.84 (1.97–4.10)	<0.001
	12 months		253	27.2	2.20 (1.70–2.83)	<0.001
	18 months		308	36.4	1.54 (1.22–1.95)	<0.001
	24 months		305	46.4	1.51 (1.18–1.94)	<0.001
	6 months	*EGFR*/*MET*-dependent resistance	41	13.1	4.45 (2.64–7.51)	<0.001
	12 months		79	30.3	2.20 (1.50–3.24)	<0.001
	18 months		113	32.2	1.67 (1.20–2.32)	0.002
	24 months		125	49.0	1.38 (0.98–1.93)	0.07
	6 months	*EGFR*/*MET*-independent resistance	94	20.2	2.49 (1.65–3.74)	<0.001
	12 months		174	26.4	2.20 (1.65–2.93)	<0.001
	18 months		195	43.1	1.46 (1.11–1.93)	0.007
	24 months		180	45.2	1.62 (1.21–2.16)	0.001



Note: HR >1 denotes a higher hazard of death in the group with identified resistance alterations versus those without identified resistance. Inverse probability of treatment weighting (IPTW) was applied using an average treatment effect on the treated (ATT) approach. Propensity scores were estimated via logistic regression, adjusting for age, sex, race, ethnicity, year of metastatic diagnosis, smoking history, Charlson Comorbidity Index score, *EGFR* exon 19 deletion, *EGFR* exon 21 L858R substitution, and closed enrollment status. Weights for the comparison cohort were truncated at 97.5% to limit the influence of extreme weights.
rwOS, real-world overall survival.

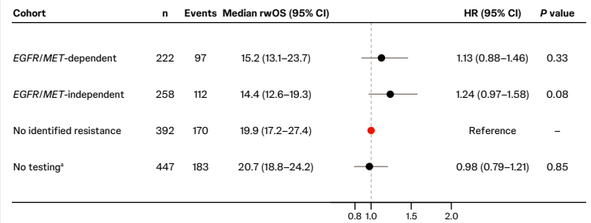
Figure 5: Distribution of subsequent LoTs after 1L osimertinib stratified by resistance testing status[a]



Note: Percentages may not sum to 100% due to rounding. Index date is the start of subsequent LoT (2L) initiation. EGFR TKI–containing therapies included osimertinib, afatinib, erlotinib, gefitinib, and other EGFR-directed TKIs. Non-EGFR TKIs included MET inhibitors and other non-EGFR TKIs. Chemotherapy combinations included chemotherapy combined with immunotherapy or antiangiogenic therapy. Other included additional infrequently used therapies.
[a]Identified within 12 months prior to subsequent LoT initiation. [b]No testing subgroup included those without testing within a 12-month window before the index date.
1L, first-line; 2L, second-line; LoT, line of therapy.

Figure 6: Weighted HRs of rwOS for resistance alterations among the study population that received a subsequent LoT

Cohort	n	Events	Median rwOS (95% CI)	HR (95% CI)	*P* value
EGFR/*MET*-dependent	222	97	15.2 (13.1–23.7)	1.13 (0.88–1.46)	0.33
EGFR/*MET*-independent	258	112	14.4 (12.6–19.3)	1.24 (0.97–1.58)	0.08
No identified resistance	392	170	19.9 (17.2–27.4)	Reference	–
No testing[a]	447	183	20.7 (18.8–24.2)	0.98 (0.79–1.21)	0.85



Note: HR >1 denotes a higher hazard of death in the group with identified resistance alterations versus those without identified resistance. Inverse probability of treatment weighting (IPTW) was applied using an average treatment effect on the treated (ATT) approach. Propensity scores were estimated via logistic regression, adjusting for age at next LoT, sex, race, ethnicity, year of metastatic diagnosis, smoking history, Charlson Comorbidity Index score, *EGFR* exon 19 deletion, *EGFR* exon 21 L858R substitution, and closed enrollment status. Weights for the comparison cohort were truncated at 97.5% to limit the influence of extreme weights. Index date is the start of subsequent LoT (2L) initiation.
[a]No testing subgroup included those without testing within a 12-month window before the index date.
2L, second-line; LoT, line of therapy; rwOS, real-world overall survival.

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Lung Cancer

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