



2026 World Conference on Lung Cancer

SEPTEMBER 12 – 15, 2026 | SEOUL, REPUBLIC OF KOREA

On-target acquired resistance to zongertinib and strategy to overcome it - in vitro study using *HER2* ex20 insertion models

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AI Use Disclosure

- No generative AI tools were used in the preparation of this poster.

Introduction

- The development of HER2-targeted tyrosine kinase inhibitors (HER2-TKIs) for *HER2*-mutant NSCLC has recently accelerated.
- Agents such as zongertinib and sevabertinib have demonstrated promising efficacy in previously treated patients and are expected to play an important role in clinical practice.¹⁻³
- However, differences in efficacy among these agents and the mechanisms of acquired resistance remain poorly understood.

1. Heymach JV, et al. First-Line Zongertinib in Advanced HER2-Mutant Non-Small-Cell Lung Cancer. *N Engl J Med* 2026;394:1675-1684.

2. Heymach JV, et al. Zongertinib in Previously Treated HER2-Mutant Non-Small-Cell Lung Cancer. *N Engl J Med* 2025;392:2321-2333.

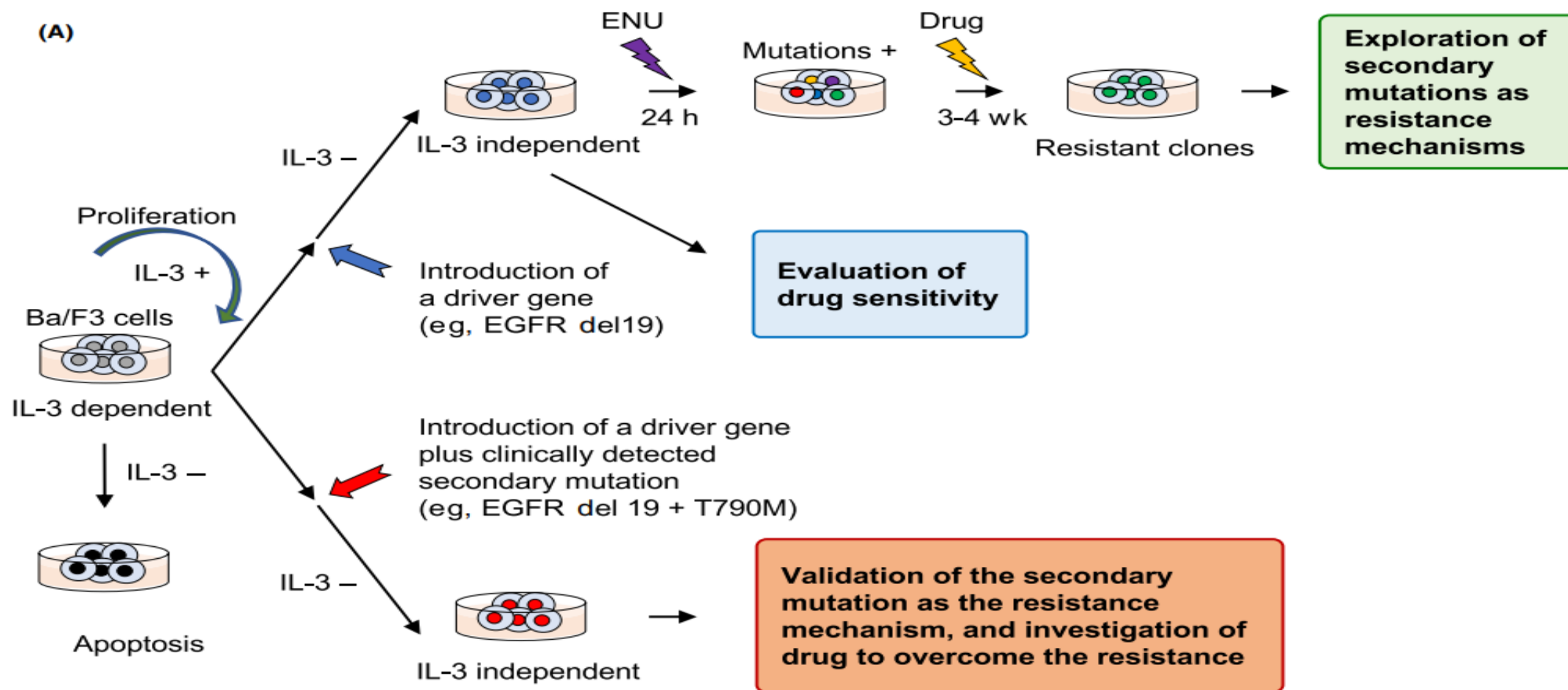
3. Le X, et al. Sevabertinib in Advanced HER2-Mutant Non-Small-Cell Lung Cancer. *N Engl J Med* 2025;393:1819-1832.

Methods

- We examined efficacy of zongertinib, sevabertinib and other TKIs with HER2 inhibitory activity (erlotinib, afatinib, poziotinib, mobocertinib, and osimertinib) using murine pro-B-cell line (Ba/F3) models harboring one of three most common *HER2* exon 20 insertions (A775_G776insYVMA (YVMA), G776delinsVC (VC) and P780_Y781insGSP (GSP)).
- We then explored on-target acquired resistance mechanisms to zongertinib by establishing resistant clones using chronic drug exposure technique after N-ethyl-N-nitrosourea mutagenesis.
- Efficacy of above TKIs, against acquired resistant Ba/F3 cells with secondary mutation, was examined to explore potential strategy to overcome it.
- We also evaluated if these TKIs could overcome C805S mediated resistance to poziotinib.⁴

4. T. Koga, et al. Activity of a novel HER2 inhibitor, poziotinib, for HER2 exon 20 mutations in lung cancer and mechanism of acquired resistance: An in vitro study. Lung Cancer 2018;126:72-79.

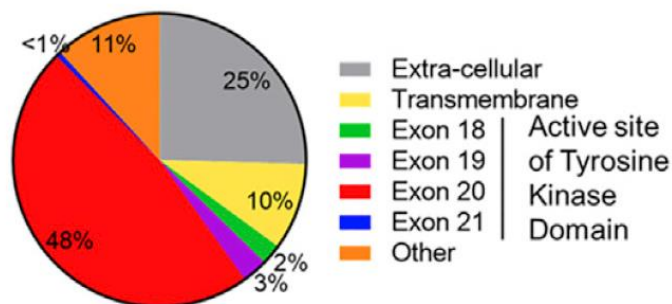
Ba/F3 model as tools for mechanistic analysis of resistance to TKI



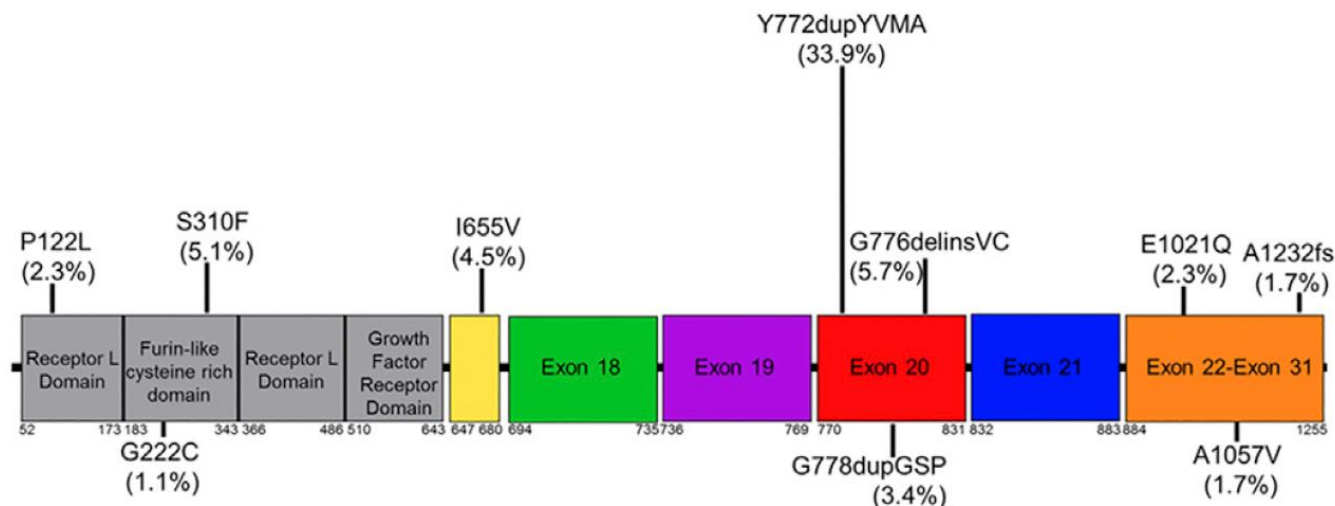
5. T. Koga, et al. Utility of the Ba/F3 cell system for exploring on-target mechanisms of resistance to targeted therapies for lung cancer. Cancer Sci 2022;113:815-827.

Frequencies of *HER2* exon 20 insertions in NSCLC

C



D



- Three representative *HER2* exon 20 insertion variants (Y772dupYVMA, G776delinsVC, and G778dupGSP) were selected, all of which have previously been shown to exhibit transforming ability in Ba/F3 cell models.^{4,6}

4. T. Koga, et al. Activity of a novel HER2 inhibitor, poziotinib, for HER2 exon 20 mutations in lung cancer and mechanism of acquired resistance: An in vitro study. Lung Cancer 2018;126:72-79.

6. Robichaux JP, et al. Pan-Cancer Landscape and Analysis of ERBB2 Mutations Identifies Poziotinib as a Clinically Active Inhibitor and Enhancer of T-DM1 Activity. Cancer Cell. 2019;36:444-457.

Efficacy of zongertinib, sevabertinib and other TKIs against Ba/F3 cells with various *HER2* exon 20 mutations

A. Summary of IC₅₀

IC ₅₀ (nM)							
	erlotinib	afatinib	poziotinib	mobocertinib	osimertinib	zongertinib	sevabertinib
YVMA	>1000	11	1.8	10	269	10	7.1
VC	125	0.8	0.1	0.1	10	3.6	1.2
GSP	>1000	5.8	0.4	3.8	112	2.9	2.7

B. Summary of sensitivity index

sensitivity index							
	erlotinib	afatinib	poziotinib	mobocertinib	osimertinib	zongertinib	sevabertinib
YVMA	>1000	16	9	28	67	5	1.6
VC	4.2	1.2	0.5	0.3	2.5	1.8	0.3
GSP	>1000	8.4	2	11	28	1.5	0.6

Inhibitory activities of each TKI used to treat cells with various *HER2* exon 20 mutations were compared using a sensitivity index (SI, IC₅₀/C_{trough} of each drug × 100). The measured SI values were color coded as follows: green, ≤ 25; yellow, 25–200; and red, greater than 200. C_{trough}: erlotinib, 2969 nM⁷; afatinib, 69 nM⁸; poziotinib, 20 nM⁹; mobocertinib, 36 nM¹⁰; osimertinib, 400 nM¹¹; zongertinib, 200 nM¹⁻²; and sevabertinib, 450 nM³.

1. N Engl J Med 2026;394:1675-1684. 2. N Engl J Med 2025;392:2321-2333. 3. N Engl J Med 2025;393:1819-1832. 7. J.Clin.Oncol.2001;19:3267–3279. 8. J.Clin.Oncol.2010;28:3965–3972. 9. Cancer Res. Treat.2018;50:835–842.

10. JAMA Oncol. 2021;7(12):e214761. 11. N Engl J Med 2015;372:1689–1699.

Efficacy of TKIs with HER2 inhibitory activity against Ba/F3 cells with secondary zongertinib-resistant mutations

A. Summary of IC₅₀

IC ₅₀ (nM)	IC₅₀ ≤ 10nM 10 < IC₅₀ < 200nM IC₅₀ ≥ 200nM						
	erlotinib	afatinib	poziotinib	mobocertinib	osimertinib	zongertinib	sevabertinib
YVMA+S783A	>1000	3.7	1.1	10	272	96	32
GSP+G776C	>1000	28	1.4	12	208	16	87

B. Summary of sensitivity index

sensitivity index	SI ≤ 25 25 < SI < 200 SI ≥ 200						
	erlotinib	afatinib	poziotinib	mobocertinib	osimertinib	zongertinib	sevabertinib
YVMA+S783A	>1000	5.4	5.5	28	68	48	7.1
GSP+G776C	>1000	41	7	33	52	8	19

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10. JAMA Oncol. 2021;7(12):e214761. 11. N Engl J Med 2015;372:1689–1699.

Efficacy of TKIs with HER2 inhibitory activity against Ba/F3 cells with secondary poztotinib-resistant mutations

A. Summary of IC₅₀

A. Summary of IC₅₀

				IC ₅₀ ≤ 10nM	10 < IC ₅₀ < 200nM	IC ₅₀ ≥ 200nM	
IC ₅₀ (nM)	erlotinib	afatinib	poziotinib	mobocertinib	osimertinib	zongertinib	sevabertinib
YVMA+C805S	>1000	>1000	848	>1000	>1000	884	4
VC+C805S	958	780	521	>1000	>1000	966	111

B. Summary of sensitivity index

B. Summary of sensitivity index

				SI ≤ 25	25 < IC ₅₀ < 200	SI ≥ 200	
sensitivity index	erlotinib	afatinib	poziotinib	mobocertinib	osimertinib	zongertinib	sevabertinib
YVMA+C805S	>1000	>1000	>1000	>1000	>1000	442	0.9
VC+C805S	958	>1000	>1000	>1000	>1000	483	25

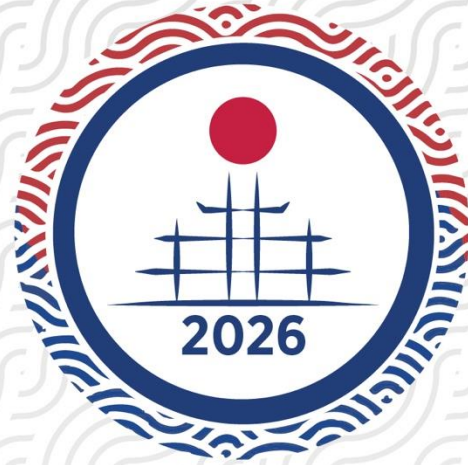
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10. JAMA Oncol. 2021;7(12):e214761. 11. N Engl J Med 2015;372:1689–1699.

Conclusions

- These findings indicate that distinct compound mutations confer differential resistance to HER2-TKIs depending on the original *HER2* exon 20 insertion.
- Zongertinib-resistant mutations, such as YVMA+S783A and GSP+G776C, remained sensitive to poziotinib and sevabertinib, whereas compound mutations associated with poziotinib resistance, including YVMA+C805S and VC+C805S, were effectively inhibited by sevabertinib.



Thank You.