

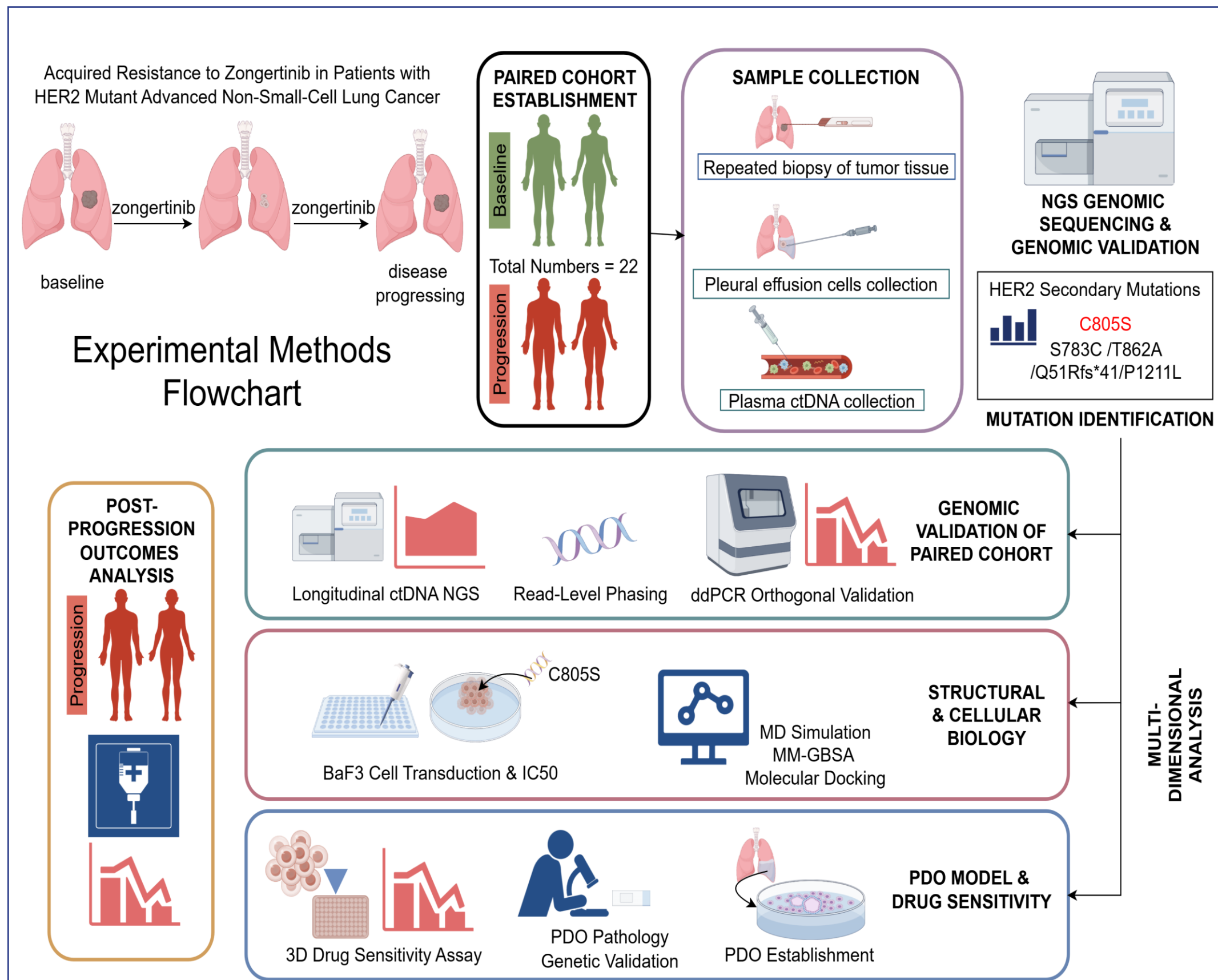
Acquired Resistance to Zongertinib in Patients with HER2-Mutant Advanced Non-Small Cell Lung Cancer

Kai Yin¹, Yue-Li Sun¹, Ling-Chao Shi², Yue Zhu¹, Chong-Rui Xu¹, Yang-Si Li¹, Xiao-Yan Bai¹, Bing-Fei Xu¹, Jia-Xin Lin¹, Si-Yang Maggie Liu¹, Mei-Mei Zheng¹, An-Na Li¹, Ju-Hua Yang³, Dong-Qin Zhu³, Qian Cui⁴, Ze-Xin Chen⁵, Xiao-Jun Ou⁵, Bin-Chao Wang¹, Hua-Jun Chen¹, Jin-Ji Yang¹, Xue-Ning Yang¹, Qing Zhou¹, Zhen Wang¹, Peng Li⁶, Wen-Zhao Zhong¹, Yi-Long Wu^{1, #}, Hai-Yan Tu^{1, #}
¹Guangdong Lung Cancer Institute, Guangdong Provincial Key Laboratory of Translational Medicine in Lung Cancer, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Southern Medical University, Guangzhou, 510080, China. ²Institutes of Physical Science and Information Technology, Anhui University, Hefei 230601, China. ³Nanjing Geneseeq Technology Inc., Nanjing, Jiangsu, China. ⁴Department of Pathology, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, 510080, China. ⁵Guangdong Research Center of Organoid Engineering and Technology, Guangzhou 510530, China. ⁶Institute of Drug Discovery, Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences; 510530, Guangzhou, China.
[#]Corresponding author: Yi-Long Wu & Hai-Yan Tu, E-mail: wuyilong@live.cn & thy0934789@163.com;

INTRODUCTION

- Activating *HER2* mutations occur in approximately 2%–4% of non-small-cell lung cancers (NSCLC)¹⁻³.
- Zongertinib has demonstrated substantial clinical activity in patients with *HER2*-mutant NSCLC, but acquired resistance inevitably emerges⁴.
- Although secondary *HER2* alterations have been observed in the setting of acquired resistance, their clinical prevalence, temporal emergence, and functional significance during zongertinib treatment remain poorly defined.

Study design

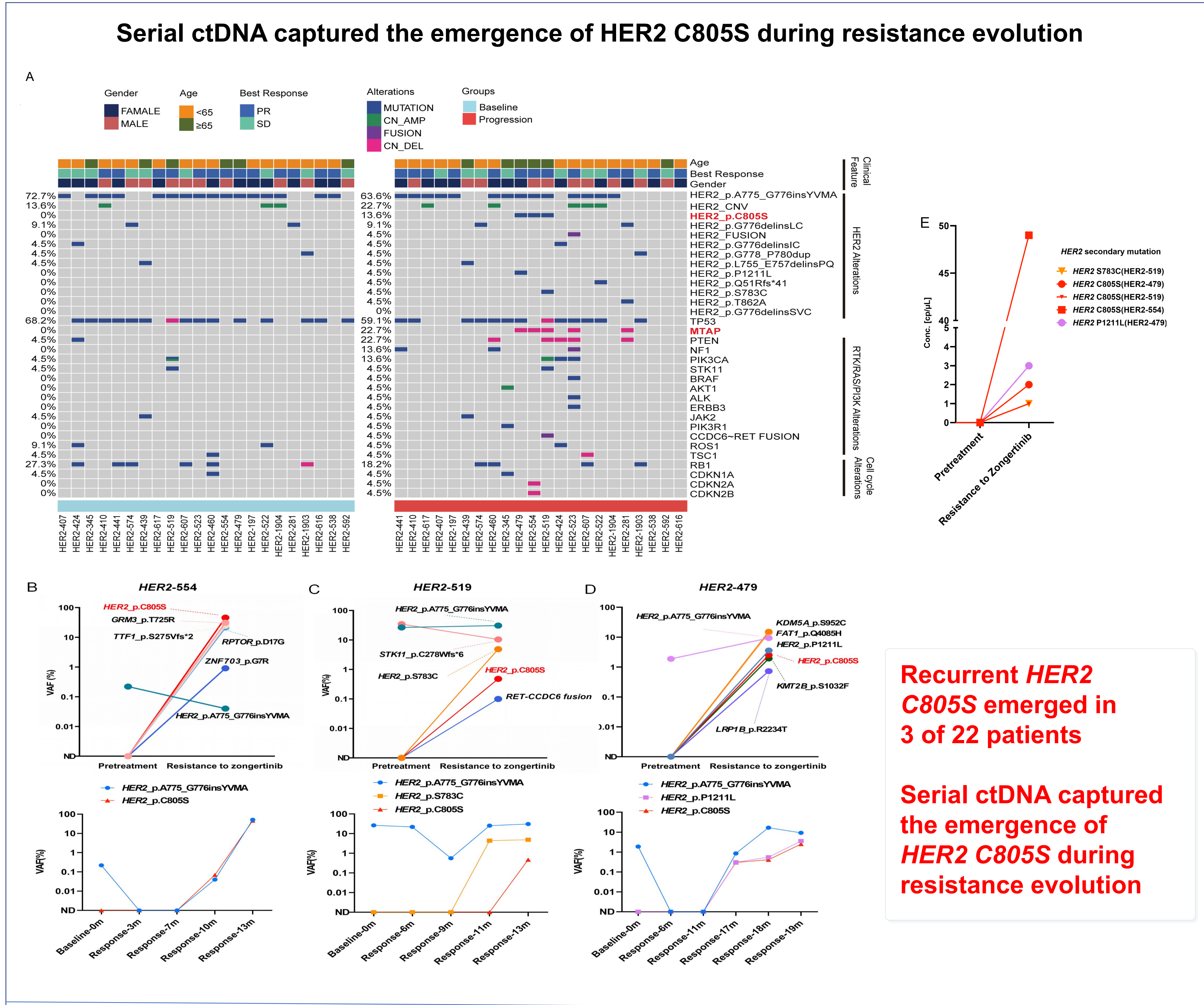


REFERENCES & ACKNOWLEDGEMENTS

- References:
- Hong, L et al. NPJ Precis Oncol 8, 217. 10.1038/s41698-024-00720-9.
 - Pahuja, K.B et al. Cancer cell 34, 792-806.e795. 10.1016/j.ccell.2018.09.010.
 - Friedlaender, A. Nature Reviews Clinical Oncology 19, 51-69. 10.1038/s41571-021-00558-1.
 - Heymach, J.V. et al. The New England Journal of Medicine 392, 2321-2333. 10.1056/NEJMoa2503704.

*graphical elements created using Figdraw.

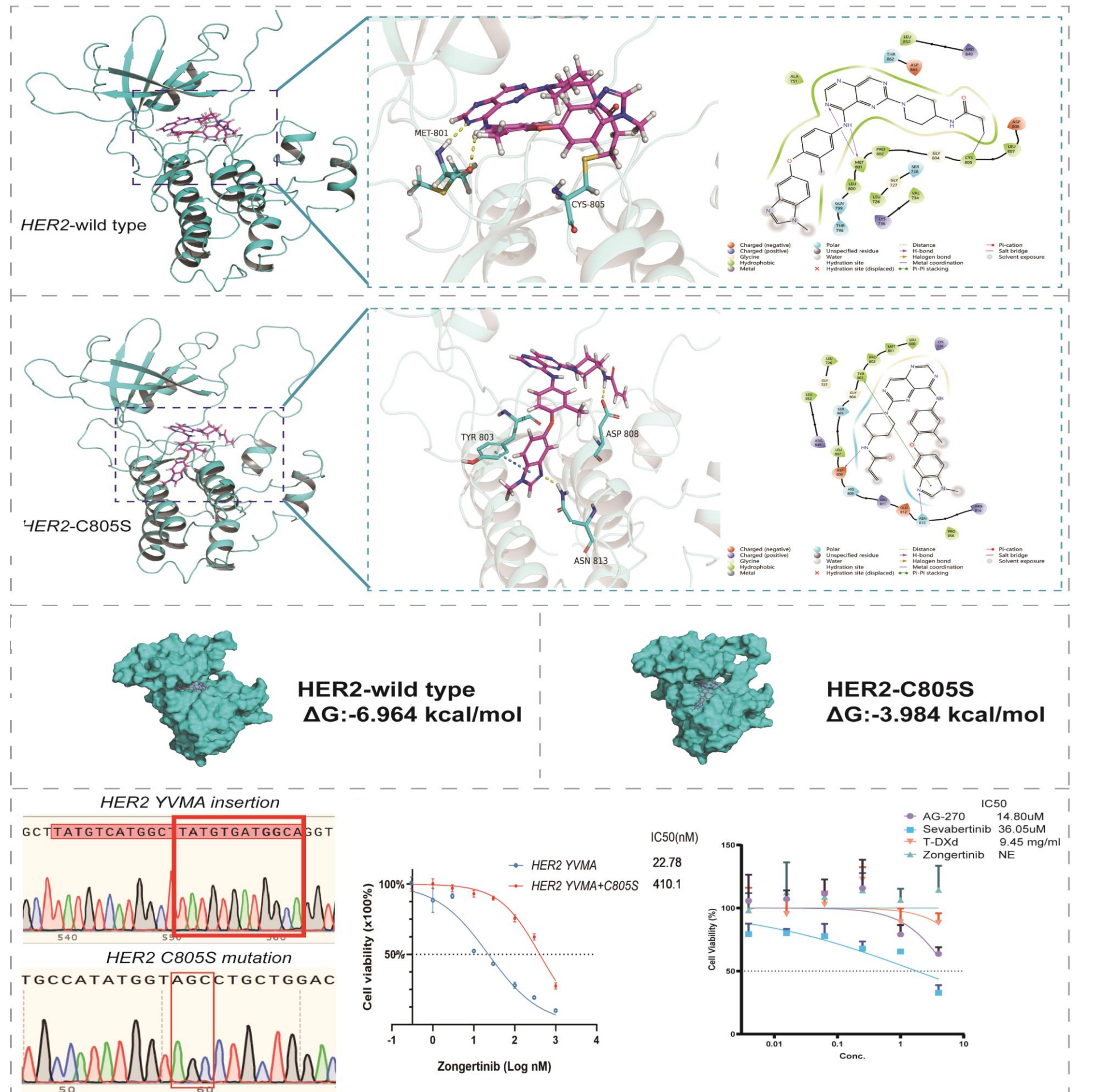
RESULTS



Recurrent **HER2 C805S** emerged in 3 of 22 patients

Serial ctDNA captured the emergence of **HER2 C805S** during resistance evolution

C805S disrupts the covalent binding of zongertinib



The *HER2* C805S-harboring PDO was resistant to zongertinib but retained sensitivity to sevabertinib and trastuzumab deruxtecan.

CONCLUSION

HER2 C805S is a recurrent acquired on-target resistance alteration after zongertinib in *HER2*-mutant NSCLC.

Clinical implications

- Serial ctDNA may help track emerging resistance.
- C805S impairs covalent zongertinib engagement.
- Alternative *HER2*-directed therapies may retain activity after resistance.

