

P1.375: Clinical Characteristics, Genomic Subtypes, and Outcomes of HER2-Altered NSCLC: A Multicenter Real-World Study in Taiwan

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INTRODUCTION

Background

HER2 mutations, amplifications, and overexpression are biologically distinct biomarkers in NSCLC with evolving therapeutic strategies. However, real-world clinical and genomic data for HER2-altered NSCLC in Asian populations remain scarce. We investigated the clinical characteristics, genomic subtypes, and treatment outcomes of HER2-altered NSCLC using a multicenter real-world cohort in Taiwan.

Objective

- To characterize the molecular landscape and compare line-specific real-world outcomes across conventional and HER2-directed treatment strategies.

METHODS

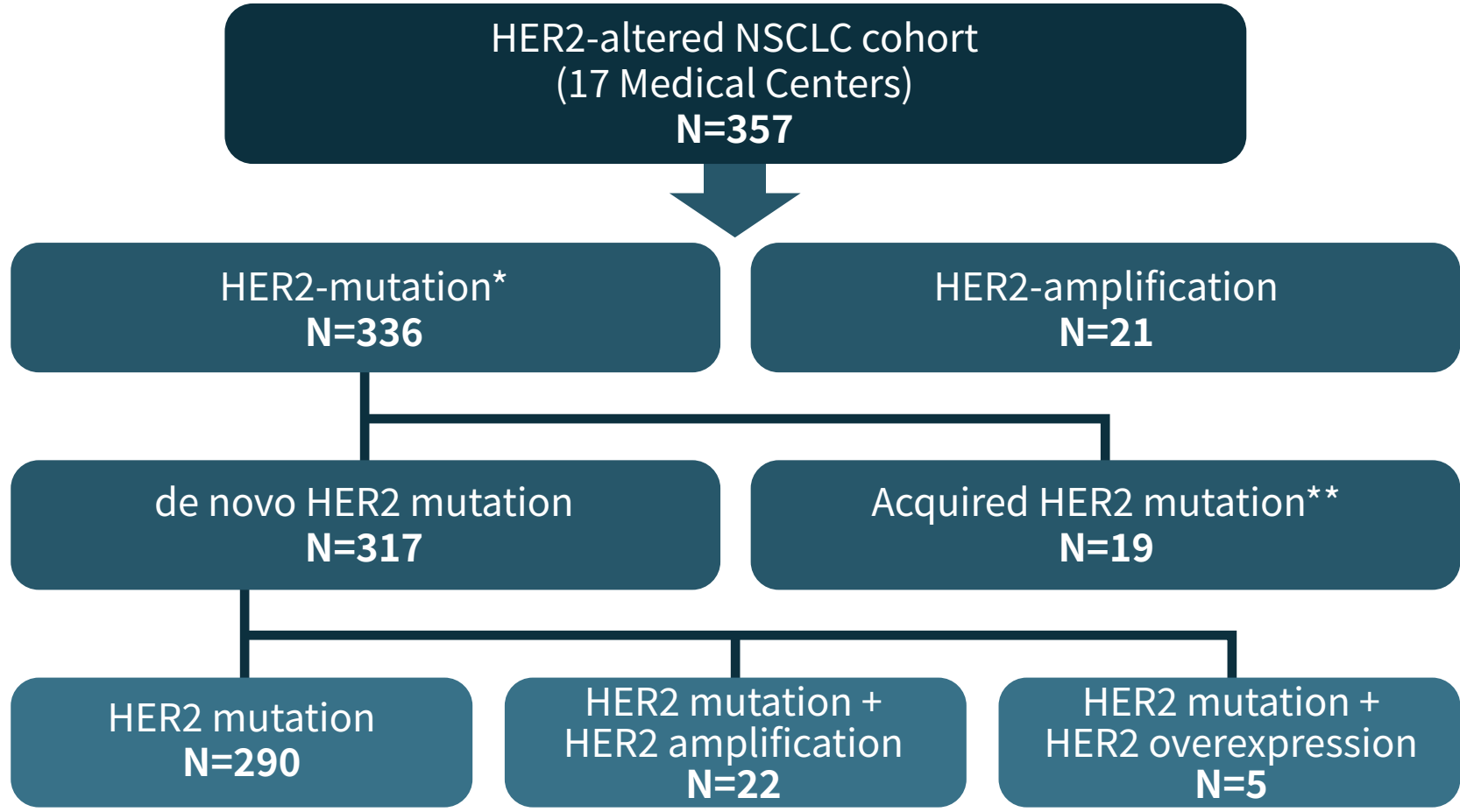
Design and Setting:

- Retrospective cohort across 17 medical centers in Taiwan, 2016–2025.
- Primary treatment cohort: patients with de novo HER2-mutant NSCLC.

Outcomes and Analyses:

- Outcomes presented: first-line PFS and OS.
- Kaplan–Meier estimates, 2-sided log-rank tests, and multivariable Cox regression.
- Treatment comparisons were exploratory because treatment assignment was not randomized.
- ADCs were analyzed as a pooled class and included HER2-directed agents (T-DXd and T-DM1) and TROP2-directed agents (Dato-DXd and sacituzumab govitecan).

Cohort Derivation:



DISCUSSION AND CONCLUSION

Principal Findings

- TKIs for HER2 alterations and the pooled ADC group showed the longest observed first-line PFS (11.8 and 13.5 months), compared with chemotherapy (5.7 months) and chemoimmunotherapy (6.9 months).
- Treatment sequencing was heterogeneous: 23 patients received an ADC in 1L and 60 in 2L, while 66 had no documented 2L at data cutoff.
- TP53 co-mutation independently predicted worse OS in both the overall HER2-mutant cohort (aHR, 1.59; P = .020) and the de novo first-line cohort (aHR, 1.88; P = .002).
- ECOG PS 2–4, stage IV disease, bone and adrenal metastases, and TP53 co-mutation were independently associated with worse OS.
- Exploratory safety: Pneumonitis occurred in 11 of 112 patients treated with later-line T-DXd (10%; grade 1, n=4; grade 2, n=2; grade unknown, n=5).

Interpretation

- These findings support prospective evaluation of HER2-directed therapies earlier in the treatment course and highlight ECOG PS, metastatic burden, and TP53 status as important factors for risk stratification.
- Earlier-line evaluation of HER2-directed therapies should assess efficacy and safety, particularly T-DXd-related pneumonitis.

RESULTS

Figure 1. Baseline characteristics and metastatic patterns of the study cohort.

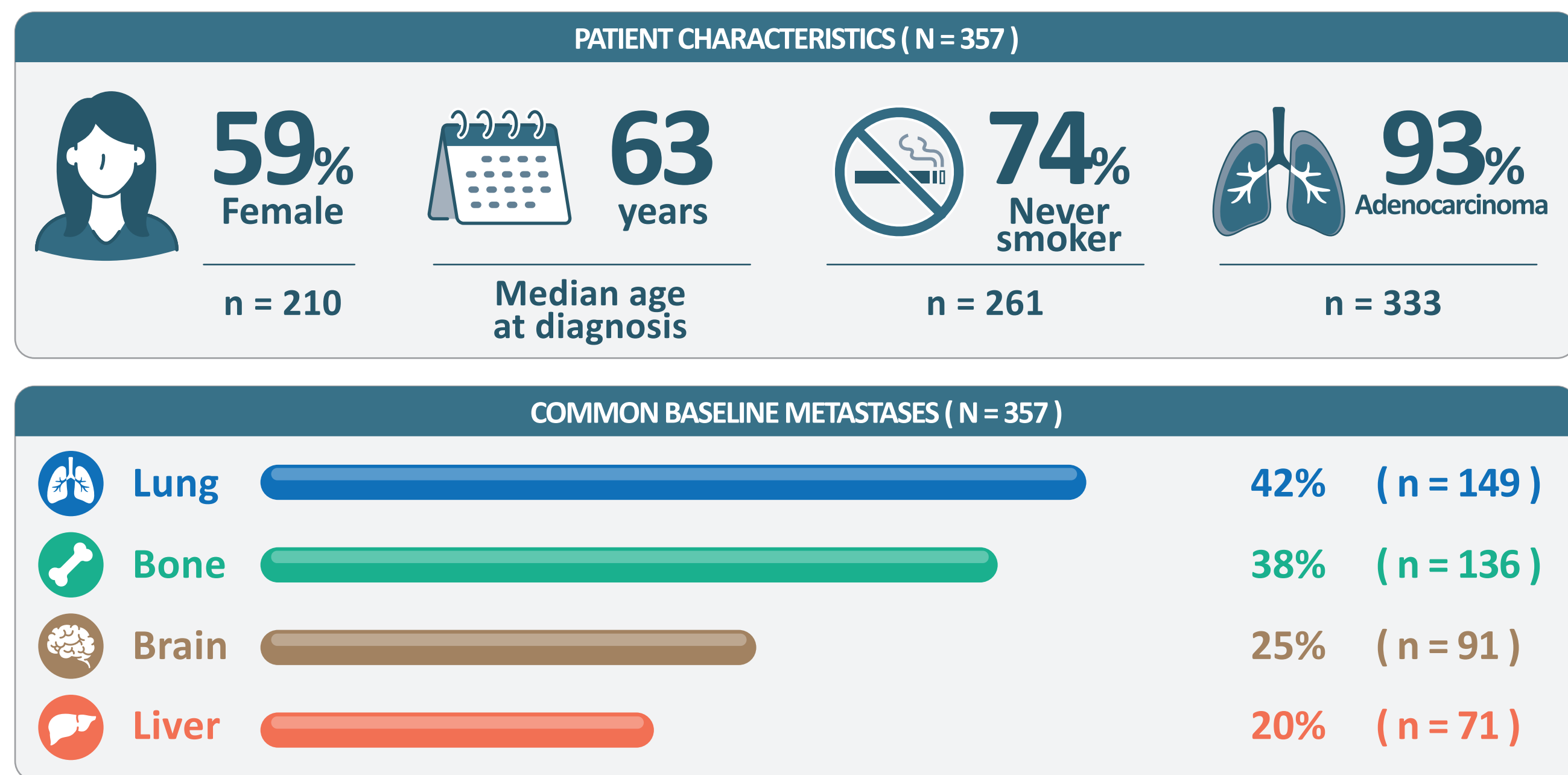


Figure 2. Distribution of ERBB2 variants across HER2 protein domains in the study cohort.

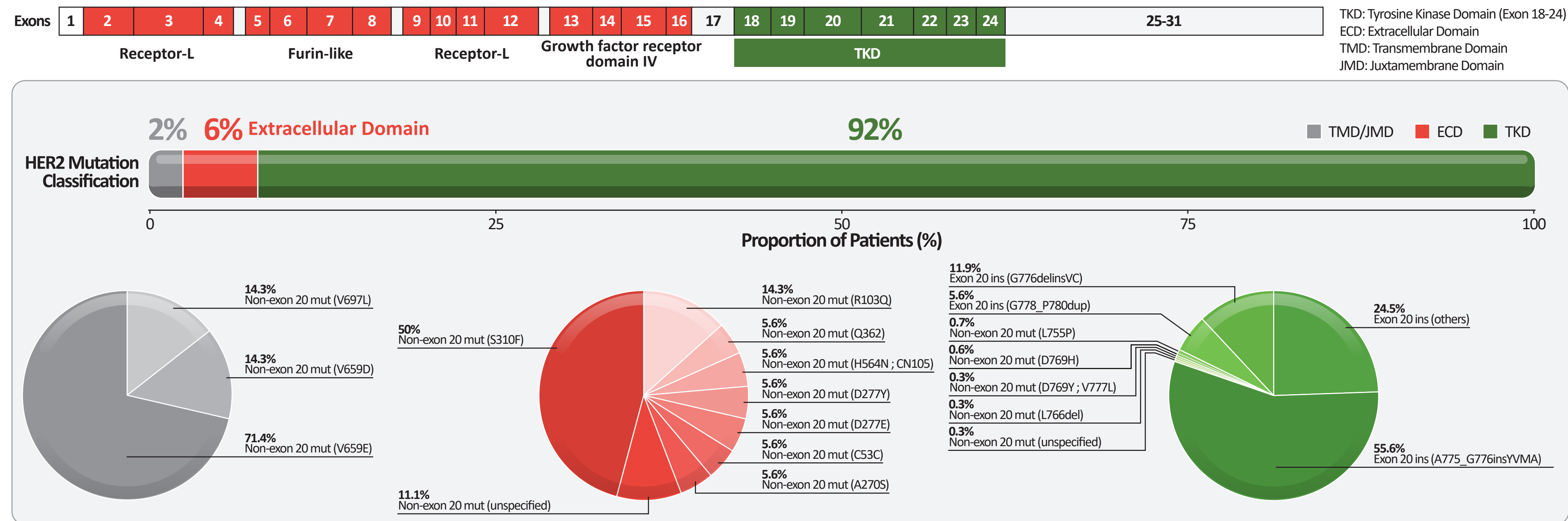


Figure 3. Overall survival by TP53 co-mutation status. Patients with TP53 co-mutation had significantly shorter median OS.

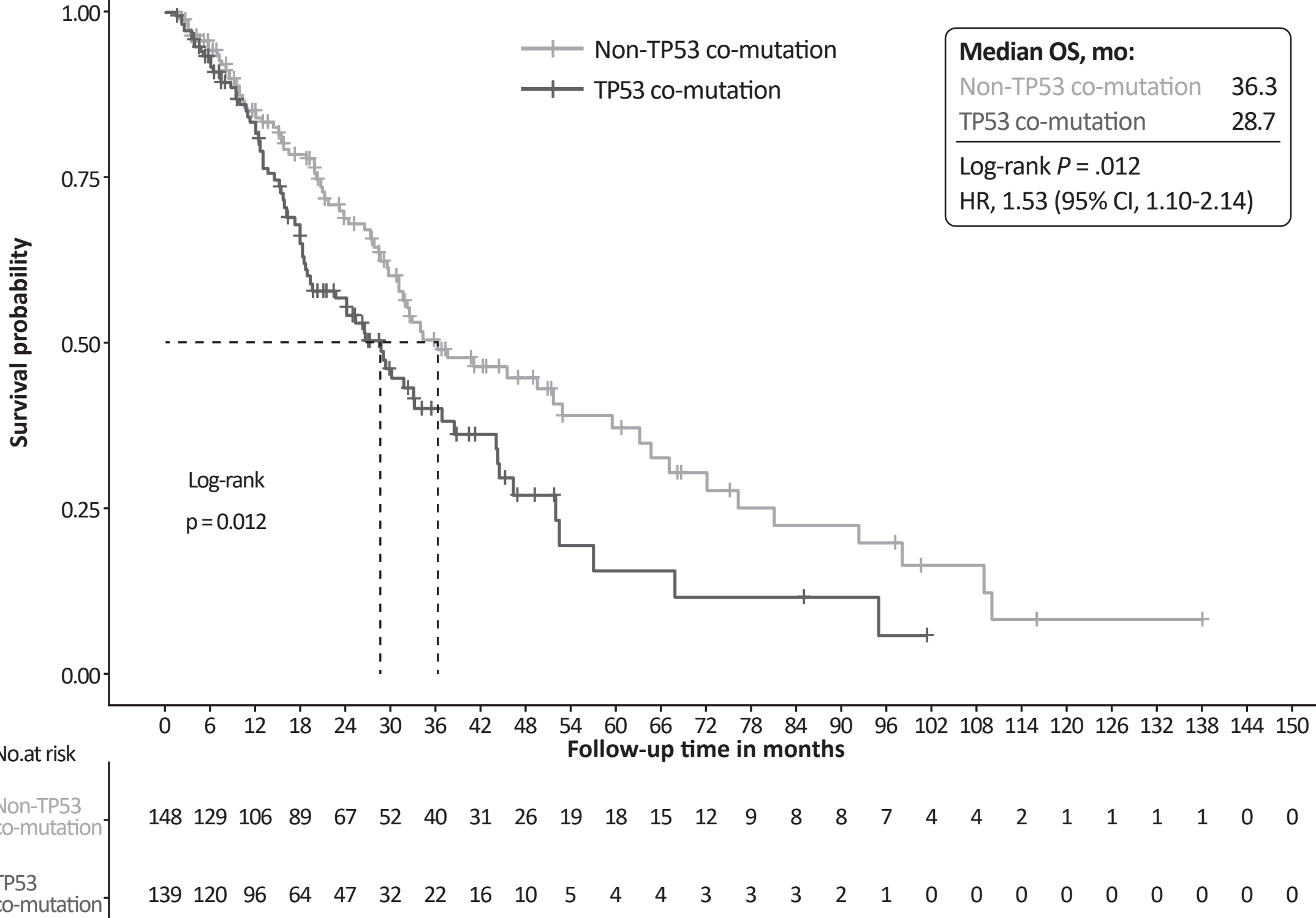


Figure 4. First-line PFS by treatment modality in de novo HER2-mutant NSCLC*

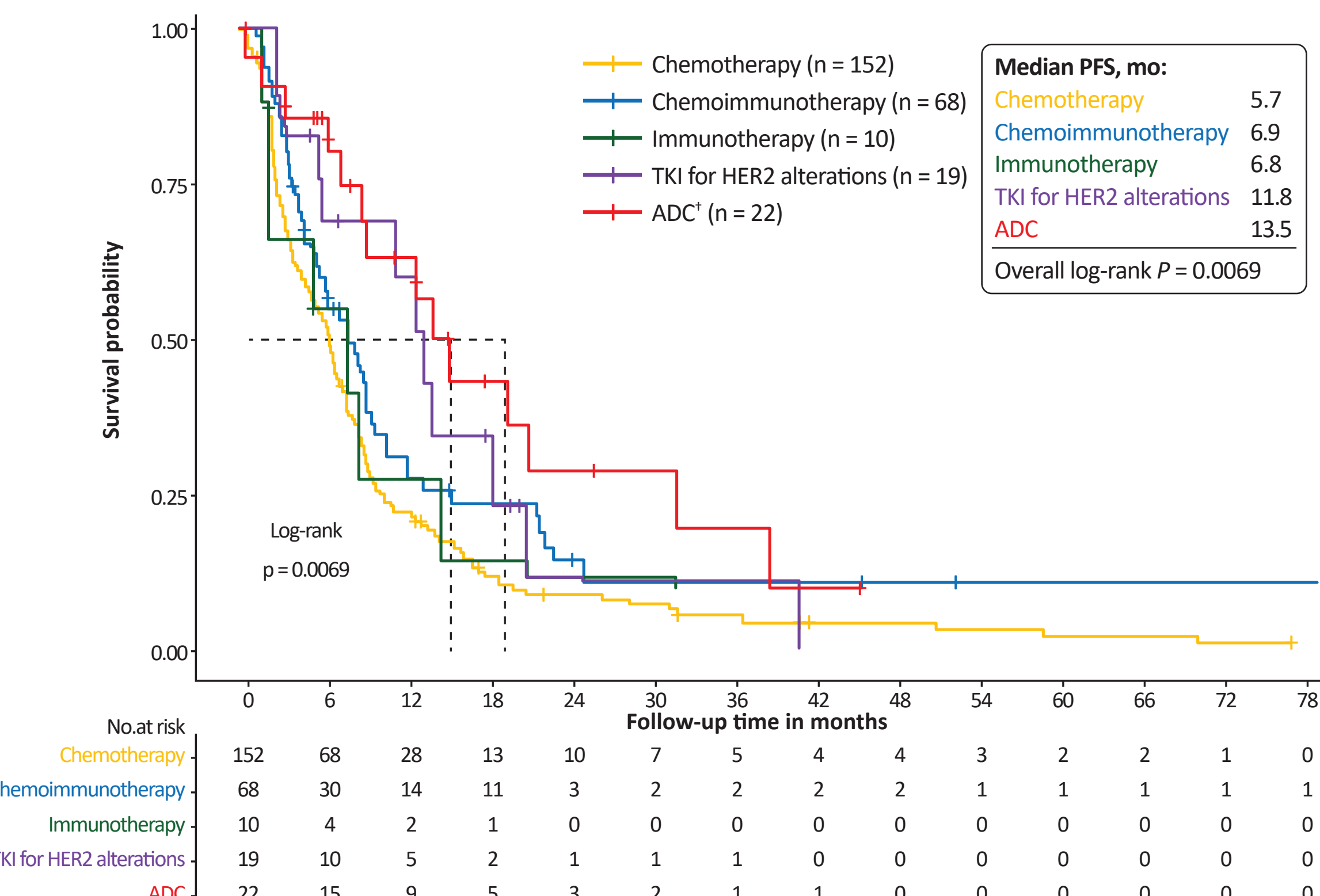


Figure 5. First- to second-line treatment sequencing patterns.

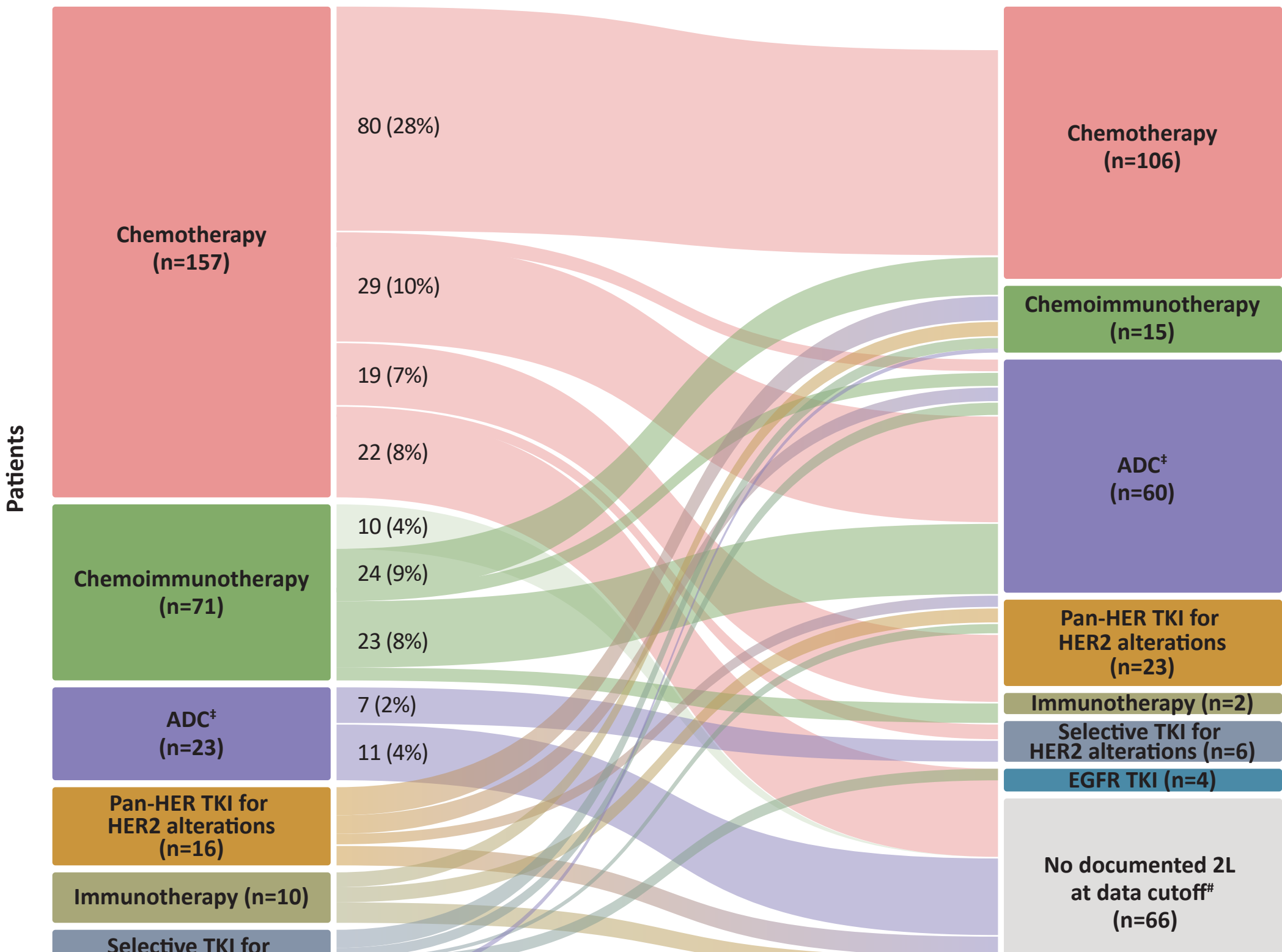
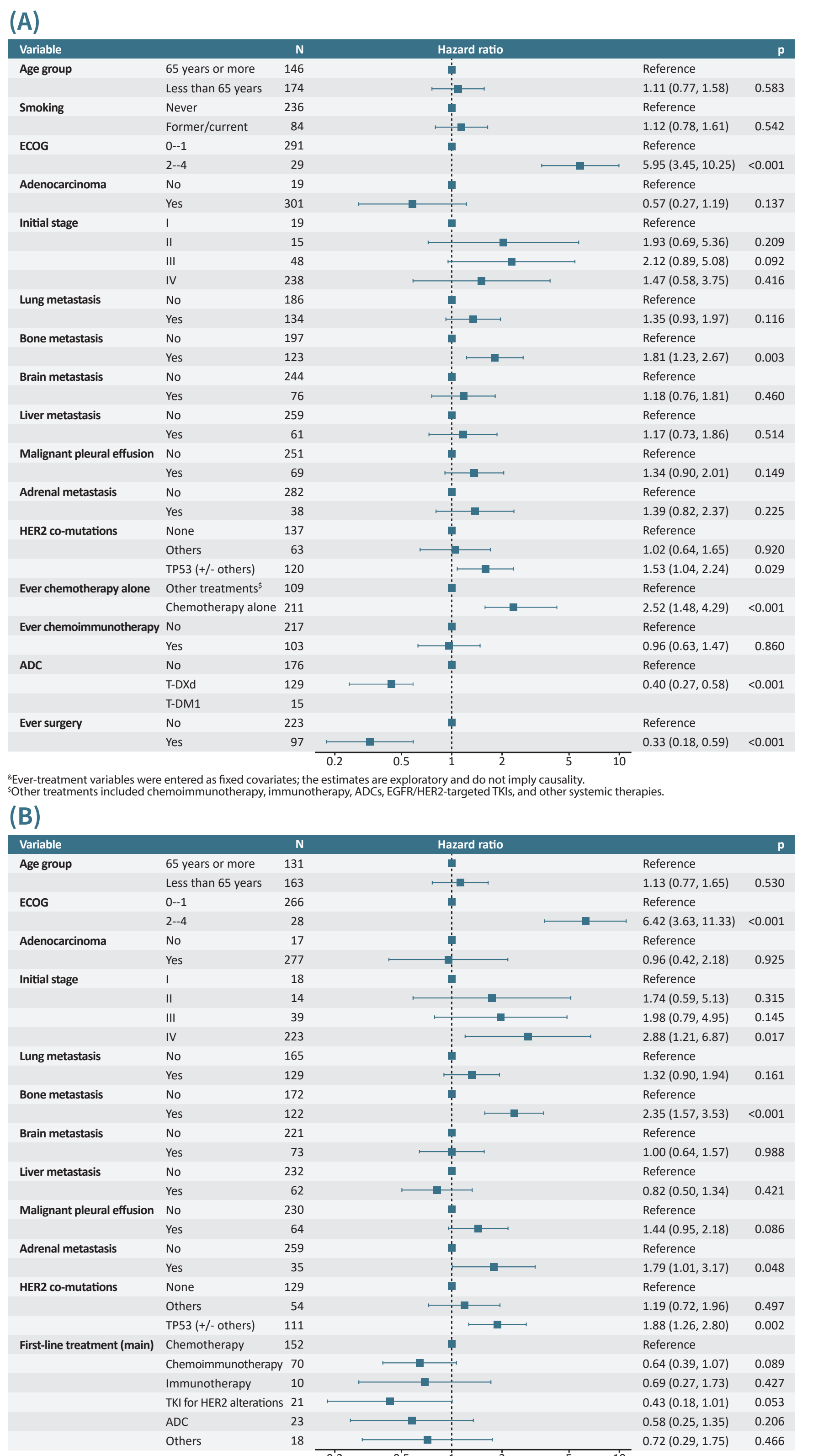


Figure 6. Multivariable factors associated with OS: (A) HER2-mutant cohort*; (B) de novo HER2-mutant first-line cohort



REFERENCES & ACKNOWLEDGEMENTS

Abbreviations

1L, first-line; 2L, second-line; ADC, antibody–drug conjugate; aHR, adjusted hazard ratio; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; TROP2, trophoblast cell-surface antigen 2.

Key References

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Artificial Intelligence (AI) Use Disclaimer

No AI tool was used to generate or alter the study data or perform the statistical analyses.

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