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INTRODUCTION

- HER2-directed therapies have demonstrated clinical activity in *HER2* mutated lung adenocarcinoma, with limited data specifically in benefit for HER2 overexpressing non-small cell lung cancer (NSCLC)
- Squamous cell carcinoma (SCC) remains largely underrepresented in key trials
- Prevalence of this therapeutic target in NSCLC remains poorly characterized
- The aim of this study was to evaluate *HER2* alterations by IHC, FISH and NGS testing to characterize their prevalence and concordance in adenocarcinoma and SCC

METHODS

Design:

- Retrospective analysis of 9,669 NSCLC samples

Procedures:

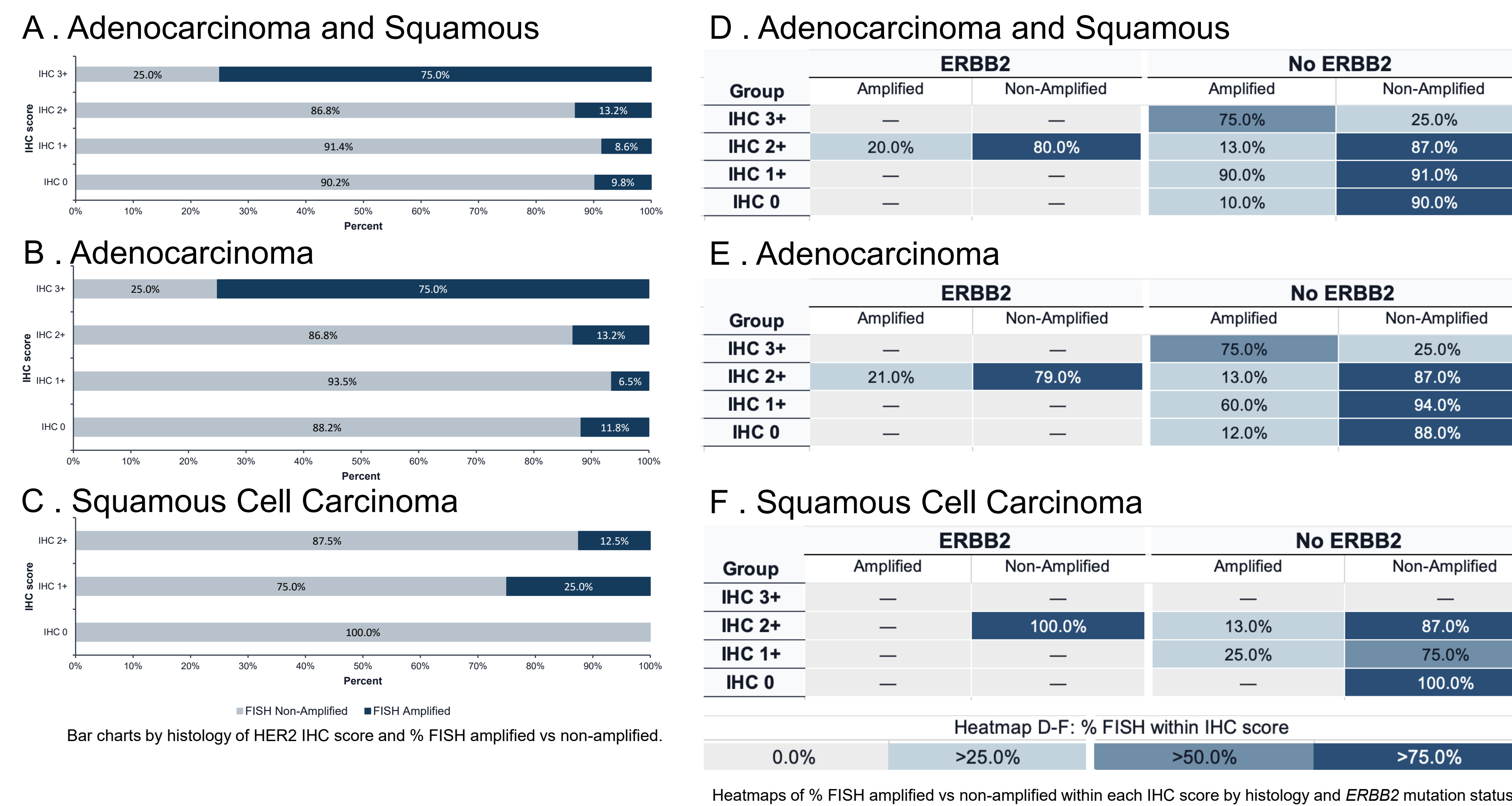
- HER2 protein expression by immunohistochemistry (IHC) using ASCO/CAP breast cancer scoring guidelines (0/1+/ 2+/ 3+)
- HER2* amplification (amp) by fluorescence in situ hybridization (FISH; HER2/CEP17 $\geq$ 2.2)
- Next-generation sequencing (NGS) to identify *HER2* mutations

Statistical Analysis:

- Pearson's chi-squared Test or Fisher's Exact Test depending on cell count

RESULTS

Figure 1. Concordance between HER2 IHC score and FISH amplification status by histology and *ERBB2* mutation status.



- Co-occurring HER2 amplification by FISH was present in 6 of 8 (75.0%) IHC 3+ cases and 147 of 1,117 (13.2%) IHC 2+ cases
- ERBB2* mutation status and amplification generally identify different tumor populations.

Figure 3. Site of *ERBB2* Mutational Domains in (A) Adenocarcinoma (n=107) and (B) Squamous cell carcinoma (n=6)

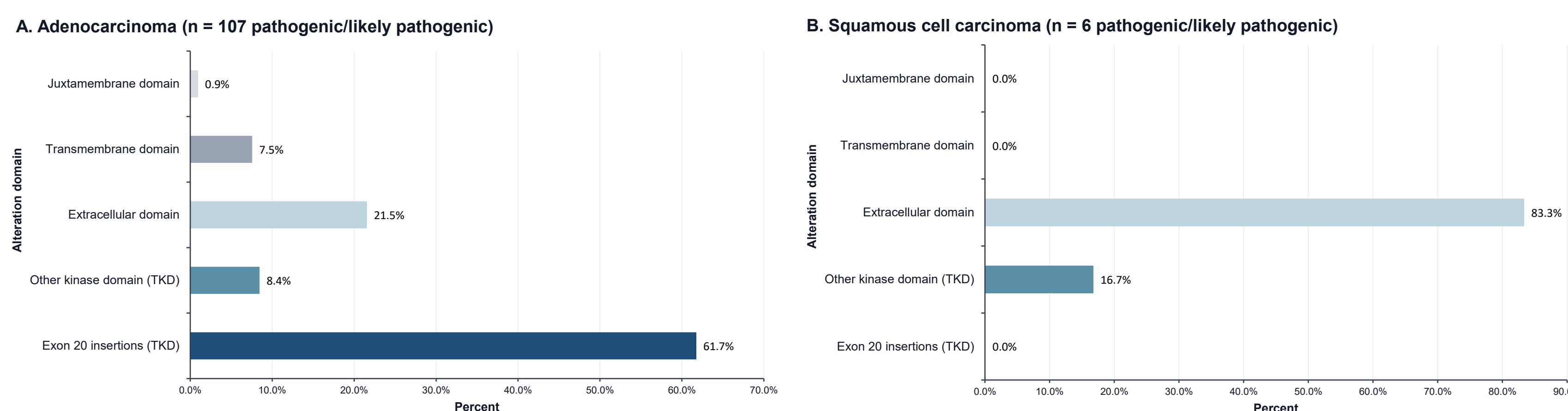


Figure 2. Overlap of HER2 alterations across testing modalities.

9,669 unique specimens were identified

All underwent NGS:

- 4,702 (50.0%) had evaluable IHC
- 3,985 (42.4%) underwent FISH
- 1,401 (14.9%) were tested by all three modalities

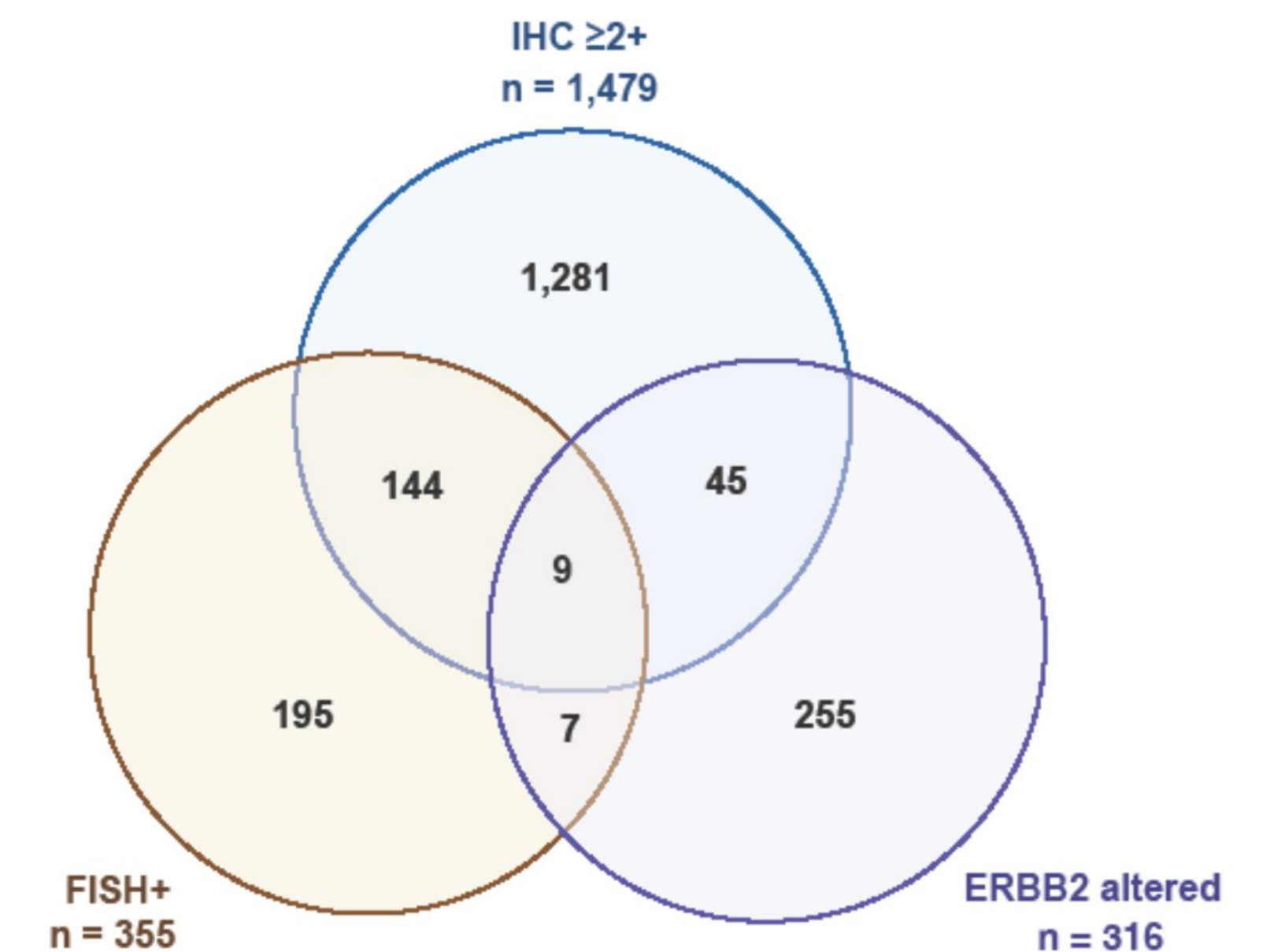
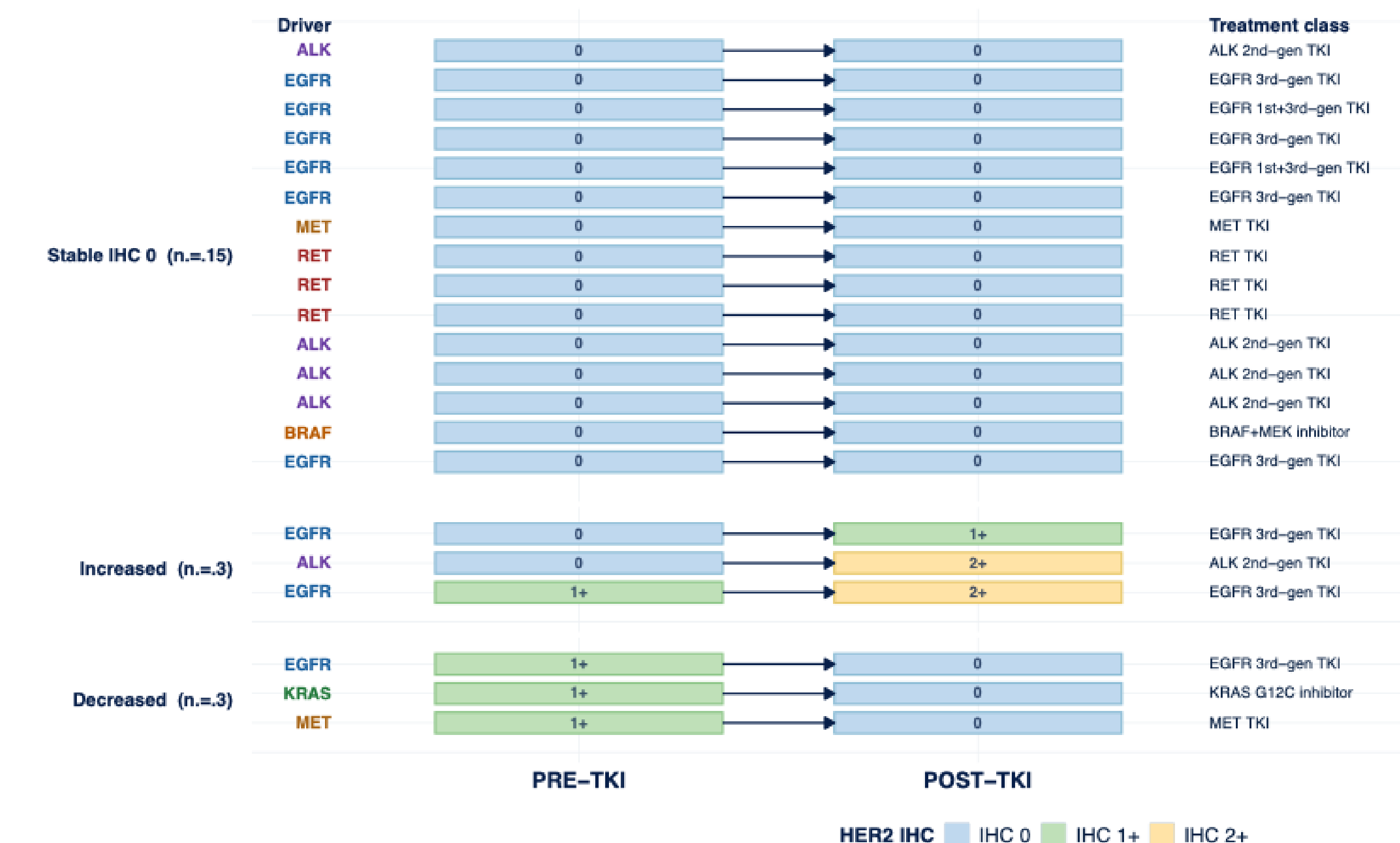


Figure 4. Patient-level paired HER2 IHC changes before and after TKI exposure in an independent institutional cohort.



DISCUSSION AND CONCLUSION

- HER2 is not a single biomarker in NSCLC. Overexpression, amplification and mutations represent distinct patient populations and occur more frequently in adenocarcinoma than in SCC.**
- ERBB2* mutational domains differed by histology.** *ERBB2* exon20 insertions were most common in adenocarcinoma and absent in SCC; however, extracellular domain mutations were present in SCC.
- Testing modality as well as histology should be considered when considering HER2 status and selecting HER2-directed therapies.

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