

P2.142: Dynamic Changes and Clinical Significance of HER2 Expression Pre- and Post-Treatment in Non-Small Cell Lung Cancer

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INTRODUCTION

Human epidermal growth factor receptor 2 (HER2) overexpression is an important oncogenic driver mutation in non-small cell lung cancer (NSCLC). The accelerated FDA approval of trastuzumab deruxtecan (T-DXd) for unresectable or metastatic HER2-positive (IHC 3+) solid tumors has opened new therapeutic avenues for NSCLC. However, the dynamic changes of HER2 expression throughout treatment and its role in therapeutic resistance remain unclear.
Objective Compare paired HER2 IHC before treatment and at progression after TKI versus chemoimmunotherapy, and assess associations with acquired resistance.

METHODS

RETROSPECTIVE · SINGLE CENTER · PAIRED BIOPSIES

1 PATIENT COHORT

107 unresectable NSCLC cases with matched pre-/post-treatment specimens (biopsy or cytology)

2 GROUP

TKI-resistant group (TKI group) N=71
Chemoimmunotherapy-resistant group (Chemo/IO group) N=36

3 HER2 IHC SCORING

≥2 pathologists
ASCO/CAP gastric criteria for biopsy specimen
Positive—IHC 1+/2+/3+
Negative—IHC 0 or nuclear or cytoplasmic staining

4 PAIRED ANALYSIS

Expression change | negative → positive conversion
Treatment and histology associations

DISCUSSION AND CONCLUSION

- HER2 expression exhibited temporal heterogeneity, with status changes occurring after both chemoimmunotherapy and TKI therapy, more frequently following TKI therapy.
- HER2 upregulation may represent a bypass resistance mechanism when classic EGFR on-target mutations are absent.
- Reassessment of HER2 expression using re-biopsy at progression is suggested for selecting patients eligible for HER2-targeted therapy.
- Nuclear/cytoplasmic staining was enriched in SqCC; its biological and clinical significance remains uncertain.

REFERENCES & ACKNOWLEDGEMENTS

References

1. Wang H, Sun W, Wang C, et al. Comprehensive Analysis of HER2 status Heterogeneity Using Matched Samples among Potential Beneficiaries of Trastuzumab Deruxtecan Therapy in Non-Small Cell Lung Cancer. Clin Lung Cancer. 2026 Apr;27(3):201-211.e1. doi: 10.1016/j.clcc.2025.11.015. Epub 2025 Nov 21. PMID: 41391966.
2. Pittiyarachchi O, Tan AC. Trastuzumab deruxtecan in HER2 overexpressing non-small cell lung cancer (NSCLC). Transl Lung Cancer Res. 2025 Feb 28;14(2):314-322. doi: 10.21037/tlcr-24-968. Epub 2025 Feb 24. PMID: 40114960; PMCID: PMC11921179.
3. Takezawa K, Pirazzoli V, Arcila ME, et al. HER2 amplification: a potential mechanism of acquired resistance to EGFR inhibition in EGFR-mutant lung cancers that lack the second-site EGFR T790M mutation. Cancer Discov. 2012 Oct;2(10):922-33. doi: 10.1158/2159-8290.CD-12-0108. Epub 2012 Sep 5. PMID: 22956644; PMCID: PMC3473100.
4. Lin Y, Xue Q, Zhang B, et al. Clinicopathologic and prognostic value of HER2 alterations in non-small cell lung cancer. Respir Res. 2026. doi:10.1186/s12931-026-03864-3
5. Yoshizawa A, Sumiyoshi S, Sonobe M, et al. HER2 status in lung adenocarcinoma: a comparison of immunohistochemistry, fluorescence in situ hybridization (FISH), dual-ISH, and gene mutations. Lung Cancer. 2014 Sep;85(3):373-8. doi: 10.1016/j.lungcan.2014.06.007. Epub 2014 Jul 7. PMID: 25047676.
6. Ohashi K, Ninomiya K, Yoshioka H, et al. Impact of HER2 expression on EGFR-TKI treatment outcomes in lung tumors harboring EGFR mutations: A HER2-CS study subset analysis. Lung Cancer. 2020 Dec;150:83-89. doi: 10.1016/j.lungcan.2020.09.024. Epub 2020 Oct 1. PMID: 33096420.

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The authors used ChatGPT only for language polishing and grammar checking during the writing of this work. No artificial intelligence tools were employed for research design, data analysis, interpretation of findings, or conclusion generation. The authors assume full responsibility for all scientific content and the final manuscript.

RESULTS

Table 1. Clinicopathologic and molecular characteristics of patients according to treatment group

Characteristic	Overall (n=107)	TKI (n=71)	Chemo/IO (n=36)
Age, years, median (range)	65 (35-86)	64 (44-86)	65 (35-80)
Sex, n (%)			
Male	65 (60.7%)	32 (45.1%)	33 (91.7%)
Female	42 (39.3%)	39 (54.9%)	3 (8.3%)
Histology, n (%)			
Adenocarcinoma (AC)	74 (69.2%)	60 (84.5%)	14 (38.9%)
Squamous cell carcinoma (SqCC)	22 (20.6%)	5 (7.0%)	17 (47.2%)
Other	11 (10.3%)	6 (8.5%)	5 (13.9%)
Pre-treatment HER2 IHC pattern, n (%)			
0 (including nuclear/cytoplasmic staining)	62 (57.9%)	33 (46.5%)	29 (80.6%)
1+	31 (29.0%)	27 (38.0%)	4 (11.1%)
2+	14 (13.1%)	11 (15.5%)	3 (8.3%)
3+	0 (0.0%)	0 (0.0%)	0
Post-treatment HER2 IHC pattern, n (%)			
0 (including nuclear/cytoplasmic staining)	63 (58.9%)	35 (49.3%)	28 (77.8%)
1+	32 (29.9%)	27 (38.0%)	5 (13.9%)
2+	9 (8.4%)	6 (8.5%)	3 (8.3%)
3+	3 (2.8%)	3 (4.2%)	0

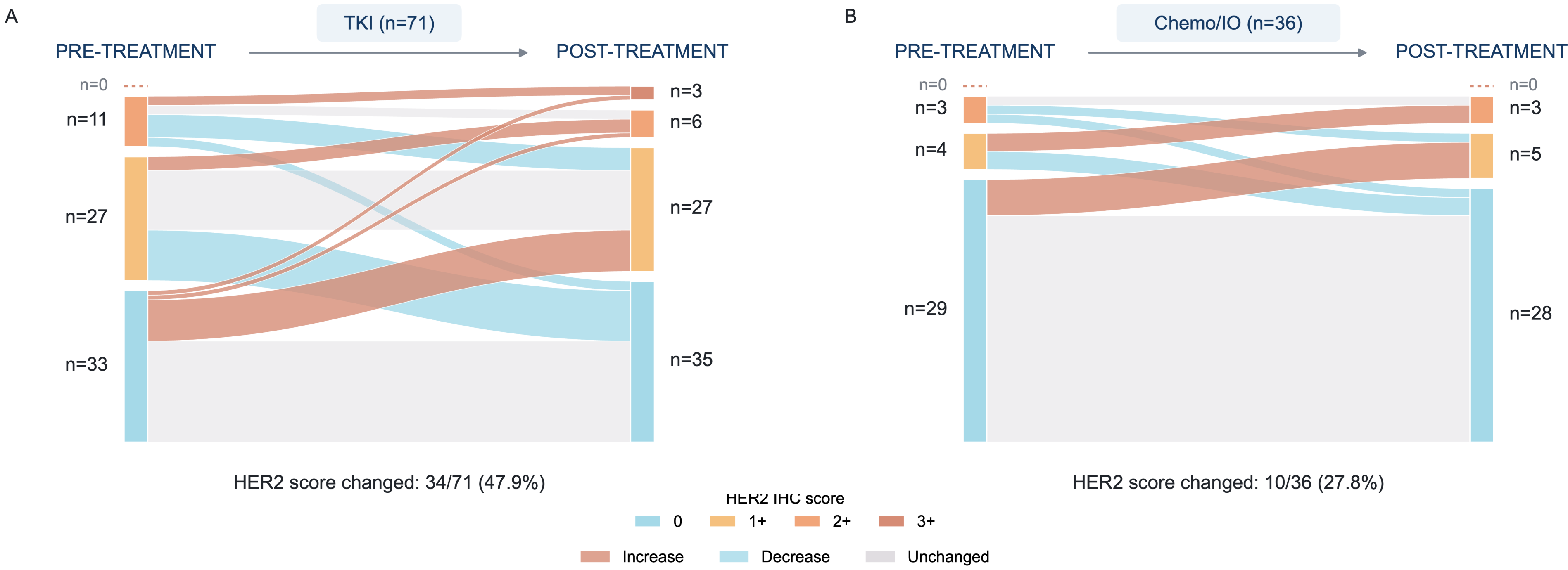


Fig.1 Dynamic changes in HER2 expression from pre- to post-treatment

All HER2 IHC 3+ cases (n=3) occurred in patients with disease progression in the TKI group; baseline HER2 IHC was 2+, 2+, and 0, respectively.

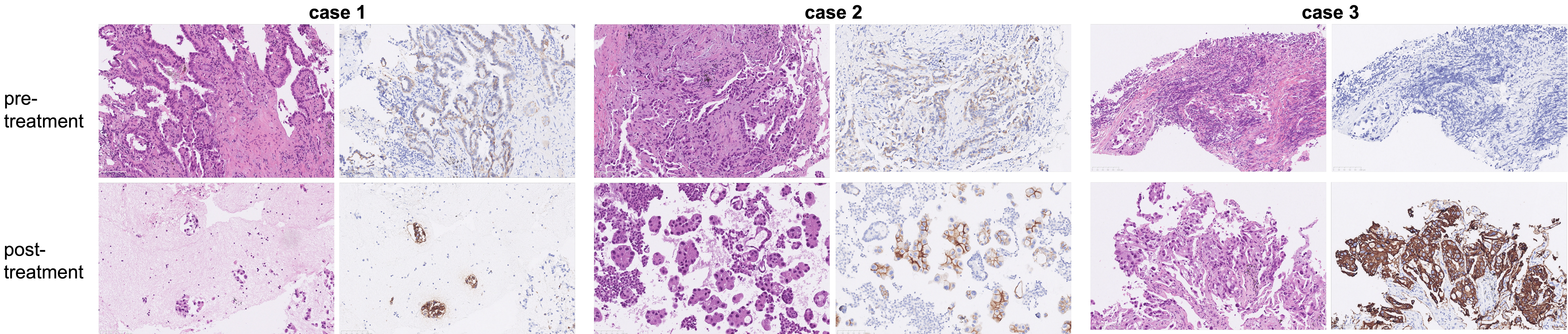


Fig.3 Representative paired cases showing conversion to HER2 IHC 3+ at progression. Case 1 changed from HER2 IHC 2+ to 3+; Case 2 changed from HER2 IHC 2+ to 3+; Case 3 changed from HER2 IHC 0 to 3+.

1. HER2 expression changed more frequently in the TKI than in the Chemo/IO group (47.9% vs 27.8%; P=0.046), and in AC than in SqCC group (48.6% vs 4.5%; P<0.001).
2. Among pre-treatment HER2-negative patients, 33.3% (11/33) in the TKI group converted to HER2-positive at disease progression, showing an increasing trend compared with the Chemo/IO group (4/29, 13.8%; P=0.07)
3. In HER2-negative patients resistant to EGFR-TKIs without T790M or C797S mutations, 39.1% (9/23) converted to HER2-positive, which was significantly higher than that in the Chemo/IO group (13.8%; P=0.036)
4. HER2 nuclear and/or cytoplasmic staining was more frequently observed in SqCC (7/22, 31.8%) than in AC (2/74, 2.7%; P<0.001)

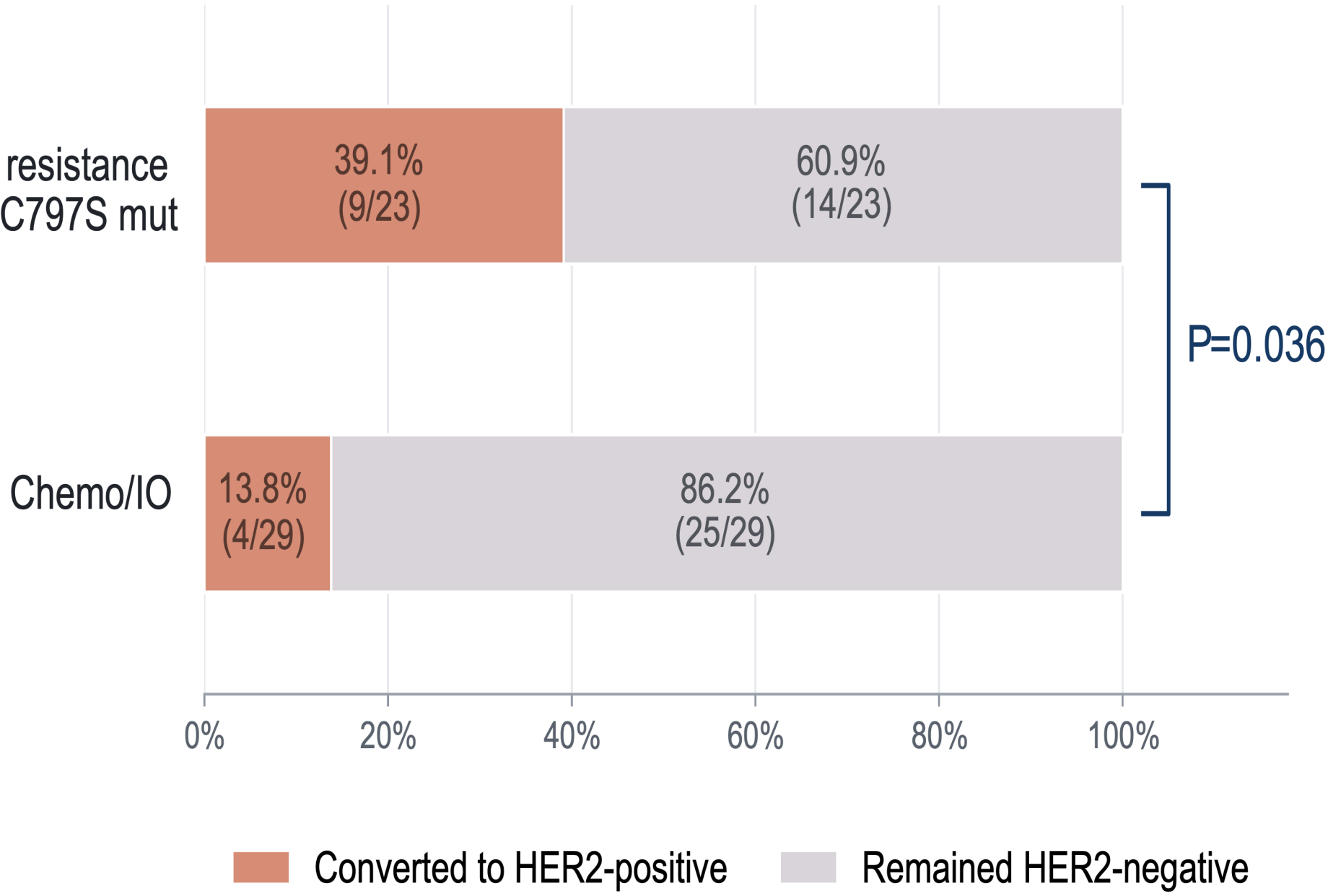


Fig.2 HER2-positive conversion at progression