HER2-status assesment with High-Affinity Probes

Rationale: Current HER2 status assessment using the companion diagnostic antibody (clone 4B5, Ventana) does not always align with observed patient responses to the antibody-drug conjugate Trastuzumab deruxtecan (T-Dxd) or other HER2 targeted therapies. To address this inconsistency, new HER2 classifications (e.g., HER2 low and ultra-low) have been introduced, highlighting the need for more precise and functionally relevant diagnostic tools.

Method: We developed High-Affinity Probes (HAPs) to enable precise detection of the Trastuzumab binding site on fixed tumor samples. HAPs are engineered molecular tools with exceptional specificity and sensitivity, designed to provide *in situ* quantification of therapeutic binding site accessibility and density across a wide range of therapeutic molecules.

Results: Staining patterns and intensities obtained using Trastuzumab HAPs were fundamentally different from conventional HER2 staining with the 4B5 clone, with no apparent correlation between the two methods. This discrepancy underscores the need for further clinical validation to evaluate the predictive value of Trastuzumab HAPs in identifying patients likely to respond to HER2-targeted therapies.

Conclusion: Existing CDx methods may not accurately reflect the therapeutic binding potential of Trastuzumab in all patients, potentially leading to suboptimal treatment decisions. Trastuzumab HAPs may offer additional insights into HER2-binding site accessibility. Future clinical validation is warranted to determine their role in patient stratification.

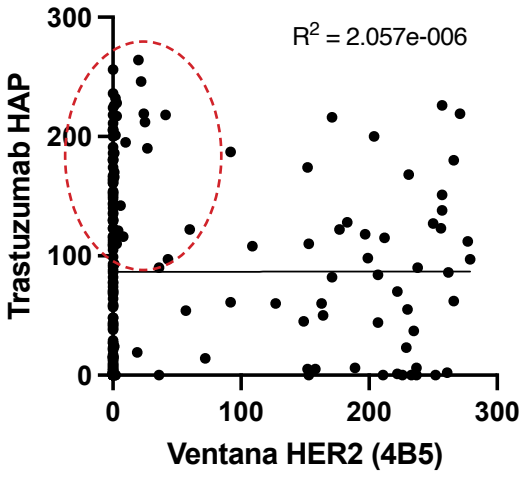

Fig. 1: Correlation analysis of Trastuzumab HAP and HER2 (4B5) H-Scores in matched breast cancer cases (n =204). Red circle indicates the HER2 low/ultra-low group that still shows significant signal with Trastuzumab HAP.

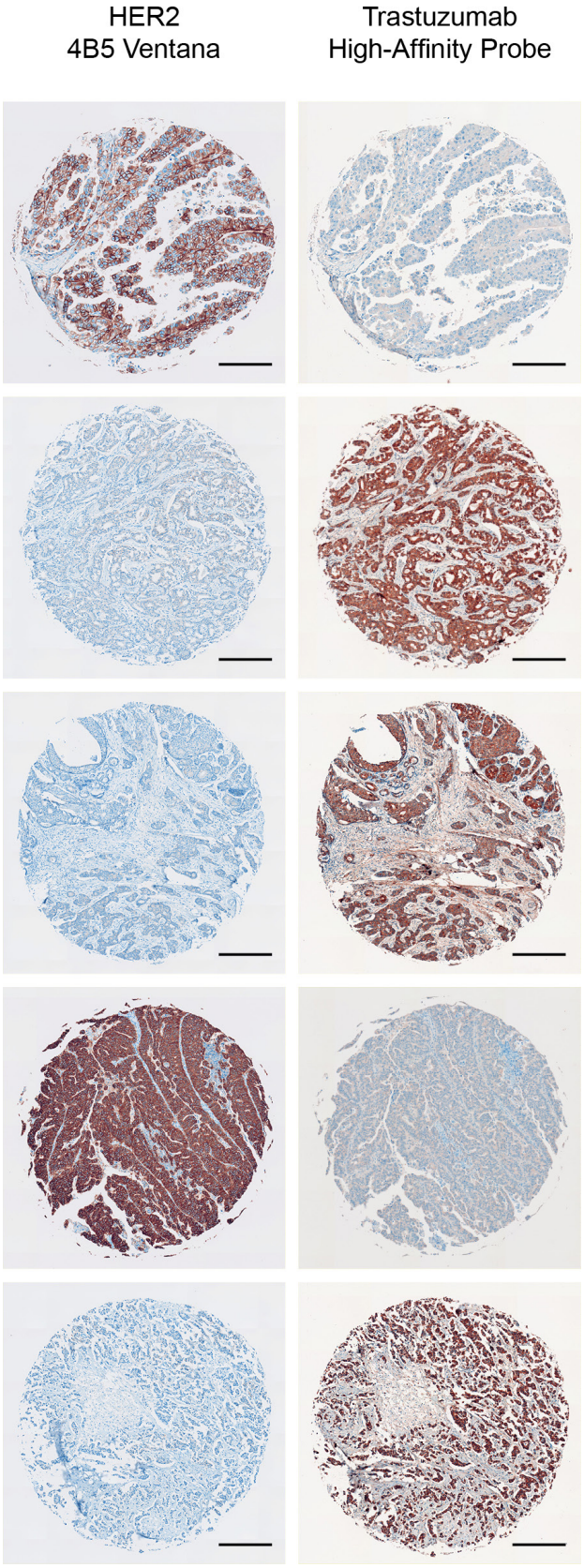

Fig. 2: Staining intensity and distribution of selected breast cancer cores from the screening cohort. Some cases show strong 4B5 staining while showing very little to no binding affinity to Trastuzumab. Cores with low or ultra-low HER2 4B5 scores still show high binding affinity for Trastuzumab as assessed via HAPs.

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