Poster 48

Prevalence of HER2-ultralow Among Advanced Breast Cancer Patients with Historical IHC 0 Status

Anushree Iyengar, MPH[1], Sandhya Mehta, MS, PhD[2], Hannah Barman, PhD[1], Nivedita Rangarajan, MS[1], Sue-Ann Woo, PhD[2], Simone T. Sredni, MD, PhD[3], Rosemarie Di Donato, MD[3], Safak Simsek[1], Erinn P. Downs, DO[4], Aziza Nassar, MD, MPH[5], Darren M. Wilson, PA, BRMP[6], Katherine Krieser, MSc[6], Elise Bieri Patzke, MA, CSM[6], Natalie Kyek, PMP[6], Jason Hipp, MD, PhD[6], Tyler Wagner, PhD[1]

[1]Inference, Inc., Cambridge, MA; [2]Daiichi Sankyo, Inc., Basking Ridge, NJ; [3]AstraZeneca, LLC, Gaithersburg, MD; [4]Mayo Clinic, Scottsdale, AZ; [5]Mayo Clinic, Jacksonville, FL; [6]Mayo Clinic, Rochester, MN

Objective

- To assess the prevalence of HER2-ultralow expression in patients with advanced BC based on re-scored HER2 IHC 0 biopsy slides

Conclusions

- About 3 in 5 advanced BC patients originally classified as HER2 IHC 0 met the HER2-ultralow criteria by at least one pathologist, implying that significant number of additional patients may benefit from HER2 targeted therapy.
- The relatively low concordance between HER2 expert pathologists in identifying lower levels of HER2 expression suggests the need for increased precision enabled by digital tools, leveraging AI, training for community practice pathologists, and continuing to follow best practice recommendations in determining HER2 IHC status.

Plain language summary

Why did we perform this research?
Advanced breast Cancer patients historically classified as IHC 0 but who meet HER2-ultralow criteria (very low levels of HER2 protein expression detected) can also benefit from HER2-targeted therapy - trastuzumab deruxtecan.[1] This study aimed to assess the prevalence of HER2-ultralow expression among US patients with advanced BC historically classified as IHC 0.

How did we perform this research?
This retrospective study was conducted using archived HER2 IHC 0 biopsy samples from 300 advanced BC patients identified using EHR data (Jan 2017-Jan 2023) from 3 Mayo Clinic sites in the US. One biopsy slide per patient was digitized, scanned, and independently re-scored by two Mayo Clinic pathologists.

What were the findings of this research and what are the implications?
About 3 in 5 advanced BC patients originally classified as HER2 IHC 0 met HER2-ultralow criteria as reviewed by at least one pathologist, implying that significant number of additional patients may benefit from HER2 targeted therapy. As expected, relatively low concordance was observed between pathologists in identifying lower levels of HER2 expression suggesting the need for development of best practices, more training and leveraging AI assisted digital tools for classification of lower levels of HER2 expression.

References

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Abbreviations

AI, artificial intelligence; ASCO-CAP, American Society of Clinical Oncology–College of American Pathologists; BC, breast cancer; EHR, electronic health record; HER2, human epidermal growth factor receptor 2; HR, Hormone Receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; US, United States.

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Corresponding author email address: sandhya.mehta@daiichisankyo.com

Introduction

- Historically, patients with BC were classified as HER2-positive (IHC 3+ or IHC 2+/ISH+) or HER2-negative (IHC 0, IHC 1+ and IHC 2+/ISH-)[1]
- The recent approval of trastuzumab deruxtecan (T-DXd) based on DESTINY-Breast06 and DESTINY-Breast04 clinical trials is leading to reconsideration of the HER2-negative spectrum to include HER2-low (IHC1+ or IHC 2+/ISH-), HER2-ultralow (IHC 0 with membrane staining) and IHC 0 with no membrane staining.[2-3]
- With the advent of T-DXd as a treatment option for this patient population, it is crucial to determine the prevalence of HER2-ultralow in the U.S. for personalized treatment strategies.

Methods

- A retrospective study was conducted for patients with advanced BC (stages III-IV) who had HER2-stained tissue biopsies documented as IHC 0 within Mayo Clinic Electronic Medical Records (EMR) data between 2017-2023
- Of all advanced BC patients with available biopsies, the most recent biopsy slides from any local or metastatic tissue/site (one per patient) for 300 patients were selected for analysis.
- Patients who received systemic treatment for another primary cancer (except non-melanoma skin cancer), participated in a clinical trial, had <2 clinical visits or had a record of HER2-positive criteria during the study observation period (January 2018–January 2023) were excluded.
- One biopsy slide per patient (IHC assay: VENTANA Pathway anti-HER2/neu (4B5) Rabbit Monoclonal Primary Antibody) was digitized and scanned at 40x magnification and 0.26µm/pixel scan resolution leveraging dynamic Z-stacks of each high-power field for real-time focus assessment and continual refinement.
- Two board-certified pathologists from Mayo Clinic (who were blinded to the previous interpretations of each specimen) independently scored and reported HER2 status and tumor stain percentage for each slide based on 2023 ASCO-CAP guidelines.[3]
- Patients were considered HER2-ultralow if their biopsy slide was scored as IHC 0 with (1-10%) membrane staining.
- Cohen's κ was used to quantify agreement between pathologists.

Results

- A total of 300 patients were identified and re-scored. Most (97%, n=292) had IHC 0 documentation within 30 days of the reviewed biopsy slide.
- The mean (SD) patient age was 57.8 (13.5) years, and most patients were White (89%). Majority were HR+ (63.67%) with median no. of metastatic sites 3.0 [2.0, 4.0].
- Most patients (95%, n=285) remained classified as IHC 0 (either HER2-ultralow or no observable staining) by at least one pathologist. Of these, 60% (n=171) were determined as HER2 ultra-low by at least one pathologist (**Figure 1**). HER2-ultralow prevalence per pathologist ranged from 43% to 45% (**Figure 1**).
- The overall inter-pathologist concordance rate was 57% (**Table 1**). Patients with no observable HER2 IHC staining accounted for 61% of the concordant patients (n/N=104/171; **Table 1**).

Figure 1. Estimated HER2 Ultra-low Prevalence Among Patients With IHC 0 Advanced BC

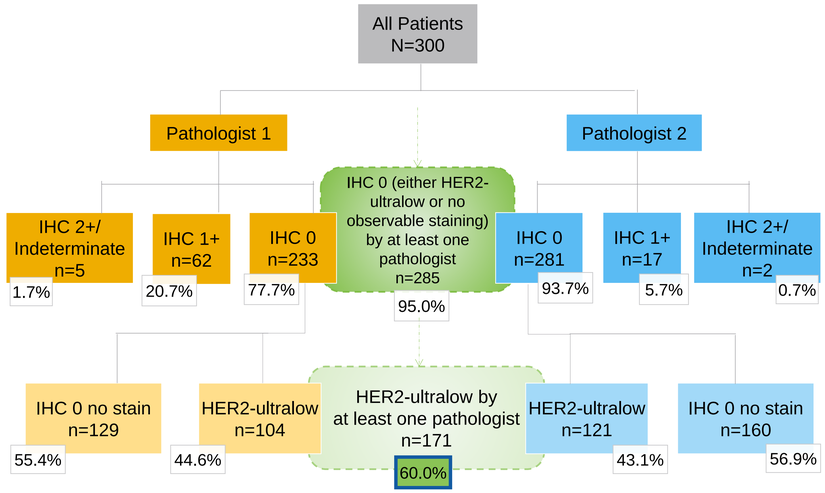

Table 1. Concordance Among Pathologists' Review of IHC Biopsy Slides[a]

	Pathologist 2 (P2) (n=300)				
Pathologist 1 (P1) (n=300)	**P2 IHC 0 with no observable IHC staining**	**P2 HER2-ultralow (IHC 0 with membrane staining)**	**P2 IHC 1+**	**P2 IHC2+/ Indeterminate**	**P1 Total**
P1 IHC 0 with no observable IHC staining	**104 κ=0.47**	**23**	**2**	**0**	**104**
P1 HER2-ultralow (IHC 0 with membrane staining)	**48**	**54 κ=0.17**	**2**	**0**	**129**
P1 IHC 1+	**7**	**44**	**11 κ=0.21**	**0**	**62**
P1 IHC 2+/ Indeterminate	**1**	**0**	**2**	**2 κ=0.57**	**5**
P2 Total	**121**	**160**	**17**	**2**	**300**
			Concordance		**171 (57%)**
			Discordance		**129 (43%)**

Figure 2. Slide Images (unanimously scored by all pathologists as: A) having no observable staining; B) HER2-ultralow (annotated staining with arrows); C) IHC 1+