HER2 expression is Associated with Pathologic Complete Response to Neoadjuvant Chemo-Immunotherapy among Patients with Stage 1-3 TNBC

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Presentation ID: PS4-10-04

Introduction

- Novel antibody-drug conjugates have brought significant attention to HER2-low expression as a critical predictive biomarker.
- Evidence supporting HER2-low breast cancer as distinct biological subtype remains limited.
- We demonstrated that HER2-low triple-negative breast cancer (TNBC) exhibits a unique immune-evasive epigenetic and transcriptomic profile compared to HER2-zero[1].
- In this study, we aimed to assess the clinical response of patients with early-stage TNBC to neoadjuvant chemotherapy and immunotherapy (chemo-IO) based on HER2 status.

Methods

- Adult female patients (age 18 and older) with stage 1-3 TNBC treated with chemo-IO at the University of California Los Angeles (UCLA) and Duke Health between 6/2021-5/2024 were included.
- HER2 status was stratified as: HER2-zero (IHC 0) versus HER2-low (IHC 1+ or 2+, FISH non-amplified), or HER2 0 vs. HER2 1+ vs. HER2 2+.
- Primary outcome: pathologic complete response (pCR) rate by HER2 status.
- Univariate and multivariate logistic regression used to estimate the association between patient and tumor factors and pCR.
- Given the modest sample size, bootstrapping simulation analysis (1,000 iterations) was performed to estimate the underlying population pCR rates more robustly.

[1]Bedoya-López AF*, Ahn S*, Ensenyat-Mendez M, et al. Epigenetic determinants of an immune-evasive phenotype in HER2-low triple-negative breast cancer. *NPJ Precis Oncol*. 2025 Aug 16;9(1):287

Results

- 165 patients included: HER2-zero, n=50; HER2-low, n=115, **Table 1.**
- Median age was 55 years [IQR 45-64].
- No differences in patient or tumor characteristics noted between groups, except for race and ethnicity.
- Patients of self-reported Black race had the highest proportion of HER2-low TNBC (88.4%) compared to White (66.7%), Asian (71.4%), and Hispanic (44.4%) patients, p=0.001.

Table 1. Clinicopathologic Characteristics by HER2 status

	All Patients (N=165)	HER2 Status			HER2 Status			
		Zero (N=50)	Low (N=115)	P-Value	0 (N=50)	1+ (N=72)	2+ (N=43)	P-Value
Age (Years) – Median (IQR)	55 (45 - 64)	53.5 (41 - 65)	56 (46 - 64)	0.31	53.5 (41 - 65)	52 (45 - 64.5)	59 (51 - 64)	0.21
Race and Ethnicity				**0.001**				**0.007**
Hispanic	18 (10.9%)	10 (20%)	8 (7%)		10 (20%)	5 (6.9%)	3 (7%)	
Non-Hispanic Asian	14 (8.5%)	4 (8%)	10 (8.7%)		4 (8%)	4 (5.6%)	6 (14%)	
Non-Hispanic Black	43 (26.1%)	5 (10%)	38 (33%)		5 (10%)	26 (36.1%)	12 (27.9%)	
Non-Hispanic Other	3 (1.8%)	3 (6%)	0 (0%)		3 (6%)	0 (0%)	0 (0%)	
Non-Hispanic White	81 (49.1%)	27 (54%)	54 (47%)		27 (54%)	33 (45.8%)	21 (48.8%)	
Unknown	6 (3.6%)	1 (2%)	5 (4.3%)		1 (2%)	4 (5.6%)	1 (2.3%)	
Clinical T Category				0.27				0.17
cT0/IS	1 (0.6%)	0 (0%)	1 (0.9%)		0 (0%)	1 (1.4%)	0 (0%)	
cT1	30 (18.2%)	10 (20%)	20 (17.4%)		10 (20%)	9 (12.5%)	11 (25.6%)	
cT2	113 (68.5%)	30 (60%)	83 (72.2%)		30 (60%)	56 (77.8%)	27 (62.8%)	
cT3	19 (11.5%)	9 (18%)	10 (8.7%)		9 (18%)	6 (8.3%)	4 (9.3%)	
cT4	2 (1.2%)	1 (2%)	1 (0.9%)		1 (2%)	0 (0%)	1 (2.3%)	
Clinical N Category				0.76				0.79
cN0	91 (55.2%)	25 (50%)	66 (57.4%)		25 (50%)	38 (52.8%)	28 (65.1%)	
cN1	56 (33.9%)	20 (40%)	36 (31.3%)		20 (40%)	25 (34.7%)	11 (25.6%)	
cN2	7 (4.2%)	2 (4%)	5 (4.3%)		2 (4%)	4 (5.6%)	1 (2.3%)	
cN3	11 (6.7%)	3 (6%)	8 (7%)		3 (6%)	5 (6.9%)	3 (7%)	
Stage				0.37				0.3
1B	17 (10.3%)	5 (10%)	12 (10.4%)		5 (10%)	6 (8.3%)	6 (14%)	
2B	72 (43.6%)	17 (34%)	55 (47.8%)		17 (34%)	31 (43.1%)	24 (55.8%)	
3B	53 (32.1%)	20 (40%)	33 (28.7%)		20 (40%)	25 (34.7%)	8 (18.6%)	
3C	23 (13.9%)	8 (16%)	15 (13%)		8 (16%)	10 (13.9%)	5 (11.6%)	
Pathological Complete Response				0.15				0.32
Yes	95 (57.6%)	33 (66%)	62 (53.9%)		33 (66%)	40 (55.6%)	22 (51.2%)	
No	70 (42.4%)	17 (34%)	53 (46.1%)		17 (34%)	32 (44.4%)	21 (48.8%)	

- Tumor size did not show a significant association with pCR rate (p=0.25), while higher clinical nodal category was associated with a lower rate of pCR to chemo-IO (cN1: 67.9%; cN2: 42.9%; cN3: 18.2%; p=0.02, **Table 2**).
- Although not statistically significant, HER2 status was associated with a clinically meaningful difference in pCR rate, with HER2-low TNBC tumors exhibiting lower rates of pCR (53.9%) compared to HER2-zero (66.0%), **Table 1**.
- Increasing HER2 expression also correlated with lower rates of pCR, with a gradual decrease in response to chemo-IO with increasing HER2 expression: HER2 0: **66.0%,** HER2 1+: **55.6**%, HER2 2+: **51.2%, Table 1**).
- A bootstrap simulation confirmed the robustness of these estimates: HER2-zero: **65.6%,** 95% CI 51.9-78.5%; HER2-1+: **55.6%**, 95% CI 44.3-67.5%; HER2-2+: **51.0%,** 95% CI 36.1-65.9%; **Figure 1**).

Table 2. Pathologic Complete Response rate by Clinical T and Clinical N category

	Clinical T Category						Clinical N Category				
	cT0/IS (N=1)	cT1 (N=30)	cT2 (N=113)	cT3 (N=19)	cT4 (N=2)	P-Value	cN0 (N=91)	cN1 (N=56)	cN2 (N=7)	cN3 (N=11)	P-Value
Pathological Complete Response						0.25					**0.02**
Yes	0 (0%)	18 (60%)	68 (60.2%)	9 (47.4%)	0 (0%)		52 (57.1%)	38 (67.9%)	3 (42.9%)	2 (18.2%)	
No	1 (100%)	12 (40%)	45 (39.8%)	10 (52.6%)	2 (100%)		39 (42.9%)	18 (32.1%)	4 (57.1%)	9 (81.8%)	

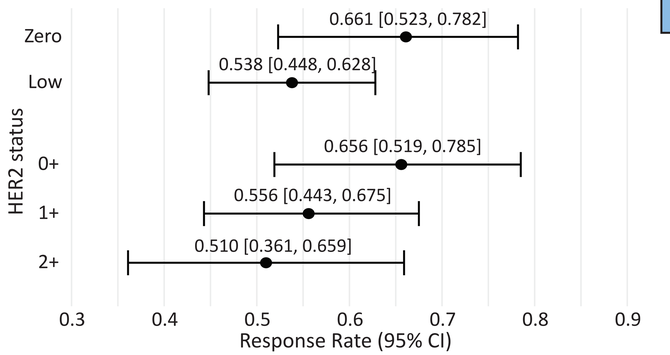


Figure 1. Bootstrapped pCR rates and confidence intervals by HER2 status, including HER2-low vs zero, and HER2-zero, HER2-1+, and HER2-2+ without FISH amplification

Conclusions

- While our analysis was underpowered to detect statistically significant differences due to the modest sample size, **the observed 12.1% absolute decrease in pCR for HER2-low TNBC tumors suggests a clinically meaningful result**.
- Furthermore, higher HER2 expression appeared to correlate with decreasing pCR rates among HER2-low tumors.
- Our results provide clinical evidence that HER2-low TNBC may be a distinct subtype less responsive to standard of care chemo-IO.
- These results underscore the need for expanded patient cohorts to further validate these associations and guide the development of tailored therapeutic strategies for this purported unique TNBC subgroup.

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Abstract Number: 1220

Presentation ID: PS4-10-04