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Correlation between trophoblast cell-surface antigen-2 (Trop-2) expression and pathological complete response (pCR) in HER2-positive early breast cancer (EBC): An exploratory analysis of the PHERGain trial

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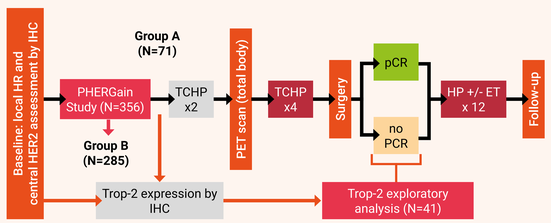
Background

- The human trophoblast cell-surface antigen-2 (Trop-2) is a transmembrane protein that is overexpressed in most cases of breast cancer (BC), with the highest expression in triple-negative breast cancer (TNBC). This expression is linked to increased aggressiveness of the tumor, metastasis, and poor prognosis [1,2].
- In Human Epidermal Growth Factor Receptor 2-positive (HER2+) tumors, the expression of Trop-2 has been shown to be the lowest [1,3].
- Antibody-drug conjugates (ADC) targeting Trop-2 are currently being developed for the treatment of BC, particularly TNBC and Hormone Receptor-positive (HR+) BC, with Sacituzumab Govitecan already approved for these tumors [4]. However, the prognostic and predictive role of Trop-2 in patients with HER2+ BC is still unknown, and to date, no studies have been specifically conducted to explore the benefit of Trop-2 targeted therapies in this tumor subtype.
- Here, we retrospectively analyzed Trop-2 expression and its correlation with clinicopathologic features as well as the pathological complete response (pCR) in HER2+ early BC patients treated with standard-of-care neoadjuvant therapy in the PHERGain study [5].

Study design

- This is an exploratory analysis of the PHERGain phase II trial, a randomized, non-comparative, open-label, strategy-based, response-adapted study for de-escalating neoadjuvant therapy in HER2+ BC patients based on early metabolic response using ^{18}F-FDG-PET and pCR **(Figure 1).**
- The analysis was performed in a cohort of 41 patients from PHERGain's Group A, who were treated with neoadjuvant therapy with docetaxel, carboplatin, trastuzumab, and pertuzumab.

Figure 1. Study design of Trop-2 exploratory analysis



Patients and Methods

Pathological evaluation of HR, HER2, and Trop-2 status

- Estrogen Receptor (ER) and Progesterone Receptor (PgR) were locally assessed, whereas HER2 status was centrally assessed according to the 2018 ASCO/CAP criteria, all of them at baseline in PHERGain trial.
- Baseline Trop-2 expression was centrally assessed by immunohistochemistry (IHC) (SP293, Abcam; Benchmark platform; Ventana Medical Systems, Inc, Tucson, Arizona). Trop-2 expression was first classified into expressing (Trop-2-positive) or not-expressing (Trop-2-negative) tumors. Then, it was classified according to the different expression levels (H-score) into low (0-9), intermediate (10-49), and high (≥50).
- The association between Trop-2 and pCR was analyzed with logistic regression models including patient characteristics. The predictive value in terms of area under the curve (AUC) was calculated using 10 repeated 5-fold cross-validation.

pCR definition and assessment

- pCR was defined as disappearance of invasive disease in the breast and axilla (ypT0/is ypN0) as determined by a local pathologist using the recommendations from the Breast International Group-North American Breast Cancer Group [6].

Results

- Among the 41 patients included, 31.7% (13/41) had node-positive disease, 63.4% (26/41) were ER-positive, and 78.0% (32/41) had HER2 3+ protein expression by IHC.
- A total of 28 (68.3%) of the tumors were Trop-2-positive and 13 (31.3%) were Trop-2-negative **(Table 1)**. Of these, 17/41 (41.46%), 14/41 (34.15%), and 10/41 (24.40%) tumors were classified as low, intermediate, and high expression groups.
- No statistically significant relationship was found between Trop-2 expression and different clinicopathologic features **(Table 1).**
- The association between pCR status and presence/absence of Trop-2 expression showed a lower percentage of Trop-2-positive patients achieving a pCR compared to Trop-2-negative patients (50.0% vs. 92.3%; [OR 0.05, 95% CI 0.002-0.36]; p adjusted =0.012) **(Figure 2).**

Results

Table 1. Patients' clinicopathologic characteristics

N (%)	Total (N=41)	Trop-2-negative (N=13)	Trop-2-positive (N=28)	P- value
Stage				
I	8 (19.5%)	2 (15.4%)	6 (21.4%)	
II	28 (68.3%)	10 (76.9%)	18 (64.3%)	0.780
IIIA	5 (12.2%)	1 (7.7%)	4 (14.3%)	
Node status				
Negative	28 (68.3%)	10 (76.9%)	18 (64.3%)	0.493
Positive	13 (31.7%)	3 (23.1%)	10 (35.7%)	
ER status				
Negative	15 (36.6%)	4 (30.8%)	11 (39.3%)	0.734
Positive	26 (63.4%)	9 (69.2%)	17 (60.7%)	
PgR				
Negative	24 (58.5%)	5 (38.5%)	19 (67.9%)	0.098
Positive	17 (41.5%)	8 (61.5%)	9 (32.1%)	
HER2				
2+ (FISH/ISH amplified)	9 (22.0%)	2 (15.4%)	7 (25.0%)	0.692
3+	32 (78.0%)	11 (84.6%)	21 (75.0%)	
SUVmax baseline				
Median (range)	10 (3.6-31.0)	8.7 (4.1-21.0)	10 (3.6-31.0)	0.404

- Trop-2 expression by H-score subgroups showed an inverse proportional correlation with pCR, with higher pCR rates in the low expression group compared to the intermediate (OR 0.12, 95% CI 0.01-0.83, p adjusted =0.045), and high (OR 0.03, 95% CI 0.001-0.29, p adjusted =0.009) Trop-2 expression groups **(Figure 3).**
- The logistic regression model including H-score and patient characteristics for predicting pCR presented a bias corrected AUC of 0.72 (95% CI, 0.67-0.76) **(Figure 4).**

Figure 2. Association between pCR status and Trop-2 expression

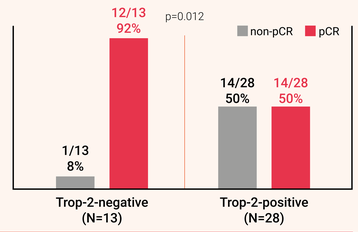


Figure 3. Association between pCR status and Trop-2 expression by H-score groups

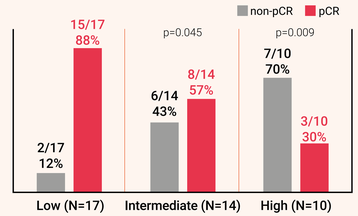
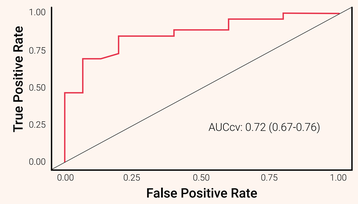


Figure 4. ROC – Multivariate logistic regression model



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Conclusion

These findings suggest a potential role of Trop-2 expression as a biomarker of resistance to neoadjuvant dual HER2 blockade in combination with chemotherapy and may be considered a strategic target for future combinations in HER2-positive early BC patients.

Scan here to view a plain language summary of this trial.

HR: hormone receptor; **HER2:** human epidermal growth factor receptor-2; **IHC:** immunohistochemistry; **TCHP:** Trastuzumab, pertuzumab, docetaxel, and carboplatin; **pCR:** pathological complete response; **H:** trastuzumab; **P:** pertuzumab; **ET:** endocrine therapy; **SUVmax:** maximum standardized uptake value; **AUCcv:** cross-validated AUC; **AUC:** Area under receiving-operating characteristic curve.