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Validation of a genomic assay in early-stage HER2+ breast cancer treated with trastuzumab and pertuzumab (HP): a correlative analysis from PHERGain phase II trial

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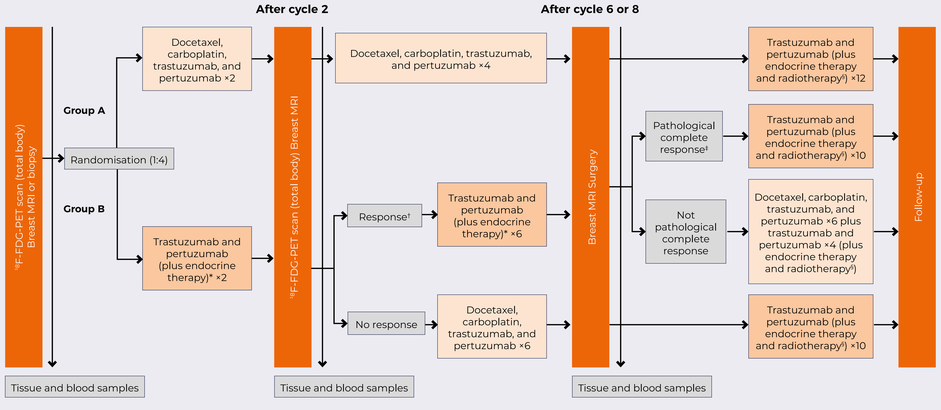
Background

- HER2DX is a 27-gene test for patients with early-stage HER2+ breast cancer[1].
- Here, we evaluated the ability of HER2DX risk score and pathological complete response (pCR) score to predict outcomes following (neo)adjuvant HP-based therapy.

Methods

- HER2DX was evaluated retrospectively on baseline pre-treatment Formalin-Fixed Paraffin-Embedded (FFPE) core tumor biopsies from the PHERGain phase II clinical trial (NCT03161353) **(Figure 1)[2].**
- This was an unplanned exploratory analysis. Primary objective was the association of HER2DX with pCR (ypT0/is ypN0). With 292 samples, the statistical power was >85% expecting an odds-ratio of 1.25 with HER2DX as a continuous variable.
- The association of HER2DX risk-score with 3-year invasive disease-free survival (iDFS) was an exploratory objective. Of note, patients with Residual Disease (RD) did not receive adjuvant T-DM1.

Figure 1. PHERGain study design.



18F-FDG-PET=18F-fluorodeoxyglucose-PET. *Patients with hormone receptor-positive early breast cancer allocated to group B received endocrine therapy concomitantly (except when on chemotherapy). Endocrine therapies given were letrozole for postmenopausal women and tamoxifen for premenopausal women. †Patients who were responders, according to adapted European Organization for the Research and Treatment of Cancer criteria, had a reduction in maximum standardised uptake value ≥40% from baseline after cycle 2. ‡Patients who obtained a pathological complete response (ypT0/is ypN0). §Endocrine therapy and radiotherapy administered as per hormone receptor status and institutional practices, respectively.

Results

- HER2DX was evaluated in 292 of 356 (82.0%) tumors **(Table 1).** Median patient follow-up was 3.6 years.
- HER2DX pCR score as a continuous and categorical variable was significantly associated with pCR in univariate and multivariate logistic regression analyses **(Table 2, Table 3, Figure 2).**
- 3-year iDFS data was available for 272 patients. Eleven out of 12 iDFS events (92%) occurred in patients with RD **(Figure 3).** Twelve out of 12 patients (100%) with an event had HER2DX high-risk disease **(Figure 4).**
- Within patients with RD, HER2DX low-risk showed a numerically better 3-year iDFS (100% vs 89.8%) than HER2DX high-risk (hazard ratio [HR]=2.70) **(Figure 5).**

Table 1. Patients characteristics

Treatment group	n	%
Overall	292	82%
Group A	55	19%
Group B	237	81%
Group B PET-responder	187	79%
Group B PET-non-responder	50	21%
Tumor stage		
cT1	45	15%
cT2	199	68%
cT3	48	16%
Nodal status		
cN0	144	49%
cN1	130	45%
cN2	18	6%
Hormone receptor status		
Negative	98	34%
Positive	194	66%
pCR rates based on treatment		
Overall	111	38%
Group A	31	56%
Group B	80	34%
Group B PET-responder	66	35%
Group B PET-non-responder	14	28%

Table 2. HER2DX pCR score (continuous variable) vs pCR

HER2DX pCR score	Odds ratio per 10-unit increase	p-value
Univariate	1.31 (1.15-1.50)	<0.001
Multivariate*	1.29 (1.10-1.54)	<0.001

Table 3. HER2DX pCR score (categorical variable) vs pCR

HER2DX pCR score		Odds ratio per 10-unit increase	p-value
Univariate	Low	Reference	-
	Medium	1.85 (0.96-3.63)	0.069
	High	3.37 (1.82-6.45)	<0.001
Multivariate*	Low	Reference	-
	Medium	1.84 (0.95-3.63)	0.080
	High	3.27 (1.54-7.09)	<0.001

* after adjusting for treatment and clinic-pathological factors such as hormone receptor status, treatment group, and PET response.

Figure 2. pCR rates across HER2DX pCR score groups

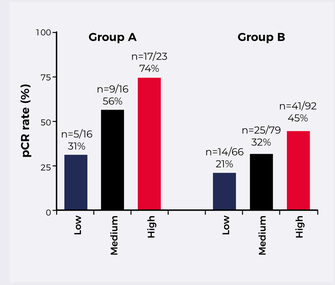


Figure 4. HER2DX risk score in patients with and without relapse at 3 years

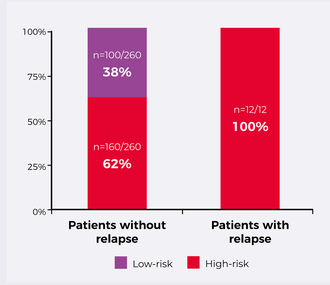


Figure 3. 3-year iDFS by pCR status in all patients with HER2DX determination

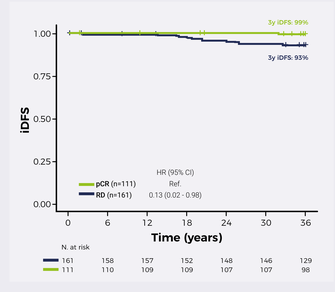
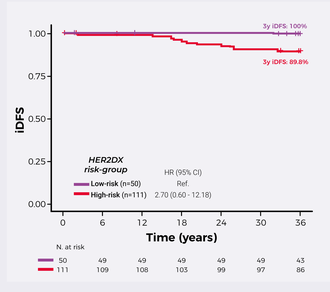


Figure 5. Patients with RD: 3-year iDFS by HER2DX risk score



Conclusions

- HER2DX pCR score reliably predicts pCR after HP-based therapy.
- HER2DX risk-score identifies patients with RD and a low risk of recurrence.
- HER2DX offers personalized insights for HER2+ breast cancer treatment, especially with HP-based therapy.

References: **1. Prat et al.**, EBioMedicine. 2022 Jan;75:103801. doi: 10.1016/j.ebiom.2021.103801. **2. Pérez-García et al.**, Lancet Oncol. 2021 Jun; 22(6):858-871. doi: 10.1016/S1470-2045(21)00122-4

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Conflicts of interest of the presenting author: **Consulting/Advisor:** Roche, AstraZeneca, Seagen, Daiichi Sankyo, Eli Lilly, Merck Sharp&Dohme, GSK, Gilead, Menarini, ExactSciences, Novartis, Pfizer, Gilead; **Honoraria:** Roche, Novartis, Pfizer, Lilly, Daiichi Sankyo; **Research funding to the Institution:** Roche, AstraZeneca, Eisai, F. Hoffman-La Roche, Guardant Health, Merck Sharp&Dohme, Pfizer, Pique Therapeutics, Puma C, Queen Mary University London; **Stock:** Initia Research; **Travel, accomodations, expenses:** Roche, Novartis, Eisai, Pfizer, Daiichi Sankyo, AstraZeneca, Gilead; **Patents:** HER2 as a predictor of response to dual HER2 blockade in the absense of cytotoxic therapy. Aleix Prat, Antonio Llombart, Javier Cortés. US 2019/0338368 A1.

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

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