AACR ANNUAL MEETING - April 5-10, 2024. Published Abstract Number: 5213

Evaluation of HER2DX risk-score in residual disease (RD) from HER2-positive (HER2+) early breast cancer (EBC) patients (pts) following neoadjuvant trastuzumab and pertuzumab (HP)-based therapy: An exploratory analysis from the PHERGain trial

José Manuel Pérez-García[1,2], Fara Brasó-Maristany[3,4], Elena Martínez-García[1], Carmen Mora Gallardo[1], Eileen Shimizu[1], Olga Boix[1], Jose Rodríguez-Morató[1], Mario Mancino[1], Laia Paré[4], Guillermo Villacampa[4], Mercedes Marín-Aguilera[4], Patricia Galván[3,4], Ana Vivancos[5], Patricia Villagrasa[4], Joel Parker[6], Charles M Perou[6], Antonio Llombart-Cussac[1,7], Javier Cortés[1,2,8], Aleix Prat[3,4,9,10,11]

1. Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain and Ridgewood, New Jersey, USA; 2. International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Barcelona, Spain; 3. Translational genomics and targeted therapies in solid tumors, Institut D'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain; 4. Reveal Genomics S L, Barcelona, Spain; 5. Cancer Genomics Group, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; 6. Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, US; 7. Hospital Arnau de Vilanova, Valencia, Spain; Universidad Católica de Valencia, Valencia, Spain; 8. Universidad Europea de Madrid, Madrid, Spain; 9. Cancer Institute and Blood Diseases, Hospital Clinic de Barcelona, Barcelona, Spain; 10. Department of Medicine, University of Barcelona, Barcelona, Spain; 11. Institute of Oncology (IOB)-Hospital Quirónsalud, Barcelona, Spain

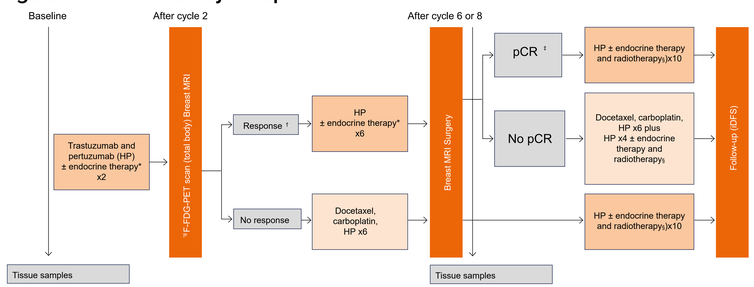
Background

- RD after neoadjuvant anti-HER2-based therapy is associated with worse outcomes.
- HER2DX is a predictive (pathological complete response [pCR] score) and prognostic (risk-score) genomic assay validated in baseline (BL) tumor samples from HER2+ EBC pts[1].
- We hypothesis that changes in HER2DX risk-score at RD may provide additional prognostic information on the development of distant recurrences.

Methods

- This retrospective analysis included 14 pts from group B of the PHERGain trial (NCT03161353).
- Group B pts had centrally confirmed, stage I-IIIA, HER2+ EBC and were treated with HP (± endocrine therapy), with chemotherapy added for pts without PET response 2 HP-cycles or pCR after surgery[2] (**Figure 1**).
- From the 14 pts, 6 developed distant recurrences after 3-year follow-up (invasive Disease-Free Survival [iDFS] event) and 8 matched controls did not.
- HER2DX was evaluated on tumor samples collected before treatment initiation (BL) and at surgery (RD).
- The primary objective was to determine the association of HER2DX risk-score in RD with the development of distant recurrences.
- Seconday objective was to identify changes in gene expression changes and in HER2DX gene signatures in BL vs RD, and their association with distant recurrences.
- Cox regression models evaluated the association of variables with distant recurrence. Paired SAM with a false discovery rate <5% identified differences in gene expression between BL and RD samples.

Figure 1. PHERGain study Group B



¤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

- Median follow-up was 4.04 years.
- Five (83.3%) of 6 pts with distant recurrences had HER2DX high-risk scores at BL. The 8 control pts had HER2DX high-risk scores at BL but no relapse.
- In RD, all 6 pts (100%) who relapsed had a HER2DX high-risk score, while 4 (50%) of 8 pts without distant recurrence presented a HER2DX downstaging (**Figure 2**).
- Pts with HER2DX low-risk in RD had better 3-year distant disease-free survival than high-risk pts (100% vs 50%; hazard ratio = 4.34 [1.03-18.23], p=0.045) (**Figure 3**).
- In RD, high expression of proliferation genes and low expression of immune and luminal genes was associated with a higher risk of recurrence (iDFS) (**Figure 4**).
- In paired analyses of BL and RD samples, 94 genes (50.3%) were differentially expressed in pts that did not relapse, while only 7 genes (3.7%) were differentially expressed in pts that relapsed (**Figure 5-6**).

Figure 2. HER2DX risk score in RD samples

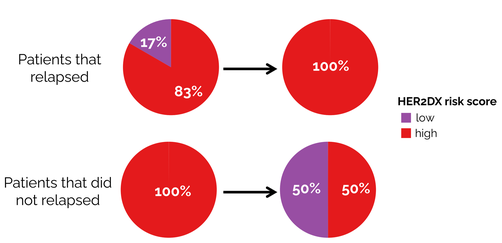


Figure 3. iDFS by HER2DX risk score in RD

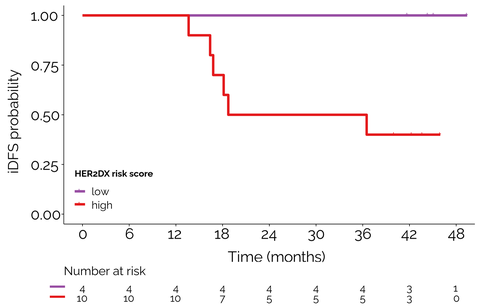


Figure 4. Gene expression in RD associated with iDFS

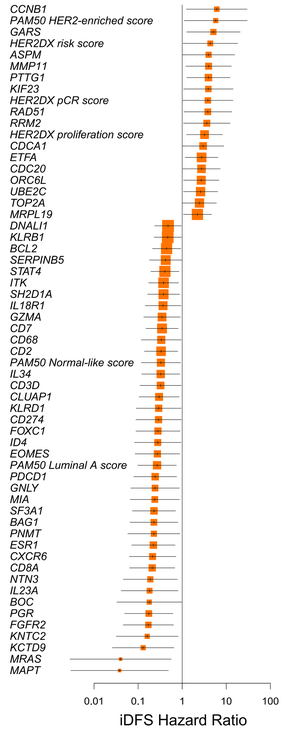


Figure 5. Differential gene expression by paired analysis of BL and RD samples in pts with or without tumor relapse

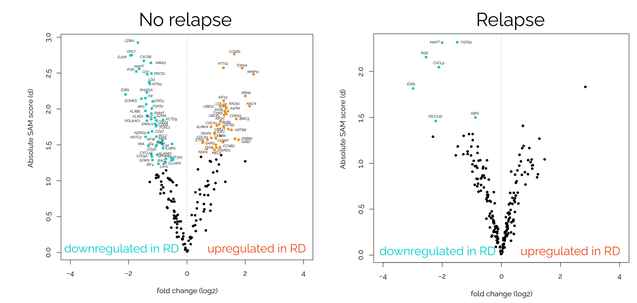
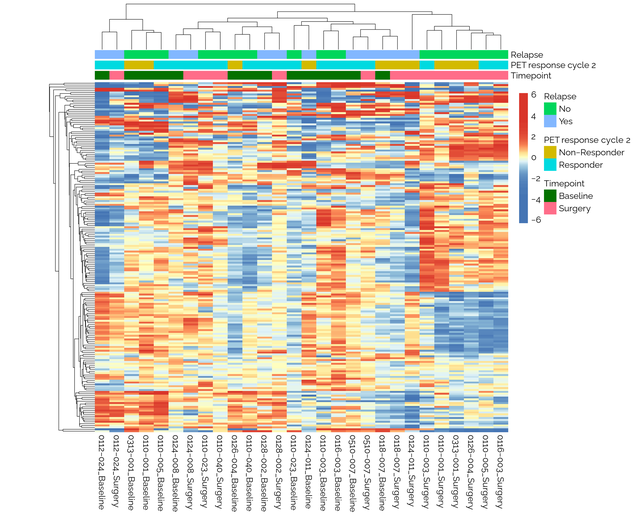


Figure 6. Unsupervised clustering of BL and RD samples using the expression of 185 genes



Conclusions

- These data suggest that HER2DX risk-score in RD provides additional information on the likelihood of developing distant recurrences.
- In RD, high expression of immune and luminal genes was associated with a reduced risk, while high expression of proliferation genes was associated with a higher risk.
- Genomic changes after anti-HER2 therapy were mainly observed in RD of pts that did not relapse.
- Prognostic impact of HER2DX downstaging merits further evaluation.

References: 1. Prat et al, EBiomedicine 2022. 2. Perez-Garcia et al, Lancet Oncol 2021.
Funding: Study sponsored by Medsir and Reveal Genomics.

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

Scan here to view a PDF of this poster.

jose.perez@medsir.org