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Validation of the HER2DX Genomic Test in First-Line Advanced HER2-Positive Breast Cancer: Identifying Long-Term Responders to THP

Marcin Kubeczko[1], Sandra Cobo[2], Rodrigo Sanchez-Bayona[3,4], Bartłomiej Pyciński[5], Jesús Soberino[6], Ewa Chmielik[7], Esther Sanfeliu[2,8,9], Maria Rey[2], Francisco Pardo[10], Angela Aguirre[2], Oleguer Castillo[2], Aleksandra Lesniak[1], Malgorzata Oczko-Wojciechowska[11], Esther Carcelero[12], Barbara Adamo[2,9,13], Maria Vidal[2,9,13], Milana Bergamino[2,9,13], Julia Maues[14], Guillermo Villacampa[15], Laia Paré[10], Patricia Villagrasa[10], Eva Ciruelos[3,4], Aleix Prat[2,9,10,13], Michal Jarzab[1], and Fara Brasó-Maristany[2,10]

1, Breast Cancer Center, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice, Poland. 2, Translational Genomics and Targeted Therapeutics in Solid Tumors, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain. 3, Medical Oncology Department, Hospital Universitario 12 de Octubre, Madrid, Spain. 4,Instituto de Investigación Sanitaria Hospital 12 de Octubre (Imas12), Madrid, Spain. 5, Faculty of Biomedical Engineering, Silesian University of Technology, Zabrze, Poland. 6, Breast Cancer Unit, IOB-QuirónSalud, Barcelona, Spain. 7, Tumor Pathology Department, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice, Poland. 8, Pathology Department, Hospital Clínic of Barcelona, Barcelona, Spain. 9, Department of Medicine, University of Barcelona, Barcelona, Spain. 10, Reveal Genomics, Barcelona, Spain. 11, Department of Clinical and Molecular Genetics, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice, Poland. 12, Pharmacy Department, Hospital Clínic Barcelona, Barcelona, Spain. 13, Clínic Barcelona Comprehensive Cancer Center, Barcelona, Spain. 14, GRASP, GRASP, Baltimore, MD, United States of America. 15, Statistics Unit, Vall d'Hebron Institute of Oncology, Barcelona, Spain.

Background

- The HER2DX genomic test is a standardized, quantitative assay (Prat et al. EBioMedicine 2022) with demonstrated prognostic value in first-line advanced HER2+ breast cancer treated with trastuzumab, pertuzumab, and chemotherapy (THP) (Sánchez-Bayona et al. NPJ Breast Cancer 2025, Cortés et al. SABCS 2024).
- Here, we validated the test in an independent cohort (n=122) and explored its association with long-term outcomes in a combined real-world population (n=215).

Methods

- HER2DX was performed at a central laboratory on baseline tumor tissue from 122 consecutive patients with advanced HER2+ breast cancer treated with first-line THP at the Breast Cancer Center, Maria Sklodowska-Curie National Research Institute of Oncology, Gliwice (Poland).
- In addition, we evaluated a 93-patient real-world cohort from Spain (Sánchez-Bayona et al. NPJ Breast Cancer 2025) with updated survival data.
- Outcomes were assessed using pre-established ERBB2 score cutoffs. Multivariable Cox models were adjusted for clinicopathological variables. Prognostic value was also assessed in the subgroup of patients achieving a response (partial or complete) to first-line THP. An improved version of the test, called HER2DX metastatic prognostic score (HER2DX-METS), which combines the HER2DX ERBB2 score with additional molecular signatures, was trained in the Spanish cohort and validated in the Polish cohort.

Results

- Patient characteristics are reported in **Table 1**. HER2DX ERBB2 and HER2DX-METS score distributions are represented in **Figure 1**.
- In the Polish cohort, the high ERBB2 mRNA group had significantly improved outcomes compared to the medium/low groups (**Figure 2**). In the combined cohort (n=215), the high ERBB2 group had significantly longer PFS (median 33.8 months, 95% CI 25.6-52.5) and OS (median not reached) compared to the medium/low group (median PFS 12.5 months, 95% CI 9.79-25; median OS 37.1 months, 95% CI 25.4-47.9) (**Figure 3-4**).
- The objective response rate was significantly higher in the high HER2DX ERBB2 group (84.4%) compared to the low group (52.0%; p <0.001). In multivariable models, the ERBB2 score remained independently prognostic.
- Notably, in the subgroup of patients with fewer than three metastatic sites, those with high ERBB2 scores experienced a median PFS of 51.7 months (95% CI 28.6–NA) and a median OS that was not reached, compared to 20.3 months (95% CI 10.4-41.5) and 42.4 months (95% CI 27.6-55.8) in the medium/low group (**Figure 5**).
- Among patients with a response to THP, those with high ERBB2 scores had a median PFS of 33.9 months (95% CI 26.9-61) and median OS not reached, compared to 17.6 months (95% CI 10.3-42.9) and 37.1 months (95% CI 25.4-51.1) in the medium/low group, respectively (**Figure 6**).
- In the Polish dataset, HER2DX-METS score was moderately correlated with the HER2DX ERBB2 score and the high-risk group had significantly worse PFS and OS (**Figure 7**).
- Likelihood ratio testing confirmed that HER2DX-METS added significant prognostic information beyond ERBB2 for OS (χ^2=10.944, p=0.004) and showed a trend for PFS (χ^2=5.673, p=0.059). In contrast, ERBB2 did not add prognostic value beyond HER2DX-METS for either OS (χ^2=0.051, p=0.820) or PFS (χ^2=0.093, p=0.760).

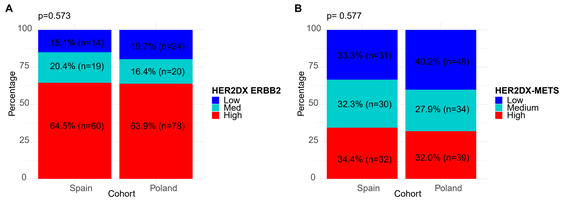


Figure 1. Distribution of (A) HER2DX ERBB2 score and (B) HER2DX-METS score in the Spanish and Polish cohorts.

Results

Table 1. Patient characteristics

	Polish cohort (n=122)		Spanish cohort (n=93)		Combined cohort (n=215)	
Median age (range)	59.2 (36.0-85.7)		57.0 (30.0-87.0)		58.0 (30.0-87.0)	
Sex (n, %)						
Female	122	100	92	98.9	214	99.5
Male	0	0	1	1.1	1	0.5
Menopausal status (n, %)						
Premenopausal	35	28.7	19	21.3	54	25.1
Postmenopausal	87	71.3	70	78.7	157	73
HER2 IHC status (n, %)						
3+	88	73.3	62	68.1	150	69.8
other	32	26.7	29	31.9	61	28.4
Hormone receptor status (n, %)						
Negative	48	41	35	37.6	83	38.6
Positive	69	59	58	62.4	127	59.1
Metastatic pattern (n, %)						
Visceral disease	52	42.6	68	73.1	120	55.8
Brain metastasis	1	0.8	12	12.9	13	6
Bone-only disease	26	21.3	15	16.1	41	19.1
Metastatic burden (n, %)						
<3 metastatic sites	87	71.3	60	64.5	147	68.4
≥3 metastatic sites	35	28.7	33	35.5	68	31.6
Type of advanced disease (n, %)						
De novo	88	72.1	49	52.7	137	63.7
Relapse	34	27.9	44	47.3	78	36.3
Type of biopsy analyzed (n, %)						
Primary	14	11.5	61	65.6	75	34.9
Metastatic	108	88.5	32	34.4	140	65.1

Figure 2. Association of HER2DX ERBB2 score with (A) PFS and (B) OS in the Polish cohort.

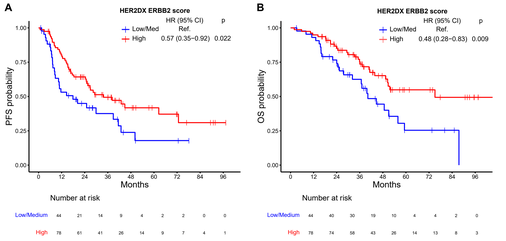


Figure 3. Association of HER2DX ERBB2 score with (A) PFS and (B) OS in the combined cohort.

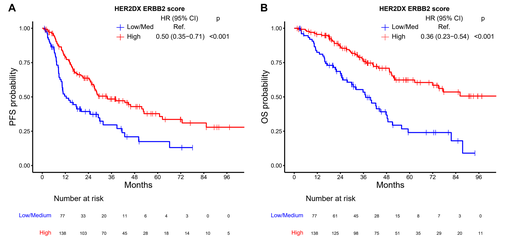


Figure 4. Univariable and multivariable analyses of (A) PFS and (B) OS in the combined cohort.

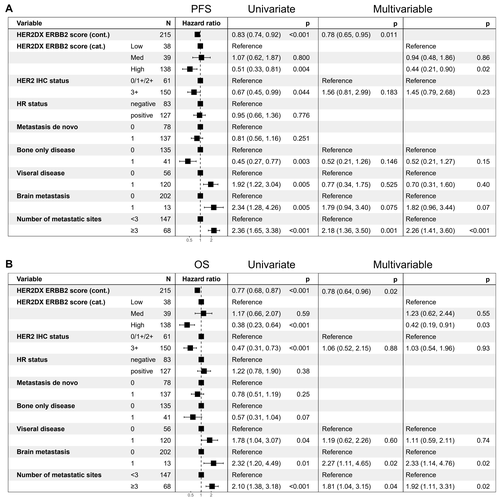


Figure 5. Association of HER2DX ERBB2 mRNA score with (A) PFS and (B) OS in patients with fewer than 3 metastatic sites of the combined cohort.

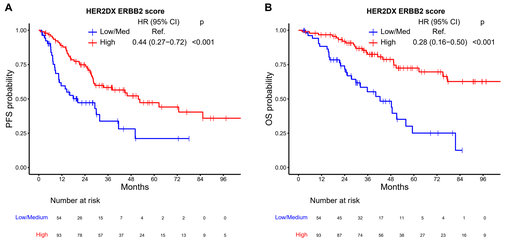


Figure 6. Association of HER2DX ERBB2 mRNA score with (A) PFS and (B) OS in patients achieving partial or complete response after THP of the combined cohort.

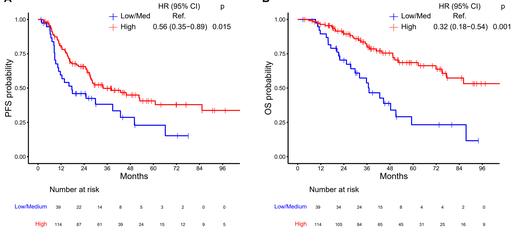
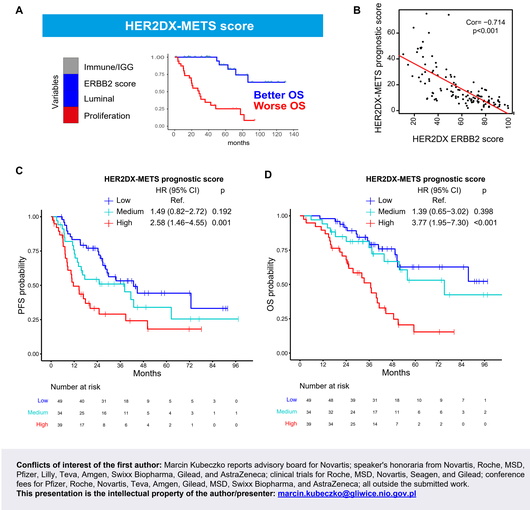


Figure 7. Association of (A) HER2DX METS-score with (B) HER2DX ERBB2 score, (C) PFS and (D) OS in the Polish cohort.



Conclusions HER2DX independently predicts outcomes in advanced HER2+ breast cancer treated with first-line THP and may guide decisions on taxane duration or THP versus first-line T-DXd. In patients with <3 metastatic sites, ERBB2-high cases achieved a median PFS on THP of 4.3 years, with OS not reached.

Conflicts of interest of the first author: Marcin Kubeczko reports advisory board for Novartis; speaker's honoraria from Novartis, Roche, MSD, Pfizer, Lilly, Teva, Amgen, Swixx Biopharma, Gilead, and AstraZeneca; clinical trials for Roche, MSD, Novartis, Seagen, and Gilead; conference fees for Pfizer, Roche, Novartis, Teva, Amgen, Gilead, MSD, Swixx Biopharma, and AstraZeneca; all outside the submitted work.
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