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Development of the HER2DX Predictor of Brain Metastasis in Advanced HER2-Positive Breast Cancer Treated with First-Line THP

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Background

- Central nervous system (CNS) is a clinically significant site of progression in advanced HER2-positive (HER2+) breast cancer. Identifying patients at higher risk could guide surveillance and treatment strategies.
- Prior work has demonstrated the strong prognostic value of the HER2DX ERBB2 score 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). In addition, the HER2DX metastatic prognostic score (HER2DX-METS), an integrated model combining ERBB2 with additional molecular signatures, was developed to predict overall survival (OS) (Kubeczko et al. SABCS 2025, **#PS5-01-23**).
- Here, we describe the development and validation of the HER2DX CNS progression score, a distinct genomic tool specifically designed to predict brain metastasis risk.

Methods

- Transcriptomic data were analyzed from 215 patients with HER2-positive advanced breast cancer treated with first-line trastuzumab, pertuzumab, and chemotherapy (THP), including 93 cases from Spain and 122 from Poland. All tumor samples were processed using the standardized HER2DX gene expression platform.
- CNS progression data were available for 214 of 215 (99.5%) patients.
- Biological features associated with CNS progression were explored in the combined cohort, and a genomic score was developed using key signatures. Coefficients were derived in the Spanish cohort, and the final score was validated in the Polish cohort. Cox models and km plots were used to evaluate the association of each variable with CNS progression, and other clinical endpoints such as OS.

Results

- In the combined cohort of 214 patients, the median follow-up was 37.1 months. A total of 53 patients (21.9%) developed brain metastases. No statistically significant differences in CNS progression (27.2% and 23.0%) and time to CNS progression (hazard ratio [HR] 0.90, 95% CI 0.51-1.56, p-value=0.70) were observed between the Spanish and Polish cohorts.
- Clinical variables associated with CNS progression included younger age and having ≥3 metastatic sites. In contrast, hormone receptor status, HER2 IHC, menopausal status, biopsy site (primary vs. metastatic), bone disease, and best overall response to THP were not associated with brain metastasis (**Figure 1**).
- HER2DX assay identified 3 main genomic patterns associated with CNS progression: HER2DX ERBB2 score was associated with higher risk of CNS progression, while the HER2DX luminal score and a novel immune-related signature were associated with lower risk (**Figure 2-3**).
- The distribution HER2DX CNS progression score in the Spanish and Polish cohorts is represented in **Figure 4.**
- The HER2DX CNS progression score was not associated with PFS or OS, confirming its specificity for CNS progression (**Figure 5**). On the contrary, the HER2DX-METS score (Kubeczko et al. SABCS 2025, **#PS5-01-23**) was not associated with CNS progression. As expected, both HER2DX scores were not found correlated (Pearson correlation coefficient = -0.049) .
- In the Polish set, the 3-year cumulative incidence of CNS progression was 39.2% in the HER2DX CNS progression high-risk group vs. 13% in the intermediate-risk group vs. 4.3% in the low-risk groups (**Figure 6A**).
- In the combined set, the 3-year cumulative incidence of CNS progression was 41.1% in the HER2DX CNS progression high-risk group vs. 26.1% in the intermediate-risk group vs. 15.5% in the low-risk groups (**Figure 6B**).

Conflicts of interest of the first author: R.S.-B. reports advisory/consulting/speaker fees from Roche, AstraZeneca, Novartis, Lilly, Daiichi Sankyo, Pfizer, Eisai, GlaxoSmithKline, Reveal Genomics, and Gilead; travel expenses from Pfizer, AstraZeneca, Gilead, Novartis, and Roche.

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Results

Figure 1. Association of clinical variables with CNS metastasis in the combined cohort.

Variable		N	HR	HR (95% CI)	p
Age		214		0.98 (0.96, 1.00)	0.05
Metastatic sites	<3	147		Reference	
	≥3	67		3.21 (1.86, 5.54)	<0.001
Hormone Receptor Status	negative	82		Reference	
	positive	127		0.70 (0.41, 1.21)	0.20
HER2 IHC	other	60		Reference	
	3+	150		2.13 (0.96, 4.74)	0.06
Menopausal status	postmenopausal	157		Reference	
	premenopausal	53		1.49 (0.82, 2.70)	0.19
Biopsy site	metastatic	139		Reference	
	primary	75		0.71 (0.39, 1.30)	0.27
Bone-only disease	no	134		Reference	
	yes	41		0.46 (0.21, 1.04)	0.06
Best overall response to THP	SD/PD	57		Reference	
	PR/CR	152		0.78 (0.42, 1.44)	0.42



Figure 2. HER2DX genomic patterns associated with CNS progression.

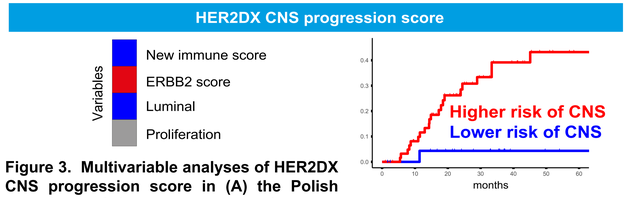


Figure 3. Multivariable analyses of HER2DX CNS progression score in (A) the Polish cohort and (B) the combined cohort.

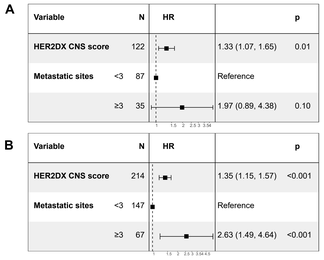


Figure 4. Distribution of HER2DX CNS progression score.

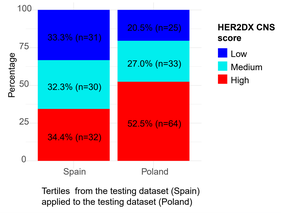
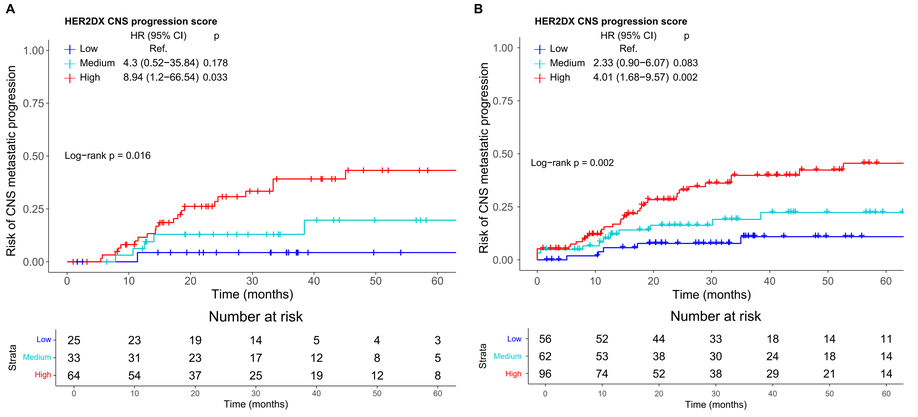


Figure 5. Association of HER2DX ERBB2, HER2DX-METS and HER2DX CNS score with survival.

			CNS metastatic progression		PFS		OS	
Variable		**N**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
HER2DX ERBB2 score	Low	38	Reference		Reference		Reference	
	Medium	39	1.09 (0.32, 3.77)	0.890	1.07 (0.62, 1.87)	0.800	1.17 (0.66, 2.07)	0.590
	High	137	2.04 (0.80, 5.17)	0.133	0.51 (0.33, 0.81)	0.004	0.38 (0.23, 0.64)	<0.001
HER2DX METS score	Low	71	Reference		Reference		Reference	
	Medium	70	1.14 (0.61, 2.11)	0.680	1.55 (0.98, 2.44)	0.061	2.19 (1.16, 4.14)	0.020
	High	73	0.81 (0.39, 1.67)	0.574	2.69 (1.73, 4.17)	<0.001	5.68 (3.16, 10.19)	<0.001
HER2DX CNS score	Low	56	Reference		Reference		Reference	
	Medium	62	2.33 (0.90, 6.07)	0.083	0.97 (0.59, 1.58)	0.898	0.88 (0.48, 1.58)	0.660
	High	96	4.01 (1.68, 9.57)	0.002	1.32 (0.85, 2.05)	0.212	1.28 (0.77, 2.12)	0.350



Figure 6. Cumulative risk of CNS metastatic progression acording to HER2DX CNS progression score in the (A) Polish and (B) combined cohorts.



The HER2DX CNS progression score is a novel, biology-informed genomic tool that independently predicts brain metastasis in HER2+ advanced breast cancer treated with first-line THP. These findings support its potential integration into clinical workflows to personalize CNS surveillance and intervention strategies.