1MO Prognostic and biologic significance of HER2-low expression in early breast cancer

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Background: Approximately 50% of HER2-negative breast cancers (BC) show HER2-low expression. It is unclear however whether HER2-low BC should be considered an individual biologic entity, prognostically distinct from HER2-zero BC.

Methods: Data were collected from an institutional database including all consecutive patients with BC who underwent surgery at Dana-Farber Brigham Cancer Center from 1/2016 to 3/2021. Tumors were defined as HER2-low if they had a HER2 IHC score of 1+ or 2+ with negative FISH, and HER2-zero if they had a HER2 IHC score of 0. Clinicopathologic characteristics and disease outcomes were compared between the two cohorts.

Results: 5235 HER2-negative BC patients were eligible for analysis; 4429 estrogen receptor (ER)+, 67 ER-low (1-9%), 739 ER-negative. Hormone receptor(HR)-expression was significantly more common among HER2-low compared with HER2-zero BC (89.9% vs 80.9%, $p<0.001$). Most other clinicopathological differences were explained by the different rate of HR+ tumors. When evaluated as a continuous variable, ER expression was significantly associated with HER2 expression ($p<0.001$), and the rate of HER2-low tumors increased progressively with increasing ER expression (Table). Among patients receiving neoadjuvant chemotherapy (n=657), those with HER2-zero tumors had higher pCR rates compared with HER2-low (27% vs 17%, p=0.002). However, statistical difference was lost when separately analyzing HR+ (8% vs 14%, p=0.078), ER-low (25% vs 38.9%, p=0.46), HR+ without ER-low (6.9% vs 10.4%, p=0.277), TNBC (30.8% vs 35.4%, p=0.40) and when adjusting for confounders. No difference in disease-free survival or overall survival was observed among patients with HR+ tumors or TNBC depending on HER2-low expression.

Table: 1MO Proportion of tumors with HER2-low versus HER2-zero expression according to tumor subtype and ER expression

	TNBC	ER-low (1-9%)	ER-moderate (10-49%)	ER-high (50-95%)	ER-very-high (>95%)
HER2-low	40%	46%	55%	58%	62%
HER2-zero	60%	54%	45%	42%	38%

Conclusions: Our results do not support the interpretation of HER2-low BC as a distinct biologic subtype. HER2-low expression is continuously associated with the level of ER expression. ER-low tumors are enriched among HER2-zero cases and may confound prognostic analyses.

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2MO Development of a prognostic gene-expression signature for early stage HER2-positive breast cancer patients

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Background: With increasing evidence showing the complexity of HER2-positive breast cancer, this study aimed to identify a gene-expression signature with potential prognostic value to assist therapeutic decision in the early disease setting.

Methods: Gene-expression profiles of NeoALTTO tumor biopsies before and after 2 weeks of neoadjuvant treatment were generated by microarrays (Clariom S, ThermoFisher). Genes associated with event free survival (EFS) were selected at the two time points with Cox univariate analysis and combined by multivariate approaches. Independent technical and clinical validation were sought.

Results: Overall, 180 patients were analyzed (NeoALTTO cohort, median follow-up 6.7 yrs [IQR 6.1-6.8]; 53 events). The expression of 18 genes combined by principal component analysis (S18) was significantly associated with EFS in the trastuzumab (T)-arm (Hazard Ratio for each unit increment [HR] 2.4, 95%Confidence Interval [CI] 1.6-3.5) and in the entire NeoALTTO cohort (HR 1.7, CI 1.4-2.2). Notably, S18 showed no overlap with HER2 and/or ESR1 genes and/or their signaling. A more parsimonious signature of five genes (S5) was next developed. Both S18 and S5 retained their prognostic value independently of pathological complete response, age, tumor size, estrogen receptor and node status both in the T-arm and in the entire NeoALTTO cohort. The prognostic value of S18 was technically confirmed by RNAseq in the T-arm (HR 2.1, CI 1.4-3.1) and entire cohort (HR1.3, CI 1.03-1.7) whereas the S5 was confirmed within the T-arm alone (HR 1.5, CI 1.1-1.9). An additional technical validation is currently ongoing by customized open arrays. The prognostic capability of S18 was clinically confirmed by in silico analysis of the Italian GHEA expanded access study of adjuvant trastuzumab (HR 1.9,CI 1.2-2.9). Currently, we are seeking to validate the prognostic value of S5 in the NSABP B-31 study and results are expected to be presented at the congress.

Conclusions: These findings hold the potential to accurately identify patients with early HER2-positive breast cancer at low risk of relapse when treated with trastuzumab-based therapy and may be useful to select patients for single or dual anti-HER2 therapies.

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3MO Association of the research-based HER2DX signatures with survival in early-stage triple-negative breast cancer (eTNBC)

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Background: The HER2DX assay is prognostic in early-stage HER2-positive breast cancer by integrating tumor and nodal staging, and the expression of 3 gene signatures tracking immunoglobulin (IGG)-mediated immunity, proliferation, and luminal