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Molecular characterization of HER-2 low patients identifies basal-enriched subset with poor clinical outcomes in real-world data

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INTRODUCTION

A recent prospective, multicenter, Phase 3 trial demonstrated that patients with lower levels of HER2-expression (HER2-low) derive significant benefit from treatment with trastuzumab deruxtecan—an HER2 antibody-drug-conjugate and resulted in FDA-approval for this population. The HER2-low patient population in the study was enriched with luminal disease but is clinically heterogeneous and outcomes have not been extensively characterized due to the lack of annotated multimodal real-world data (RWD).

METHODS

We retrospectively analyzed 1,545 breast cancer samples sequenced via the Tempus xT assay (DNA-seq and whole-exome capture RNA-seq). Only tumors with known HER2 status (IHC and/or FISH) were included. A HER2 RNA gene signature was developed by comparing HER2- (IHC 0+) and HER2+ (IHC 3+ or IHC 2+ and FISH+) tissue samples—controlling for HR status—to identify genes associated with HER2 over-expression. This signature was used to further classify HER2-low samples (determined by IHC 1+ or IHC2+ and FISH-) via hierarchical clustering of the RNA signature in the selected gene set. Real-world progression-free survival (rwPFS) was evaluated based on progression and death captured through manual expert abstraction for a subset of stage 4 patients who were sequenced within five years of initial diagnosis and estimated via Kaplan-Meier analysis.

Characteristic	Overall (N=1,545)
Age at diag. (yrs) (n=1,521)	
Median (Q1, Q3)	55.948 (45.896, 64.301)
Gender (n=1,544)	
Female	1534 (99.4%)
Race (n=838)	
White	623 (74.3%)
Black or African American	142 (16.9%)
Asian	33 (3.9%)
Other	40 (4.8%)
Ethnicity (n=502)	
Hispanic or Latino	88 (17.5%)
Not Hispanic or Latino	414 (82.5%)
Stage (n=920)	
I	20 (2.2%)
II	66 (7.2%)
III	88 (9.6%)
IV	745 (81.0%)
HER2 status	
HER2-	464 (30%)
HER2-low	920 (59.5%)
HER2+	161 (10.4%)

Table 1. Demographic and clinical characteristics

SUMMARY

- Multimodal RWD reveals that HER2-low breast cancers are comprised of distinct molecular subtypes.
- A cluster of HER2-low, predominantly basal-like patients had shorter progression-free survival than other molecularly-based clusters.
- Further prospective studies are urgently needed to assess treatment response in this heterogenous emerging HER2-low distinct population.

RESULTS

HER2-low clustering of the RNA signature demonstrates molecular heterogeneity that is not explained by clinical characteristics

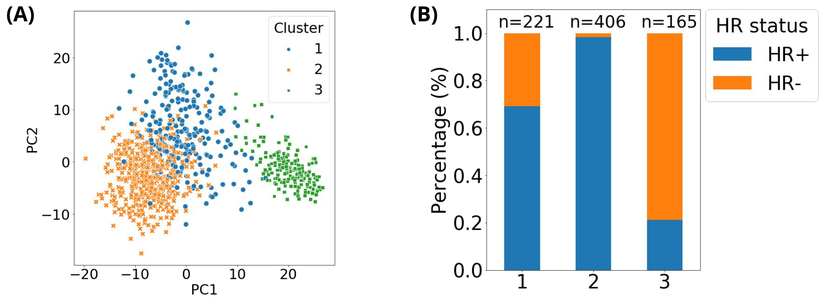


Figure 1. (A) Principal component analysis and clustering of HER2-low patients based on RNA expression in the selected gene set (see Methods). (B) While cluster 2 is strongly enriched in HR+ samples, clustering is not determined by HR status. Stage and IHC-status were similar across clusters.

PAM50 subtype analysis independently demonstrates heterogeneity in HER2-low population

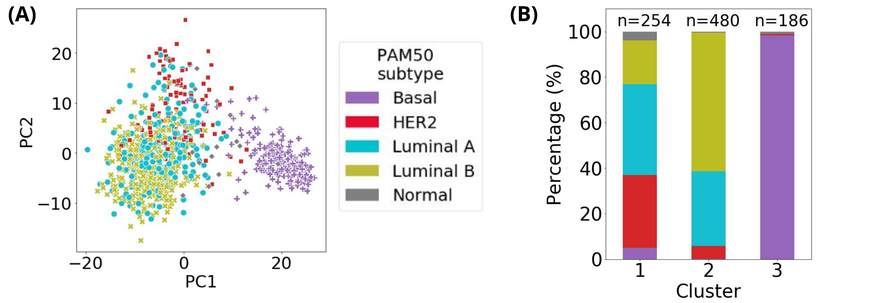
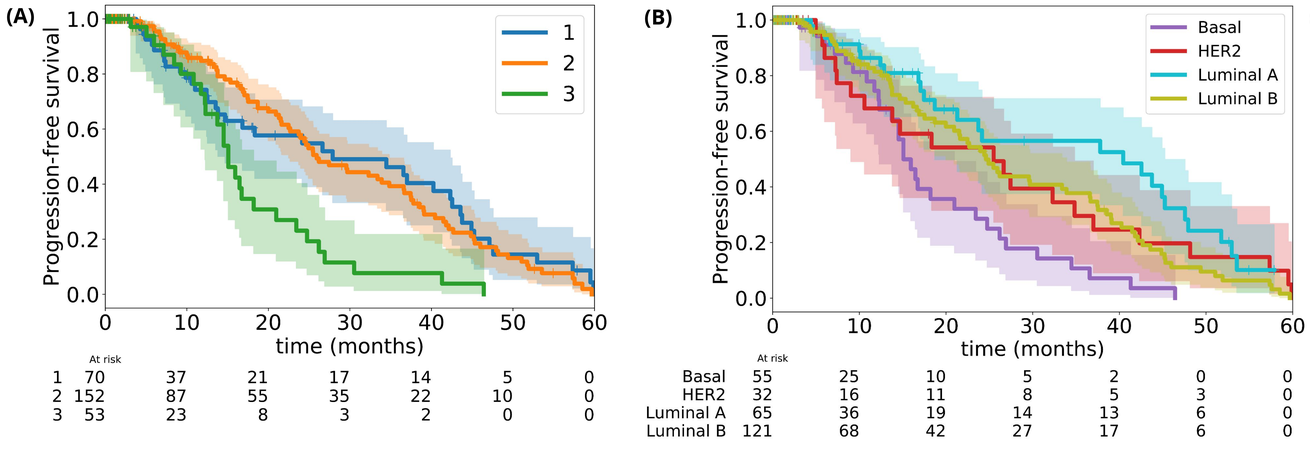


Figure 2. (A) Visualization of the same principal components as in Figure 1A, with samples colored according to PAM50 subtype assignments. (B) Analysis of independently derived clusters according to PAM50 subtyping shows that cluster 3 is predominantly basal-like while clusters 1 and 2 are heterogeneous.

Progression free survival differs according to independent clustering and PAM50 subtyping, with worse outcomes in cluster 3, basal-like cluster



(C)

	Median PFS (months)	HR (p-value)
Clusters		
1	27.9	–
2	25.9	–
3	15.1	2.38 (<0.001)
PAM50 subtypes		
Basal	15.1	2.2 (<0.001)
HER2	25.5	–
Luminal A	40.4	–
Luminal B	24.6	–

Figure 3. (A) Among stage IV patients, patients in cluster 3 had a median PFS that was significantly shorter than patients in clusters 1 and 2 combined (HR 2.38, p<0.001). (B) Similarly, PFS in stage IV patients varied according to PAM50 subtypes with basal patients having a median PFS that was significantly shorter than combined Luminal A, Luminal B, and HER2 patients (HR 2.2, p<0.001; note that Normal-like PAM50 subtype samples are excluded from this analysis due to low numbers). (C) Median PFS for all groups and HR values.