Molecular and prognostic profiling of HR+/HER2+ Metastatic Breast Cancer (MBC): insights from circulating tumor DNA (ctDNA)-based genomic analysis

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BACKGROUND

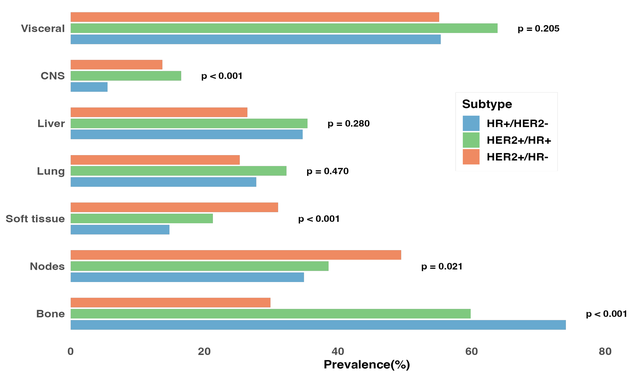
- Hormone receptor–positive/HER2-positive metastatic breast cancer (HER2+/HR+ MBC) represents a biologically distinct subtype, characterized by crosstalk between estrogen receptor (ER) and HER2 signaling pathways.
- The treatment landscape for HER2+ MBC is rapidly evolving, with recent data from the DESTINY-Breast09 trial supporting consideration of T-DXd in the first line and the PATINA trial demonstrating that adding the CDK4/6 inhibitor palbociclib to maintenance therapy significantly prolonged progression-free survival in patients with HR+/HER2+ disease. The aim of this analysis was to compare genomic profiles and outcomes across HR+/HER2–, HER2+/HR+, and HER2+/HR– subtypes through ctDNA assessment.

MATERIALS AND METHODS

- This retrospective study analyzed a multi-institutional cohort of 1318 patients (pts) with MBC and ctDNA testing with the Guardant360 NGS panel within a large academic consortium (PMAC).Associations between single nucleotide variants (SNVs), copy number variations (CNVs) and breast cancer subtypes were tested by multinomial logistic regression (MLR) in terms of Relative Risk Ratio (RRR). The impact of prognosis was evaluated through Cox regression for overall survival (OS), defined from time of baseline ctDNA collection.

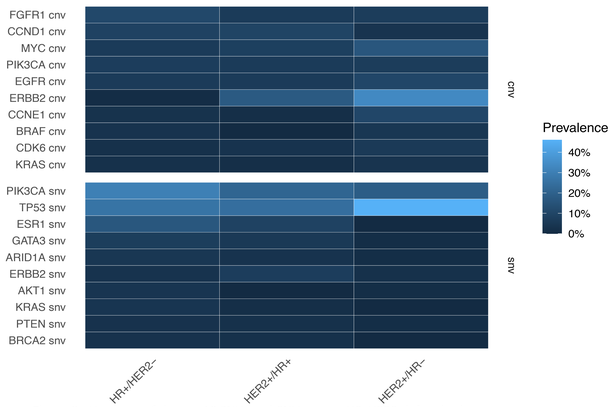
RESULTS

- Among 1318 pts with MBC, 1104 (83.8%) had HR+/HER2–, 127 (9.6%) HER2+/HR+, and 87 (6.6%) HER2+/HR- disease.
- Multivariable MLR, designed with HR+/HER2- as the reference subtype, investigated clinical variables and genomic alterations across subtypes.
- Clinically, the presence of nodal (RRR 1.82, p < 0.001) and soft tissue (RRR 2.60, p < 0.001) metastases were more common for HER2+/HR- but not for HER2+/HR+, while central nervous system (CNS) metastases were associated with both HER2+/HR+ (RRR 3.41, p < 0.001) and HER2+/HR- (RRR 2.73, p = 0.006) (**Figure 1**).



▲ **Figure 1 -** Distribution of metastatic sites across breast cancer subtypes (χ^2 test, p < 0.05)

- Considering single genes alterations (**Figure 2; Table 1**), at multivariable analysis, *PIK3CA* SNVs were less common (RRR 0.48, p = 0.009) and *ERBB2* CNVs more common (RRR 47.05, p < 0.001) for HER2+/HR+, while *ERBB2* CNVs were also associated with HER2+/HR- (RRR 85.63, p < 0.001).
- Considering pathway alterations, HER2+/HR+ had fewer *PI3K* SNVs (RRR 0.47, p = 0.003) and *ER* SNVs (RRR 0.52, p = 0.022), while in HER2+/HR- there were fewer *ER* SNVs (RRR 0.05, p = 0.004) and more *MYC* CNVs (RRR 5.10, p = 0.029).

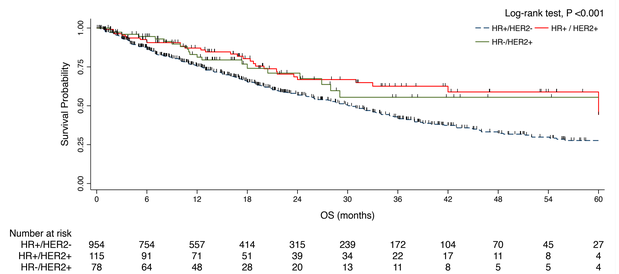


▲ **Figure 2 -** Heatmap of the top 10 SNVs and CNVs across HR/HER2 defined subtypes

	RRR	[95% conf.interval]		P>|z|
HR+ / HER2- (reference group)				
HR+ / HER2+				
Bone involvement	0.59	0.38	0.93	0.022
Node involvement	0.88	0.55	1.41	0.599
Soft tissue involvement	1.76	1	3.1	0.05
CNS involvement	3.06	1.58	5.91	0.001
MAF ≥ 3.3%	0.99	0.98	1.01	0.515
***PIK3CA* SNVs**	0.48	0.28	0.83	0.009
TP53 SNVs	0.66	0.4	1.1	0.109
***ERBB2* CNVs**	47.05	17	130.22	<0.001
MYC CNVs	0.68	0.25	1.85	0.444
CCNE1 CNVs	0.22	0.04	1.33	0.099
HR- / HER2+				
Bone involvement	0.22	0.12	0.39	<0.001
Node involvement	1.07	0.59	1.92	0.831
Soft tissue involvement	2.61	1.34	5.11	0.005
CNS involvement	1.71	0.7	4.22	0.242
MAF ≥ 3.3%	0.99	0.96	1.01	0.297
PIK3CA SNVs	0.49	0.23	1.05	0.066
TP53 SNVs	1.14	0.62	2.11	0.674
***ERBB2* CNVs**	85.63	28.05	261.4	<0.001
MYC CNVs	0.67	0.2	2.27	0.524
CCNE1 CNVs	0.95	0.19	4.66	0.951

▲ **Table 1 -** Multinomial multivariable logistic regression of individual SNVs and CNVs, with HR+ /HER2- subtype as the reference category.

- In OS analysis, both HER2+/HR+ (HR 0.55, p = 0.002) and HER2+/HR- (HR = 0.61, p = 0.027) had a significantly favorable prognostic impact compared to HR+/HER2- (**Figure 3**). Within the HR+/HER2- cohort, several pathway alterations were associated with worse prognosis, including *ER* SNVs (HR 1.33, p = 0.007), *P53* SNVs (HR 1.46, p < 0.001), *PI3K* CNVs (HR 1.54, p = 0.028) and *MYC* CNVs (HR 1.85, p = 0.001) (**Table 2**). In HER2+/HR+, a significant prognostic impact emerged for *PI3K* SNVs (HR 2.66, p = 0.016), *P53* SNVs (HR 2.46, p = 0.036) and *RTK* CNVs (HR 3.82, p = 0.004), while in HER2+/HR- it was observed only for *PI3K* CNVs (HR 79.65, p = 0.003) (**Table 2**).



▲ **Figure 3 -** Kaplan–Meier curves comparing overall survival across HR/HER2 subtypes

	HR	[95% conf.interval]		P>|z|
HR+ / HER2-				
Liver involvement	2.03	1.66	2.48	<0.001
Bone involvement	1.51	1.14	2.01	0.005
Soft tissue involvement	1.48	1.13	1.94	0.005
CNS involvement	2.13	1.45	3.12	<0.001
MAF ≥ 3.3%	1.01	0.99	1.01	0.058
ER SNVs	1.33	1.08	1.65	0.007
P53 SNVs	1.46	1.20	1.79	<0.001
PI3K CNVs	1.54	1.05	2.26	0.028
MYC CNVs	1.85	1.28	2.68	0.001
HR+ / HER2+				
MAF ≥ 3.3%	1.01	0.98	1.04	0.459
PI3K SNVs	2.66	1.20	5.89	0.016
P53 SNVs	2.46	1.06	5.70	0.036
RTK CNVs	3.82	1.53	9.54	0.004
HR- / HER2+				
MAF ≥ 3.3%	0.98	0.94	1.03	0.506
PI3K CNVs	79.65	4.30	1476.24	0.003

▲ **Table 2 - Multivariable Cox regression analysis for overall survival, showing only variables with significant prognostic impact**

CONCLUSIONS

- Our ctDNA-based analysis confirms that HER2+/HR+ MBC is a clinically and molecularly distinct subtype.
- Molecularly, HER2+/HR+ disease was characterized by markedly higher *ERBB2* amplification rates and a lower frequency of *ER* SNVs, suggesting reduced dependence on estrogen signaling despite hormone receptor positivity, and the presence of distinct mechanisms of endocrine resistance.
- Prognostically, both HER2+/HR+ and HER2+/HR– subtypes had significantly more favorable overall survival, suggesting an intrinsic advantage linked to the success of therapeutics aimed at targeting HER2.
- These findings therefore highlight the potential value of comprehensive baseline and longitudinal mutational profiling to guide initial and maintenance therapy selection and support personalized treatment approaches in HR+/HER2+ disease.

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The first author declares no conflict of interest