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Gene expression and mutation profiles in HER2-mutated metastatic breast cancer

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INTRODUCTION

HER2 activating mutations occur in 2-5% of metastatic breast cancer (MBC) patients. These mutations cluster in the kinase domains and at amino acids 309-310 in the extracellular domain. The MutHER, SUMMIT, and PlasmaMATCH clinical trials have shown neratinib monotherapy or neratinib plus fulvestrant combination produce clinical benefit in 28% to 46% in HER2-mutated MBC patients, but median progression-free survival was only 3.6 to 5.4 months. In order to improve the knowledge and outcomes for patients with HER2-mutated MBC, we compared the mutational landscape and gene expression of HER2-mutated MBC patients to HER2-amplified and HER2-wild type MBC patients.

METHODS

De-identified data from a cohort of stage 4 breast cancer patients (n=1,834) sequenced with the Tempus xT (DNA-seq of 595-648 genes, whole exome-capture RNA-seq) solid tumor assay was retrospectively analyzed. The most recent sample of the patient was used for analyses. Patients were stratified by HER2 mutational status: HER2-wild type (HER2-wt), HER2-amplifications (HER2-amps), or HER2-mutants (HER2-muts). Additionally, a sub-analysis was conducted among HER2-mutants to compare kinase domain mutations to other HER2 mutations. Patient demographic characteristics were compared between groups along with the prevalence of individual gene alterations (pathogenic/likely pathogenic short variants and copy number alterations), adjusted for false-discovery.

SUMMARY

- Co-occurring genomic alterations were different among all three groups. Notably, *ERBB3* and *CDH1* alterations co-occurred frequently in HER2mut MBC, while *ESR1* alterations co-occurred in only 4.8% of HER2mut MBC.
- Real-world data showed highest HER2 mRNA expression in HER2-amplified followed by HER2mut and HER2 wild-type MBC.
- All *ERBB3* co-alterations occurred with HER2 kinase domain mutations, while *CDH1* co-alterations were less prevalent in the HER2-kinase domain mutations group.

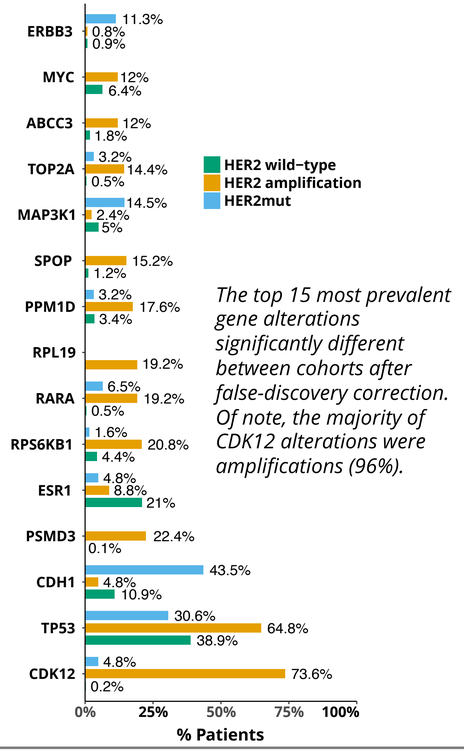
RESULTS

Table 1. *Cohort characteristics.*

Characteristic	Overall, N = 1,834[1]	HER2 wild-type, N = 1,647[1]	HER2 amplification, N = 125[1]	HER2mut, N = 62[1]	p-value[2]
Age at Diagnosis	53 (44, 62)	53 (44, 62)	49 (41, 59)	55 (50, 65)	<0.001
Unknown	8	8	0	0	
Gender					0.14
Female	1,816 (99%)	1,632 (99%)	124 (99%)	60 (97%)	
Male	16 (0.9%)	13 (0.8%)	1 (0.8%)	2 (3.2%)	
Unknown	2	2	0	0	
Race					-
White	937 (79%)	842 (80%)	61 (72%)	34 (85%)	
Black or African American	138 (12%)	123 (12%)	13 (15%)	2 (5.0%)	
Other Race	52 (4.4%)	41 (3.9%)	8 (9.4%)	3 (7.5%)	
Asian	48 (4.1%)	44 (4.2%)	3 (3.5%)	1 (2.5%)	
American Indian or Alaska Native	3 (0.3%)	3 (0.3%)	0 (0%)	0 (0%)	
Native Hawaiian or Other Pacific Islander	3 (0.3%)	3 (0.3%)	0 (0%)	0 (0%)	
Unknown	653	591	40	22	
Ethnicity					0.2
Not Hispanic or Latino	618 (87%)	553 (88%)	44 (85%)	21 (78%)	
Hispanic or Latino	92 (13%)	78 (12%)	8 (15%)	6 (22%)	
Unknown	1,124	1,016	73	35	
HR/HER2 Status					-
HR+, HER2-	1,327 (72%)	1,267 (77%)	16 (13%)	44 (71%)	
TNBC	284 (15%)	270 (16%)	3 (2.4%)	11 (18%)	
HR+, HER2+	172 (9.4%)	93 (5.6%)	73 (58%)	6 (9.7%)	
HR-, HER2+	51 (2.8%)	17 (1.0%)	33 (26%)	1 (1.6%)	
Histology					-
Invasive lobular carcinoma	79 (4.7%)	75 (4.9%)	1 (0.8%)	3 (5.3%)	
Invasive ductal carcinoma	368 (21.7%)	324 (21.4%)	35 (29.2%)	9 (15.8%)	
Mixed	17 (1%)	15 (1%)	1 (0.8%)	1 (1.8%)	
Other	26 (1.5%)	21 (1.4%)	3 (2.5%)	2 (3.5%)	
Not specified	1203 (71.1%)	1081 (71.3%)	80 (66.7%)	42 (73.7%)	
Unknown	141	131	5	5	

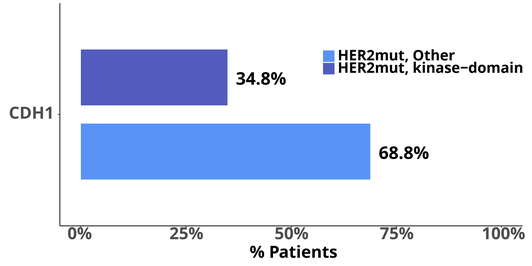
1 Median (IQR); n (%)
2 Kruskal-Wallis rank sum test; Fisher's exact or Chi-squared test

Figure 1. *Co-occurring somatic alterations*



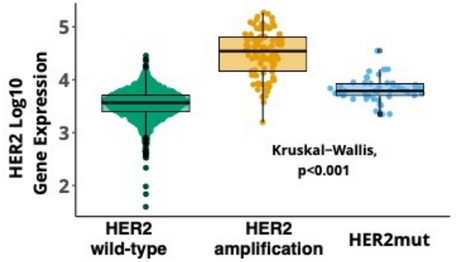
The top 15 most prevalent gene alterations significantly different between cohorts after false-discovery correction. Of note, the majority of CDK12 alterations were amplifications (96%).

Figure 2. *Prevalence of CDH1 alterations between HERmut groups.*



HER2-kinase domain mutants (N=46) exhibited significantly fewer CDH1 alterations compared to other HER2 mutants (N=16), although non-significant after fdr adjustment. All *ERBB3* alterations were missense variants (5 of which are p.E928G variants) and occurred among *HER2*-kinase mutants (not shown)

Figure 3. *HER2 RNA expression.*



Median *HER2* mRNA log10 gene expression differed among the three cohorts (*HER2* wild-type (3.56), HER2-amplification (4.54), HER2mut (3.79), *P<0.001*).

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