HER2 Alterations and Prognostic Implications in All Subtypes of Breast Cancer

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INTRODUCTION AND PURPOSE

- Amplification or overexpression of human epidermal growth factor receptor 2 (HER2) oncogene is present in approximately 15-20% of breast cancers and is a prognostic and predictive biomarker
- Additional *ERBB2*/HER2 alterations have become apparent on tumor next generation sequencing, including activating kinase domain mutations and fusions

METHODS

- DNA next generation sequencing (592-gene panel or whole exome) data from 12,153 breast samples were retrospectively reviewed for *ERBB2* alterations, with RNA whole-transcriptome sequencing (WTS) data available for 7289 (60%) samples. Gene fusions were detected using the ArcherDx fusion assay or WTS. HER2 status was determined according to 2018 ASCO-CAP guidelines
- Clinicopathologic features were retrospectively reviewed
- Overall survival was obtained from insurance claims and Kaplan-Meier estimates were calculated for defined patient cohorts
- Statistical significance was determined using Chi-square and Wilcoxon rank sum tests

RESULTS

Table 1. *ERBB2*mut frequency by clinicopathologic category

Study Cohort Characteristics	Total N (% col)	*ERBB2* mutation N (% row)	P-value
Patients	11722 (100)	378 (3.2)	
Tumors	12153 (100)	388 (3.2)	
Receptor Subtypes			
HR+/HER2+	560 (4.6)	25 (4.5)	
HR-/HER2+	435 (3.6)	18 (4.1)	
HR+/HER2-	6291 (51.8)	227 (3.6)	*<0.0001
TNBC	3464 (28.5)	66 (1.9)*	
Unknown	1403 (11.5)	52 (3.7)	
Age			
Median (range)	60 (19-90+)	64.5 (24-90+)*	
<50 years	2777 (22.9)	35 (1.3)	*<0.0001
≥50 years	9376 (77.1)	353 (3.8)*	
Histology			
Ductal	4323 (35.6)	91 (2.1)	*<0.0001
Lobular	639 (5.2)	64 (10.0)*	(compared
Other/Unknown	7191 (59.2)	233 (3.2)	to Ductal)
Site of biopsy			
Breast	4591 (37.8)	98 (2.1)	*<0.0001
Metastatic	7562 (62.2)	290 (3.8)*	
Metastatic sites			
Liver	1972 (26.1)	113 (5.7)*	
Skin/Soft tissue	716 (9.5)	39 (5.4)*	
Other	977 (12.9)	35 (3.6)*	
GYN/GU	171 (2.3)	5 (2.9)	*<0.0001
GI (non-Liver)	177 (2.3)	5 (2.8)	(compared
Bone	997 (13.2)	28 (2.8)	to breast)
Lymph nodes	1365 (18.1)	36 (2.6)	
Lung	811 (10.7)	21 (2.6)	
CNS	376 (5.0)	8 (2.1)	

Figure 1. ERBB2*mut* frequency by biopsy site.
*P<0.05 reflects comparison to 'Breast' subgroup. 'Other' subgroup comprised of chest well (34%), axilla (31%), and 48 other sites.

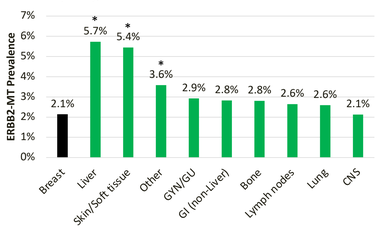


Figure 2. *ERBB2*/HER2 alterations across samples. (A) Oncoprint of *ERRB2*-mutated breast cancer samples grouped by specimen site (**metastatic**/**primary**) and receptor subtype. *ERBB2* variants associated with **HER2 Activation** and **Trastuzumab resistance** are color-coded. (B) Frequency of HER2-activating ('Activ.') and trastuzumab resistance ('Resist.') *ERBB2* alterations by receptor subtype. *P<0.05

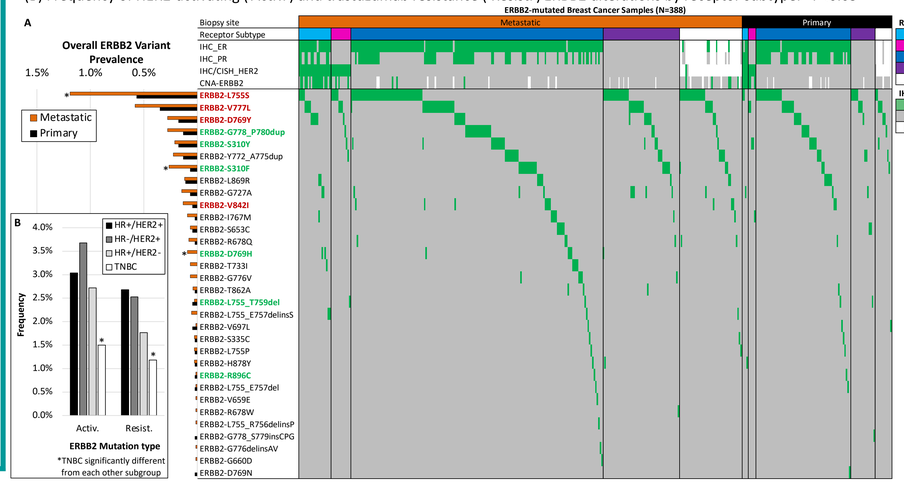


Figure 3. *ERBB2*mut frequency and copy number by HER2 IHC intensity. (A) ERBB2mut frequency and **(B)** ERBB2 copy number by HER2 IHC stain intensity. *P<0.05, ***P<0.001

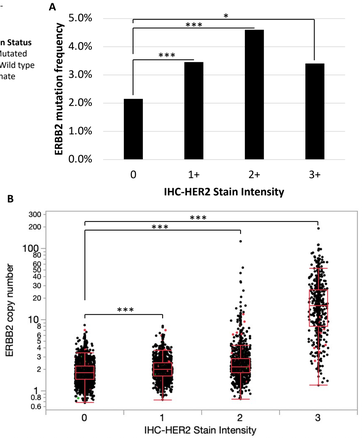


Figure 4. *ERBB2* mutations identified across paired samples.
Oncoprint of patient samples with multiple biopsies grouped by the presence of *ERBB2* alterations in both ('shared') or individual biopsies ('unique').

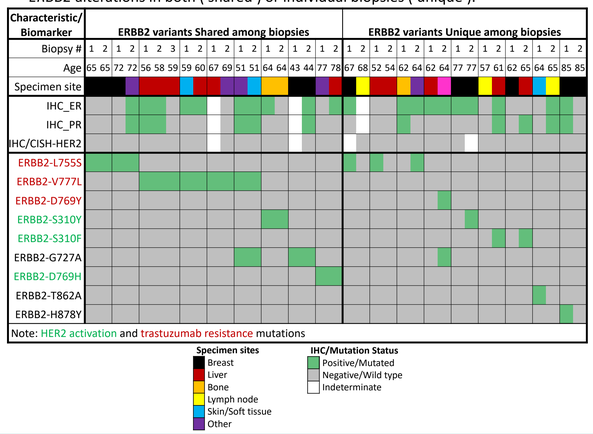
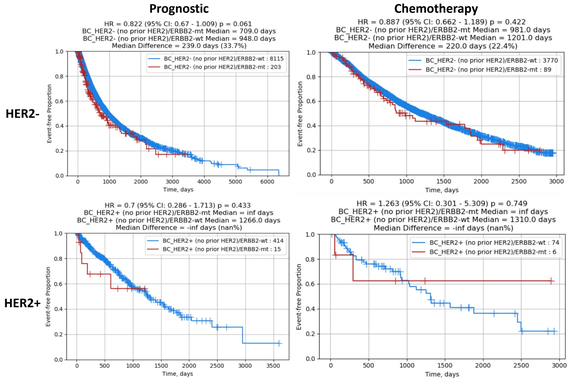


Figure 5. Prognostic and Predictive Value of ERBB2mut.
Overall survival of HER2- and HER2+ breast cancer patients, excluding those treated with HER2-targeted therapies, from time of biopsy ('Prognostic') or from start of chemotherapy.



RESULTS

- *ERBB2* mutations (*ERBB2*mut*)* were identified in 3.2% of tumors overall [Table 1]
- HER2+ tumors had a higher frequency of *ERBB2*mut compared to HER2-. *ERBB2*mut were present in 3.6% of HR+/HER2- and 1.9% of TNBC [Table 1]
- *ERBB2*mut were most common in liver metastases (5.7%) [Figure 1]
- *ERBB2*mut were more common in breast lobular compared to ductal tumors (10.0 vs. 2.1%, p<0.001) [Table 1]
- Metastatic tumors had a higher rate of *ERBB2*mut compared to locoregional breast tumors [Table 1] with increased rates of activating mutations S310F and D769H, and the resistance mutation L755S [Figure 2]
- Tumors with a score of 0 by IHC demonstrated a lower rate of *ERBB2*mut [Figure 3]
- Compared to *ERBB2*-WT, *ERRB2*mut were associated with decreased *ERBB2* transcripts levels in HER2+ samples (222 vs 441 transcripts per million [TPM], p<0.001) and increased levels in HER2- samples (73 vs 35 TPM, p<0.001)
- High tumor mutational burden (≥ 10 mut/Mb) and *ERBB3* mutations were more common in *ERBB2*mut compared to *ERRB2*-WT (16.7 vs 7.7%, p<0.001; 10.6 vs 0.8%, p<0.001)
- *ERBB2* fusions were rare (0.49%) with 97% occurring in HER2+ BC
- Of 8358 patients with outcome data, prognosis (HR 1.2, P=0.06) and response to chemotherapy (HR 1.1, P=0.42) was similar between patients with HER2- *ERBB2*mut and ERBB2-WT [Figure 5]

CONCLUSIONS

- *ERBB2*mut and fusions were observed in all breast cancer subtypes, more commonly observed in HER2+, metastatic, and lobular histology tumors, and did not influence prognosis
- These alterations may reflect response to treatment pressures in HER2+ tumors to reactivate HER2-mediated growth pathways and may represent a targetable upregulated oncogenic pathway in HER2- disease
- Ongoing identification of *ERBB2* alterations may augment treatment options for breast cancer patients and clinical outcomes from this approach are under investigation

INFORMATION

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