ESR1 Amplification Is Associated With Reduced Survival and Reduced Benefit From CDK4/6 Inhibition in Breast Cancer

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Background:

While ESR1 mutations are established mediators of endocrine resistance in breast cancer, the significance of ESR1 amplification remains poorly understood with reported amplification rates vary widely because of platform-specific differences.

We leveraged a large clinico-genomic real-world database and applied a stringent NextGen sequencing (NGS) approach to test ESR1 amplification. We identified ESR1 amplification as a molecular entity distinct from canonical estrogen-driven resistance mechanisms.

Methods:

- Breast tumors underwent NGS of DNA and RNA (WES/WTS; NextSeq and NovaSeq; Caris Life Sciences, Phoenix, AZ).
- Gene copy number was determined by CNVKit, with > = 6.0 copies defined as amplification to identify focal, high-level copy number events, minimizing misclassification of chromosome 6 copy gains.
- Real-world clinical data were obtained from insurance claims. Time on treatment (TOT) was defined treatment start to end; overall survival (OS) from tissue collection to last contact.
- Cox proportional hazards model and log-rank tests were used for survival analysis.
- Molecular comparisons used χ^2 or Mann-Whitney U with multiple-testing adjustment (q < 0.05).
- Gene set enrichment analysis was performed, with significance defined as FDR < 0.05.

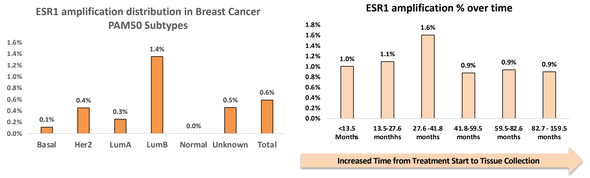
Results

1. Patient Characteristics

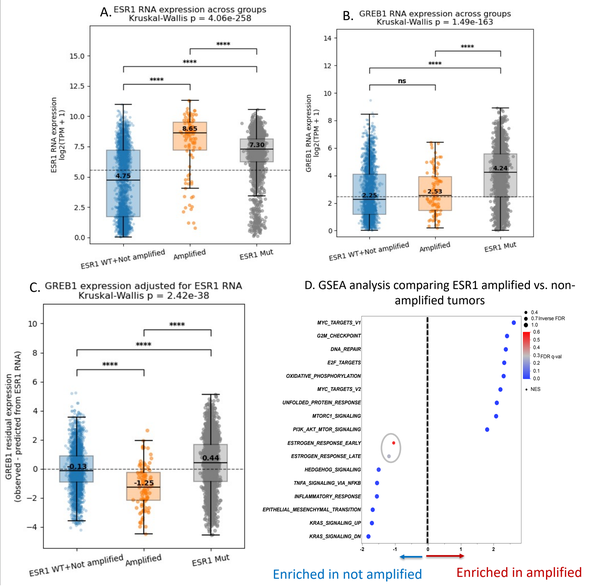
		Amplified	Not amplified	Total	p value
Age	**Median Age**	65.6	63	63	0.002
	IQR	59-73	53-72	53-72	
Gender	**Female**	165(0.59%)	27608	27773	0.1365
	Male	0(0.00%)	371	371	
Race	**Asian or Pacific Islander**	7(0.88%)	792	799	0.002
	Black or African American	11(0.29%)	3720	3731	
	White	109 (0.74%)	14571	14680	
	Other	5(0.57%)	877	882	
	Unknown	33(0.41%)	8019	8052	
Ethnicity	**Hispanic or Latino**	18(0.76%)	2335	2353	0.0465
	Not Hispanic or Latino	116(0.64%)	18106	18222	
	Unknown	31(0.41%)	7538	7569	
Subtype	**ER+ Her2-**	112(0.91%)	12218	12330	<0.0001
	Other/Unknown	47(0.49%)	9556	9603	
	Triple Negative	6(0.10%)	6205	6211	
Specimen Site	**Breast**	46(0.44%)	10463	10463	0.012
	Liver	34(0.78%)	4298	4298	0.066
	Lymph Node	25(0.81%)	3049	3049	0.102
	Bone	9(0.34%)	2643	2643	0.082
	Lung	12(0.66%)	1812	1812	0.678
	Chest/Chest Wall	12(0.81%)	1464	1464	0.221
	Skin	8(0.66%)	1201	1201	0.698
	Brain	5(0.72%)	694	694	0.61
	Other	14(0.59%)	2355	2355	0.889
Total		165(0.59%)	27979	27979	

Results

2. ESR1 amplification is particularly enriched in Luminal B subtype and does not change over time



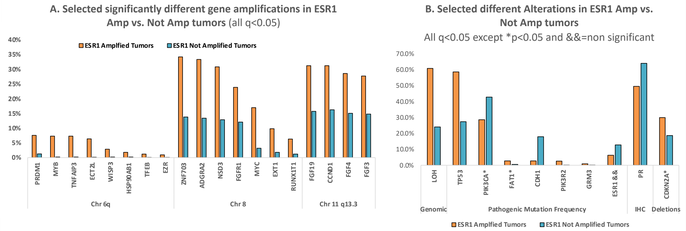
3. Transcriptomic analyses. Similar to mutations, ESR1 amplification is highly associated with increased ESR1 expression (A), however, unlike mutations, ESR1 amplification does not increase with GREB1 expression, one of the key estrogen receptor response genes, (B). As there is a moderate positive correlation between expressions of ESR1 and GREB1, we adjusted GREB1 expression with ESR1 expression and show that ESR1 amplified tumors express less GREB1 than expected for their ESR1 RNA level, opposite to ESR1 mutation(C). This is consistent with the GSEA findings (D) that estrogen-related gene sets are not enriched in ESR1 amplified tumors (blue gene sets are significantly enriched (FDR <0.05) while red and grey are not significant (FDR>0.2)



Results

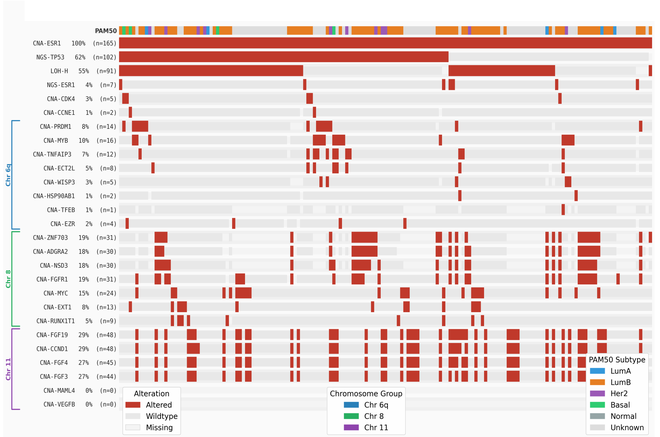
4. Distinct molecular landscape associated with ESR1 amplification

Co-amplification of various genes are seen in ESR1-amplified tumors (A) , as well as notable gLOH and TP53 prevalence (B)



5. Oncoprint of the ESR1 amplified tumors

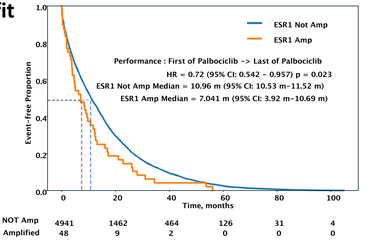
- ESR1 amplification is largely mutually exclusive with ESR1 mutations
- A higher prevalence of genomic loss of heterozygosity is seen
- The Chromosome 11q13 cluster (FGF19, CCND1, FGF4, FGF3, MAML2 and VEGFB) are often amplified in ESR1 amplified tumors
- The Chromosome 8p11 cluster (ZNF703, ADGRA2, NSD3, FGFR1) and other more scattered genes on 8q (RUNX1T1, EXT1 and MYC) are co-amplified.



Results

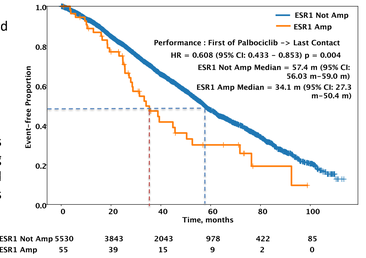
6. ESR1 Amplification association with reduced palbociclib benefit

A. Palbociclib time-on-treatment in all Breast Cancer



B. Palbociclib-associated OS in all Breast Cancer

This effect was significant after adjusting for TP53, gLOH, and CDH1 alterations



Conclusions

In this large real-world analysis, using whole-exome sequencing, we show that ESR1 amplification is a rare event in breast cancer.

ESR1 amplification carries significantly different genomic and transcriptomic features as well as clinical impact compared to the more well-established ESR1 mutations.

ESR1 amplification defines genomically unstable breast cancer subset with proliferative signaling and reduced clinical benefit from CDK4/6 inhibition, supporting its potential role as a negative predictive biomarker.

Reference

Sledge 2026, "Abstract PD10-11: Differential Benefit to Elacestrant in A Large Cohort of ER+ HER2- Breast Cancer: Impact of ESR1 Mutants and Prior Therapy" Clin Cancer Res (2026) 32 (4_Supplement): PD10-11.

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