Clinical and Molecular Landscape of ESR1 and PIK3CA Co-Mutated Hormone Receptor–Positive Metastatic Breast Cancer (HR+ MBC): Insights from 8,626 Patients Including Polyclonality and TP53 Alterations

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Abstract #1759

INTRODUCTION

Patients with HR+ MBC are treated with first-line endocrine therapy plus CDK4/6 inhibitors, but resistance often emerges through ESR1 or PIK3CA mutations (MUT). Co-mutations (co-MUT), present in ~10–15% of patients, remain poorly understood. Here, we compare molecular features, metastatic patterns and Real-world overall survival (rwOS) among patients with co-MUT vs. those with single or no mutations (no-MUT).

METHODS

We used Tempus Lens (Tempus AI, Inc., Chicago, IL) to identify patients with a primary diagnosis of MBC who had Tempus xF or xT testing from the Tempus multi-modal database (N = 8,626). Patients with tumor purity of at least 30% were assessed and all pathogenic or likely pathogenic (P/LP) somatic SNVs/indels for PIK3CA, ESR1, and TP53 were extracted. Polyclonal ESR1 and PIK3CA were defined as more than one distinct P/LP somatic SNV/indel. Tumor mutational burden (TMB) (mt/mB) was analyzed by DNA-sequencing. rwOS analyses were run for all samples collected in the year preceding any line of therapy using risk-set adjusted Cox models with the start of therapy as the index date, the later date of sequencing and treatment start as the study entry time, and a maximum follow up of 5 years.

RESULTS

- 8,646 patients met our inclusion criteria: 53% no-MUT, 32% PIK3CA-MUT, 9% ESR1-MUT, 6% co-MUT (PIK3CA + ESR1).
- Age and hormone receptor status differed by mutation group; race was similar across groups. (Table 1)
- Co-MUT group had more bone metastases; ESR1-only group had more liver and lung metastases.
- ESR1 mutations were found in about 13–16% of patients tested within 0–2 years before starting first-line therapy. The mutation rate increased to 57% among those tested two years after initiating first-line therapy. This group accounted for 24% of the overall cohort .
- PIK3CA mutations were detected in 52% tested within 1 year of first-line therapy.
- ESR1-MUT and co-MUT patients are more likely to have >3 metastatic sites.

Table 1. Demographic and Clinical Characteristics by Mutation Status

	No-MUT (N=4,561)	PIK3CA-only (N=2,747)	ESR1-only (N=779)	Co-MUT (N= 539)	p-value
ER and PR Status					<0.001
ER-, PR+	136 (3.1%)	44 (1.7%)	0 (0%)	2 (0.4%)	
ER+, PR-	1,793 (41%)	968 (37%)	152 (21%)	95 (18%)	
ER+, PR+	2,460 (56%)	1,615 (61%)	579 (79%)	417 (81%)	
Age at biopsy (IQR)	62 (51, 70)	64 (56, 72)	62 (54, 70)	65 (58, 73)	<0.001
Race, N (%)					0.069
White	2,375 (75%)	1,495 (79%)	424 (76%)	301 (80%)	
Black or African American	404 (13%)	193 (10%)	70 (12%)	37 (9.8%)	
Asian	142 (4.5%)	80 (4.2%)	25 (4.5%)	10 (2.6%)	
Other Race	257 (8.1%)	132 (6.9%)	42 (7.5%)	30 (7.9%)	
Bone metastasis, N (%)	2,245 (49%)	1,449 (53%)	455 (58%)	323 (60%)	<0.001
Liver metastasis, N (%)	1,187 (26%)	713 (26%)	434 (56%)	246 (46%)	<0.001
Lung metastasis, N (%)	952 (21%)	495 (18%)	177 (23%)	72 (13%)	<0.001
Polyclonal PIK3CA, N (%)	0 (0%)	354 (13%)	0 (0%)	99 (18%)	<0.001
Polyclonal ESR1, N (%)	0 (0%)	0 (0%)	66 (8.5%)	63 (12%)	<0.001
TP53 P/LP MUT, N (%)	1,457 (32%)	903 (33%)	170 (22%)	131 (24%)	<0.001
TMB, N (%)					<0.001
High	164 (6.3%)	277 (14%)	30 (5.7%)	48 (15%)	
Low	2,433 (94%)	1,720 (86%)	500 (94%)	278 (85%)	

Table 1. Age, hormone receptor status, metastatic sites, and sample collection year across WT, PIK3CA-MUT, ESR1-MUT, and co-MUT groups. P-values calculated via Kruskal-Wallis and Fisher's exact tests; IQR = Interquartile Range.

Table 2. Distribution of Sample Details Stratified by Assay Type

		Stratified by DNA Assay Type	
	Overall	xF	xT
Number of Observations	N=8,626	N=3,176	N=5,450
Year of Sample Collection			
Median (Q1, Q3)	2,022.00 (2,020.00, 2,023.00)	2,023.00 (2,022.00, 2,024.00)	2,021.00 (2,020.00, 2,023.00)
DNA Match Type, N (%)			
Tumor Only	5,907 (68%)	3,176 (100%)	2,731 (50%)
Tumor-Normal Matched	2,719 (32%)	0 (0%)	2,719 (50%)
Days from Initial Diagnosis to Sample Collection			
Median (Q1, Q3)	995 (29, 2,460)	1,196 (98, 2,659)	874 (0, 2,349)
DNA Assay, N (%)			
xF.v2	2,768 (32%)	2,768 (87%)	0 (0%)
xF.v3	408 (4.7%)	408 (13%)	0 (0%)
xT	101 (1.2%)	0 (0%)	101 (1.9%)
xT.v2	419 (4.9%)	0 (0%)	419 (7.7%)
xT.v3	429 (5.0%)	0 (0%)	429 (7.9%)
xT.v4	4,501 (52%)	0 (0%)	4,501 (83%)
DNA Final Tumor Percentage			
Median (Q1, Q3)	60 (50, 70)	NA (NA, NA)	60 (50, 70)
RNA Assay, N (%)			
RS	857 (19%)	0 (NA%)	857 (19%)
RS.v2	3,726 (81%)	0 (NA%)	3,726 (81%)
RNA Final Tumor Percentage			
Median (Q1, Q3)	60 (50, 70)	NA (NA, NA)	60 (50, 70)

Table 2. Description of the sample-related details.

Figure 1. Real-World Overall Survival by Mutation Status

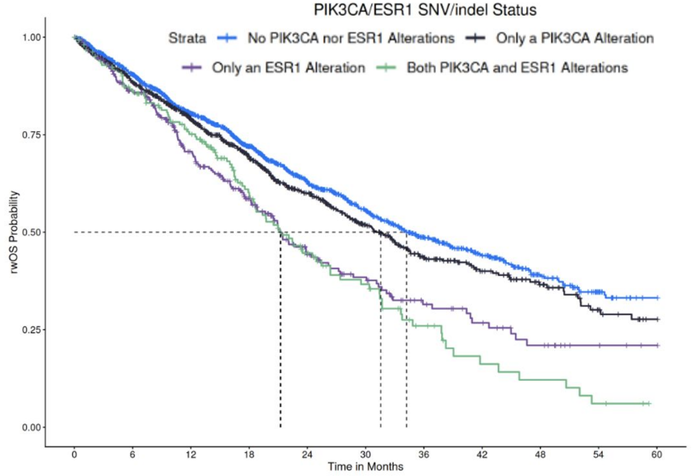


Figure 1. Kaplan-Meier curves comparing rwOS among WT, PIK3CA-MUT, ESR1-MUT, and co-MUT patients. HR and p-values shown for key comparisons.

Table 3. Real-World Overall Survival (rwOS) by Mutation Status

Characteristic	HR	95% CI	p-value
PIK3CA/ESR1 SNV/indel Status			
No PIK3CA nor ESR1 Alterations	—	—	
Only a PIK3CA Alteration	1.11	0.98, 1.27	0.1
Only an ESR1 Alteration	1.62	1.35, 1.94	<0.001
Both PIK3CA and ESR1 Alterations	1.75	1.42, 2.16	<0.001
No. of Patients	2,933		
No. of Events	1,202		

Table 3. Hazard ratios (HR), confidence intervals (CI), and p-values for rwOS comparisons among WT, single-MUT, and co-MUT groups.

RESULTS

- TP53 pathogenic/likely pathogenic mutations were found in 33% of PIK3CA-only and 24% of co-MUT tumors.
- High TMB (≥10 mut/Mb) seen in 15% of co-MUT, 14% of PIK3CA-MUT; polyclonality is more frequent in co-MUT.
- Most common variants: ESR1 p.D538G (6.4%), PIK3CA p.H1047R (14%).
- Co-MUT was detected by liquid biopsy in 40%, tissue sequencing in 61%.
- Co-MUT group had shorter rwOS (HR = 1.75, p < 0.001); TP53 mutation associated with worse survival (HR = 2.13, p < 0.001).
- Within co-MUT, TP53 status did not significantly impact OS (HR = 1.45, p = 0.083).
- Time to next treatment was shorter for co-MUT (HR = 1.65, p < 0.001) and TP53-mutant (HR = 1.60, p < 0.001) patients.

CONCLUSIONS

Co-mutant (PIK3CA + ESR1) patients had significantly shorter real-world overall survival and time to next treatment compared to wild-type patients. TP53 mutations independently predicted worse survival but did not further stratify outcomes within the co-mutant group. These findings highlight the importance of comprehensive molecular profiling to guide therapeutic strategies in advanced breast cancer. The high prevalence of co-mutations suggests dual PI3K/AKT and estrogen receptor pathway activation, supporting the need for combination targeted therapy approaches rather than single-agent strategies. Future studies should evaluate optimal sequencing of PI3K inhibitors and selective estrogen receptor degraders in co-mutant disease.

LIMITATIONS

This study is limited by its retrospective design, potential selection bias, and limited elacestrant utilization prior to FDA approval, restricting assessment of ESR1 and PI3K-targeted therapy sequencing in co-mutated patients

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