Exploration of racial differences in variants of uncertain significance (VUS), *ESR1* and *PIK3CA* mutation frequency, matched therapy use, and outcomes in metastatic breast cancer (mBC)

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Background

- Black patients are more likely to be diagnosed with mBC and have higher mortality rates than White patients, in part due to social determinants of health, higher rates of de novo mBC, and possible genomic differences by race and ethnicity.[1,2]
- Most variant classification efforts have focused on White populations, creating uncertainty about the prevalence and significance of VUS in Black patients.[3]
- It is unclear if mutation frequency differences exist in genes with known targets, such as *PIK3CA* and *ESR1*, and if differences in matched therapy rates impact real-world outcomes.[1,4]
- Here, we examined a real-world database for racial differences in VUS, *ESR1* and *PIK3CA* detected by circulating tumor DNA (ctDNA), matched therapy use, and outcomes by race for *ESR1* and *PIK3CA*.

Methods

- Patients with mBC and ctDNA (Guardant360) results post-mBC diagnosis were identified from Guardant INFORM (Guardant Health) database, which includes aggregated commercial payer claims and de-identified records with clinical genomic data and racial information, when available.
- VUS rates were analyzed by race and defined by OncoKB annotation.
- *ESR1* and *PIK3CA* mutations of interest were defined by location/oncogenicity: *ESR1* ligand binding domain (LBD) mutations and activating *PIK3CA* mutations, particularly those occurring in exons 9 and exon 20.
- Matched targeted therapy rates and real-world outcomes for patients treated with elacestrant and alpelisib were explored by race and line of therapy.
- Outcomes were assessed using real-world time to treatment discontinuation (rwTTD), time to next treatment (rwTTNT), and overall survival (rwOS), in months.
- Chi-squared tests compared proportions; log rank tests compared time to event outcomes.

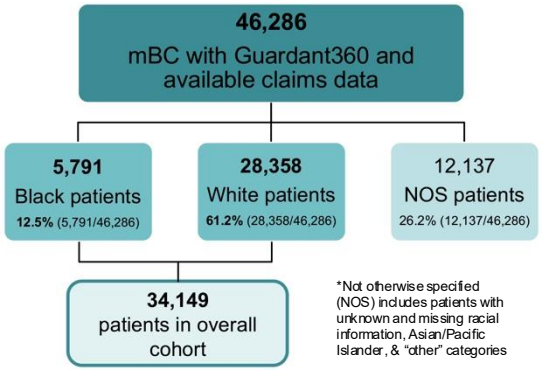


Figure 1. Patient Cohort Diagram.

References:
1. Podany (Davis) et al, *JAMA Net Open*, 2025, doi:10.1001/jamanetworkopen.2024.61899
2. Rizvi (Yu) et al, *Cancers*, 2024 doi: 10.3390/cancers16193294
3. Corpas (Fatumo) et al, *Cell Genomics*, 2025, doi: 10.1016/j.xgen.2024.100724
4. Keenan (Bardia) et al, *J Clin Oncol*, 2015, doi:10.1200/JCO.2015.62.2126

Results: VUS

Key Finding: No significant difference in VUS frequency between Black and White patients in real-world data

- Mean VUS frequency was similar between groups (2.40 Black vs 2.47 White, p>0.05)
- Rates of VUS in any gene were slightly higher in White patients (55.3% vs 53.9%, p<0.001), Table 1.
- Rates of VUS in biomarker associated mBC genes were similar between Black and White patients, Table1.

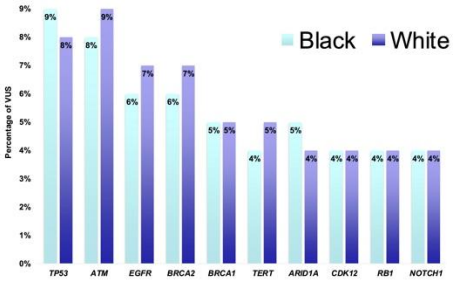


Figure 2. Genes with highest rates of VUS by race

Gene(s)	Black N=5,791		White N=28,358	
	N	%	N	%
All	3,119	53.9% (3,119/5,791)	15,688	55.3% (15,688/28,358)
PIK3CA	23	0.7%	113	0.7%
AKT1	10	0.3%	54	0.3%
PTEN	43	1.4%	170	1.1%
ESR1	24	0.4%	99	0.4%
*BRCA1/2**	87	1.5%	337	1.2%
HER2	19	0.3%	100	0.4%

*Somatic

Table 1. VUS by mBC biomarker associated gene

ESR1

- White patients had *ESR1* LBD mutation(s) more frequently than Black patients, but there was no difference in matched therapy use of elacestrant for *ESR1* LBD mutations by race, Table 2.

ESR1 mutation & Matched Therapy	Black N=5,791		White N=28,358		P-value
	N	%	N	%	
Any *ESR1*	1445	24.9% (1445/5,791)	7001	24.7% (7001/28,358)	P=0.67
ESR1 LBD	1263	87.4% (1263/5,791)	6249	89.3% (6249/28,358)	P=0.03
ESR1 LBD Therapy Matching	184	14.6% (184/1236)	842	13.5% (842/6249)	P=0.30

Table 2. *ESR1* and Matched Therapy. *ESR1* mutation prevalence and matched therapy rates by race

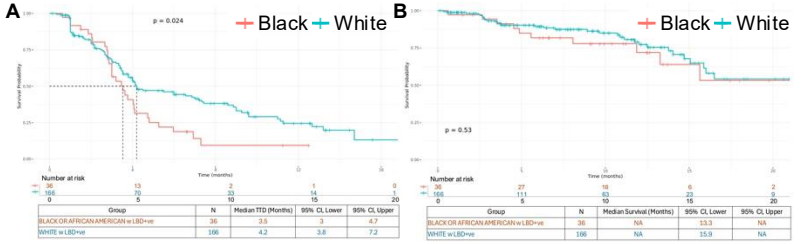


Figure 3. Real-world outcomes in *ESR1* LBD-mut pts receiving 2L elacestrant by race. Black pts with *ESR1* LBDmut and 2L elacestrant had significantly shorter rwTTD, 3.5 vs 4.2, p=0.024 (**A**) and shorter numeric rwTTNT (5.9 vs 8.9, p=0.32-not shown). However, there was no difference in rwOS between groups (**B**).

PIK3CA

Key Finding: Matched therapy use of elacestrant for *ESR1* LBD mutations and alpelisib for *PIK3CA* exon 9/exon 20 mutations was consistent across Black and White patients. However, Black patients had shorter rwTTD on 2L elacestrant.

PIK3CA mutation & Matched Therapy	Black N=5,791		White N=28,358		P-value
	N	%	N	%	
Any *PIK3CA*	1917	33.1% (1917/5,791)	10,114	35.7% (10,114/28,358)	P<0.001
PIK3CA exon 9 (codons: 532-554)	654	11.3% (654/5,791)	3996	14.1% (3996/28,358)	P<0.0001
PIK3CA exon 20 (codons: 1011-1062)	879	15.2% (879/5,791)	4302	15.2% (4302/28,358)	
PIK3CA exon 9 Therapy Matching	390	59.6% (390/654)	2507	62.7% (2507/3996)	P=0.31
PIK3CA exon 20 Therapy Matching	553	62.9% (553/879)	2797	65.0% (2797/4302)	P=0.49

- White patients had higher rates of *PIK3CA* mutation(s) than Black patients, but there was no difference in matched therapy use of alpelisib regardless of mutation type, Table 3.

Table 3. *PIK3CA* and Matched Therapy. *PIK3CA* mutation prevalence and matched therapy rates by race and mutation type

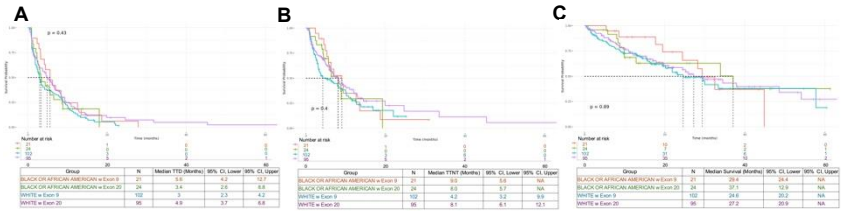


Figure 4. Real-world outcomes in *PIK3CA*-mut pts receiving 2L alpelisib by race and mutation type. rwTTD (**A**) rwTTNT (**B**) and rwOS (**C**) varied numerically by exon type and race but outcomes were not statistically significant.

Conclusions

In this large real-world analysis, no significant differences in VUS rate or *ESR1/PIK3CA*-matched therapy use between Black and White patients was observed, underscoring the need for continued inclusion of diverse populations in genomic discovery and prospective studies to clarify known outcome disparities