Clinicogenomic and Immune Profiles of Male Breast Cancer by Race: Insights from a Large Real-World Cohort

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INTRODUCTION

Male breast cancer (MBC) has been reported to account for less than 1% of breast cancer diagnoses. According to the American Cancer Society, there will be approximately 2,800 men diagnosed with breast cancer in 2025 and about 510 will die from the disease. In contrast to female breast cancer, individuals diagnosed with MBC tend to be diagnosed at older ages, tend to be predominantly hormone receptor positive, androgen receptor positive, and have a smaller percentage of lobular histology.

There have also been reported differences in rate of diagnosis and outcomes based on ethnicity. Furthermore, breast cancer incidence rates were 52% higher in Black men than white men, with some studies showing worse survival amongst Black men. The data is limited regarding disparities among MBC. This study would add to the literature with this comparison of the somatic alterations, immune phenotype, and potentially actionable germline variants in a real world database.

METHODS

Figure 1. Cohort selection

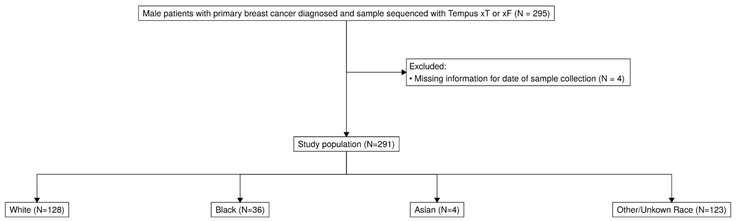


Figure 1. Patients with a primary diagnosis of breast cancer that received xF or xT testing and male at birth were selected from the Tempus database. Four patients were excluded due to missing sample collection dates. For patients with multiple samples sequenced, the sample collected earliest to primary diagnosis was selected for analysis.

- 291 male patients with primary breast cancer who underwent xF or xT testing in the Tempus multi-modal database (Tempus AI, Inc., Chicago, IL) were retrospectively identified using Tempus Lens and stratified via self-reported race documentation (N= 128 [44%] White, 36 [12%] Black, 4 [1.4%] Asian, 123 [42%] other or unknown race).
- Patients with xR testing (RNA) were classified into PAM50 subtypes using a Tempus-derived algorithm. Immune infiltration was evaluated using quanTIseq methodology. Tumor mutational burden (TMB; mutations/megabase) and microsatellite instability were assessed by tissue DNA sequencing. PD-L1 combined positive scores (CPS) were determined by Tempus immunohistochemistry PD-L1 22c3 tissue staining.
- Real world overall survival (rwOS) was defined from the time of sample collection to death, last follow-up, or a study cutoff of 7 years, and was estimated using Kaplan-Meier methodology with comparisons via the log-rank test. Other patient demographic and clinical characteristics are described as N (%) or median (IQR), and compared between White and Black by Chi-squared/Fisher's or Wilcoxon rank sum tests as applicable.

RESULTS

- HR+/HER2-negative (39%) was the most common clinical subtype; HER2-positive (7.6%) and triple-negative (7%) were less frequent, with 50% unknown.
- Luminal A and B were predominant molecular subtypes, with no significant racial difference.
- AR, PIK3CA, and TP53 were frequent somatic mutations; BRCA2 was the most common germline mutation.
- PD-L1 negativity (<1% CPS) was more frequent in Black than White patients (71% vs. 50%, p=0.5).
- M2 macrophage infiltration was significantly lower in Black patients (median 4.58 vs. 5.62, p=0.036).
- CD8+ T cell infiltration was numerically lower in Black patients (median 0.03 vs. 0.15, p=0.3).
- Median real-world overall survival was numerically lower in Black compared to White patients (19.1 vs. 23.1 months, p=0.5), though not statistically significant.

Table 1. Baseline cohort characteristics

	Overall N = 291[1]	White N = 128[1]	Black N = 36[1]	Asian N = 4[1]	Other/Unknown N = 123[1]
Age at diagnosis	63 (55, 70)	63 (55, 71)	63 (57, 68)	57 (53, 68)	63 (56, 71)
Unknown	12	3	2	0	7
Ethnicity					
Not Hispanic or Latino	126 (93%)	87 (95%)	20 (100%)	3 (100%)	16 (76%)
Hispanic or Latino	10 (7.4%)	5 (5.4%)	0 (0%)	0 (0%)	5 (24%)
Unknown	155	36	16	1	102
DNA assay					
xT	199 (68%)	85 (66%)	24 (67%)	2 (50%)	88 (72%)
xF	92 (32%)	43 (34%)	12 (33%)	2 (50%)	35 (28%)
Stage[2]					
Stage 4	131 (87%)	59 (94%)	18 (86%)	3 (100%)	51 (81%)
Stage 2	8 (5.3%)	3 (4.8%)	0 (0%)	0 (0%)	5 (7.9%)
Stage 3	6 (4.0%)	0 (0%)	3 (14%)	0 (0%)	3 (4.8%)
Stage 1	5 (3.3%)	1 (1.6%)	0 (0%)	0 (0%)	4 (6.3%)
Unknown	141	65	15	1	60
HR status[2]					
NOS/Unknown	141 (48%)	64 (50%)	19 (53%)	0 (0%)	58 (47%)
Breast Cancer: HR+, HER2-	114 (39%)	44 (34%)	13 (36%)	4 (100%)	53 (43%)
Breast Cancer: HR+, HER2+	22 (7.6%)	12 (9.4%)	3 (8.3%)	0 (0%)	7 (5.7%)
Breast Cancer: TNBC	13 (4.5%)	8 (6.3%)	1 (2.8%)	0 (0%)	4 (3.3%)
Breast Cancer: HR-, HER2+	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)
PAM50 subtype					
LumA	109 (63%)	45 (62%)	15 (68%)	1 (50%)	48 (62%)
LumB	43 (25%)	17 (23%)	3 (14%)	1 (50%)	22 (29%)
Basal	14 (8.0%)	6 (8.2%)	1 (4.5%)	0 (0%)	7 (9.1%)
Her2	8 (4.6%)	5 (6.8%)	3 (14%)	0 (0%)	0 (0%)
Unknown	117	55	14	2	46

[1] Median (Q1, Q3); n (%)
[2] Documented within 60 days of sample collection

Figure 2. Overall somatic mutation frequencies in White and Black male breast cancer patients

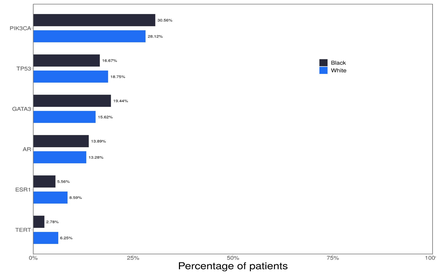


Figure 2. Frequency of somatic alterations in selected genes. Somatic alterations include pathogenic/likely pathogenic short variants, copy number variants, and fusions.

Figure 3. Immune cell infiltration

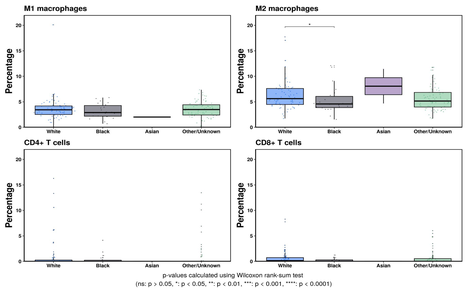


Figure 3. Immune cell infiltrate estimates in selected cell types via quanTIseq method.

Table 2. Immune biomarker results in xT-tested population

	Overall N = 199[1]	White N = 85[1]	Black N = 24[1]	Asian N = 2[1]	Other/Unknown N = 88[1]
Median TMB	3.16 (2.11, 5.26)	2.63 (1.71, 4.74)	4.39 (2.11, 5.53)	1.58 (1.05, 2.11)	3.68 (2.11, 5.00)
TMB categorical					
TMB low (<10 mut/mB)	188 (94%)	81 (95%)	22 (92%)	2 (100%)	83 (94%)
TMB high (>=10 mut/mB)	11 (5.5%)	4 (4.7%)	2 (8.3%)	0 (0%)	5 (5.7%)
MSI status					
Stable	199 (100%)	85 (100%)	24 (100%)	2 (100%)	88 (100%)
PDL1 22c3 CPS score					
< 1%	52 (60%)	17 (50%)	10 (71%)	0 (NA%)	25 (64%)
1% - 49%	34 (39%)	16 (47%)	4 (29%)	0 (NA%)	14 (36%)
>= 50%	1 (1.1%)	1 (2.9%)	0 (0%)	0 (NA%)	0 (0%)
Unknown	112	51	10	2	49

[1] Median (Q1, Q3); n (%)

Figure 4. Overall survival in White and Black patients

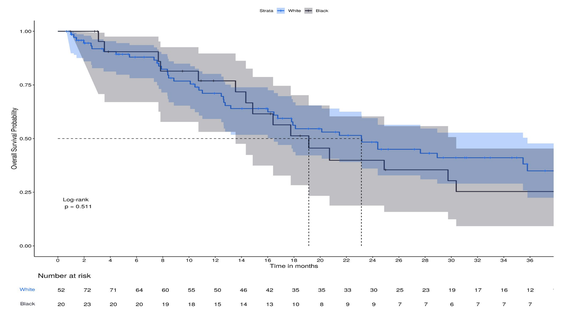


Figure 4. Overall survival (OS) is described from sample collection date to date of to death, last follow-up, or at study limit of 7 years from sample collection in the at-risk subset of patients. Median OS is compared between White and Black using a log-rank test.

CONCLUSIONS

This real-world analysis of male breast cancer patients revealed broadly similar clinicogenomic profiles between Black and White men, with notable exceptions including significantly lower M2 macrophage infiltration, numerically lower CD8+ T cell infiltration, and higher rates of PD-L1 negativity in Black patients. These immune microenvironment differences may have implications for immunotherapy response, underscoring the need for further research into the biological underpinnings and clinical impact of immune variation in racially diverse male breast cancer populations.

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