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RESEARCH

Racial disparities in outcomes of patients with stage I-III triple-negative breast cancer after adjuvant chemotherapy: a post-hoc analysis of the E5103 randomized trial

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Abstract

Purpose Breast cancer mortality is higher in Black women than other racial groups. This difference has been partially attributed to a higher proportion of triple-negative breast cancer (TNBC). However, it is uncertain if survival disparities exist in racially diverse TNBC patients receiving similar treatments. Here, we examine racial differences in disease-related outcomes in TNBC patients treated on the E5103 clinical trial.

Methods From 2007 to 2011, 4,994 patients with stage I-III HER2-negative breast cancer were randomized to adjuvant chemotherapy with or without bevacizumab. This analysis was limited to the subset of 1,742 TNBC patients with known self-reported race. Unadjusted Kaplan-Meier curves and adjusted Cox-Proportional Hazards models were used to determine breast cancer events and survival outcomes.

Results Of the analysis population, 51 (2.9%) were Asian, 269 (15.4%) Black, and 1422 (81.6%) White. Median age was 51 years. Patient characteristics, treatment arm, and local therapies were similar across racial groups. White women were more commonly node-negative (56% vs. 49% and 44% in Asian and Black women, respectively; $p < 0.01$). At a median follow-up of 46 months, unadjusted Kaplan-Meier locoregional and distant recurrence, and disease-free and overall survival, did not differ significantly by race. In Cox models adjusted for patient and tumor characteristics and treatment arm, race was not associated with any disease event. Larger tumor size and nodal involvement were consistently associated with breast cancer events.

Conclusion This clinical trial population of similarly treated TNBC patients showed no racial differences in breast cancer outcomes. Disease extent, rather than race, was associated with disease events.

Keywords Triple negative breast cancer · Racial disparities · Randomized trial

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Introduction

Despite advances in breast cancer screening and treatments, breast cancer mortality rates remain higher for non-Hispanic Black (NHB) patients compared to non-Hispanic White (NHW) patients [1], with 40% increased mortality among NHB patients across breast cancer subtypes. Triple-negative breast cancer (TNBC) represents a diverse group of aggressive cancers defined by lack of estrogen, progesterone, and human epidermal growth factor 2 (HER2) receptors. TNBC is more common in NHB patients, comprising up to 21% of breast cancer diagnoses in 2020 as compared to 11% of diagnoses in NHW patients [2]. Further, TNBC tends to present at a younger age and at a more advanced disease stage in NHB patients [3, 4].

Among patients with TNBC within national cancer registry data, NHB patients have been noted to have 7% higher breast cancer mortality and 4% higher all-cause mortality compared to NHW patients [1, 2, 5]. These findings may be partially explained by presentation at more advanced stages of disease, earlier age at diagnosis, and more aggressive tumor biology compared to NHW patients [6, 7]. Additionally, there is increasing evidence that stress secondary to experienced racism and poverty may mediate the increased mortality from TNBC [8]. Thus, some of the racial disparities in TNBC outcomes noted in the general population may be confounded by various social determinants of health including limited healthcare access or differential receipt of treatment [4, 9].

Although there appear to be disparate survival outcomes by race in patients with TNBC in population-based cancer registry studies, it is not clear whether these differences persist within clinical trial populations. Provided that certain non-biological factors are controlled for, the clinical trial setting can be helpful to determine whether racial disparities persist in an environment with more uniform access to care and treatment. The purpose of this study was to explore disease outcomes by race in patients with TNBC treated with adjuvant chemotherapy in the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN) E5103 clinical trial.

Methods

Data source

E5103 was a double-blind randomized phase III clinical trial that examined the effect of adjuvant chemotherapy with or without bevacizumab on invasive disease-free survival (IDFS) in patients with HER2-negative breast cancer. Between 2007 and 2011, 4,994 patients with node-positive or high-risk node-negative stage I-III HER2-negative disease were enrolled. Patients were randomized to adjuvant chemotherapy with or without bevacizumab. Eligible patients with TNBC included those with tumors > 1 cm or with node-positive disease. Patients were excluded if they had any prior cytotoxic chemotherapy or hormonal therapy, major surgery within 4 weeks of protocol start, and/or inadequate hepatic, renal, or hematologic function. The full study criteria have previously been reported [10]. All patients were treated with adjuvant doxorubicin and cyclophosphamide (AC) every 2–3 weeks for 4 cycles followed by paclitaxel (T) weekly for 12 weeks. Patients were randomized to either chemotherapy alone (arm A), chemotherapy with concurrent bevacizumab (arm B), or chemotherapy with concurrent and sequential bevacizumab (arm C). Randomization schema and inclusion criteria for the parent and present sub-study are outlined in Fig. 1.

Variables and endpoints

This study was an unplanned, secondary analysis of the prospective E5103 clinical data and was limited to the 1,742 patients with TNBC and known self-reported race. Exclusions included 3228 patients with hormone-receptor positive tumors, 20 patients without known self-reported race, 3 with missing tumor size, and 1 patient with no follow-up information (Fig. 1). Available patient characteristics

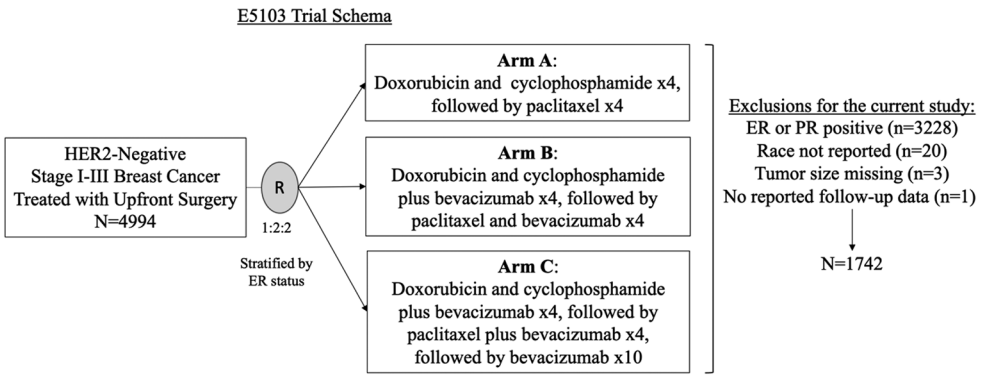

Fig. 1 E5103 schema and exclusions

included age, race, and sex, and ECOG functional status. Cancer-specific variables included tumor size, nodal status, histologic grade, lymph node involvement, and performance status. Treatment metrics such as primary surgery and local therapy, follow-up time, adverse events, and treatment arm were also included.

The endpoints for this post hoc analysis were disease events, namely locoregional recurrence (LRR), distant recurrence (DR), IDFS, and overall survival (OS). Follow-up data were collected from the time of randomization to time of event or last follow-up. LRR was defined as ipsilateral recurrence in breast, skin, chest wall, or regional nodes without concurrent DR; patients were censored at the time of a non-LRR event. DR was defined as a disease recurrence outside of the breast or ipsilateral regional nodal basin; patients were censored at the time of a non-DR event. IDFS was defined as time from the date of randomization to the first treatment failure (invasive ipsilateral, local/regional, or distant recurrence, invasive contralateral breast cancer, invasive non-breast second primary malignancy or death from any cause); cases without documented IDFS event were censored at the date of last follow-up. OS was defined as the time from date of randomization to death from any cause; otherwise, cases were censored at date last follow-up.

Statistical analysis

Descriptive statistics were used to examine patient, tumor, and treatment characteristics by race. Unadjusted Kaplan-Meier hazard curves were used to estimate 4-year LRR, DR, IDFS, and OS by race. A Cox proportional hazards regression analysis, adjusted for patient, tumor, and treatment factors, was used to identify hazard of each disease event. Covariates included race, study arm, tumor size, lymph node involvement, primary surgery, and radiation therapy. Model variables were chosen *a priori*. Hazard ratios (HR) > 1 suggested a higher hazard of disease event. All Confidence Intervals (CIs) are reported at a 95% level of significance. All *P*-values were 2 sided and $P < 0.05$ was considered statistically significant. SAS v 9.4 was used for all analyses.

Results

Cohort characteristics

A total of 1,742 patients with stage I-III TNBC enrolled in ECOG-ACRIN-E5103 trial were included in this analysis. Of these patients, 1,422 (81.6%) were White, 269 (15.4%) were Black, and 51 (2.9%) were Asian. Cohort characteristics are described in Table 1. The mean age was 51 years (range 21–82). Most patients had T2 ($n = 921$, 52.9%) or T3 tumors ($n = 98$, 5.6%) and just over half had node-negative disease ($n = 941$, 54.0%). Most patients had grade 3 disease ($n = 1714$, 88.5%). 909 patients (52.2%) underwent breast conservation and 833 (47.8%) underwent mastectomy.

Age, treatment arm, and locoregional treatment receipt were similar across racial groups (Table 1). White women were more commonly node-negative (56.1%) compared to Black (44.2%) and Asian women (49.0%), $p = 0.005$. Anatomic stage differed across racial groups, with White women having more stage I disease (25.6%), compared to 16.7% of Black women and 21.6% of Asian women ($p = 0.032$). Tumor size and grade were evenly distributed across racial groups.

Disease events by race

At a median follow-up of 46 months, the crude incidence of disease events did not differ significantly by race. Across all racial subgroups, LRR ranged from 2.0 to 8.6% ($p = 0.281$), DR ranged from 10.8 to 17.7% ($p = 0.348$), any IDFS event ranged from 17.7 to 20.5% ($p = 0.895$), and any death ranged from 9.8 to 12.7% ($p = 0.595$). Unadjusted 4-year Kaplan-Meier estimates of LRR, DR, IDFS, and OS were not significantly different by racial group (Fig. 2).

Although there were numerical differences in LRR and DR, these did not reach statistical significance: the estimated 4-year LRR rate was 8% for White patients, 11% for Black patients, and 2% for Asian patients ($p = 0.230$) and the 4-year DR rate was 14%, 12%, and 19% for White, Black, and Asian patients, respectively ($p = 0.410$).

In Cox-Proportional Hazards models adjusted for patient, treatment, and tumor factors, race was not associated with any disease event or survival (Table 2). Increasing tumor size and nodal involvement were significantly associated with all disease events and survival. T3 (vs. T1) tumor size was associated with 2-5-fold increased hazard across disease outcomes. Node-positivity was also associated with an increased hazard for each disease outcome. Mastectomy with postmastectomy radiation (compared to breast-conserving surgery with radiation) was associated with decreased LRR events and mastectomy alone was associated with increased IDFS and OS events. Age ≥ 50 was associated with decreased DR events and not associated with other outcomes.

Discussion

In this post-hoc analysis of TNBC patients treated with adjuvant chemotherapy +/- bevacizumab on the E5103 clinical trial, there were no differences observed in LRR, DR, IDFS, or OS, by race in either unadjusted or adjusted analyses.

Table 1 Cohort characteristics, stratified by race

Variable	Total $N=1742$	White $N=1422$	Black $N=269$	Asian $N=51$	P-value
Age					
Mean (range)	51.0 (21–82)	51.2 (21–82)	50.1 (25–74)	49.0 (28–55)	0.102
ECOG Functional Status					
Fully Active	1510 (86.7%)	1235 (86.9%)	231 (85.9%)	44 (86.3%)	0.908
Restricted	232 (13.3%)	187 (13.2%)	38 (14.1%)	7 (13.7%)	
Treatment arm					
Arm A	339 (19.5%)	272 (19.1%)	54 (20.1%)	13 (35.5%)	0.465
Arm B	692 (39.7%)	568 (39.9%)	101 (37.6%)	23 (45.1%)	
Arm C	711 (40.8%)	582 (40.9%)	114 (42.4%)	15 (29.4%)	
Tumor Size					
pT1	723 (41.5%)	600 (42.2%)	101 (37.6%)	22 (43.1%)	0.069
pT2	921 (52.9%)	747 (52.5%)	145 (53.9%)	29 (56.9%)	
pT3	98 (5.6%)	75 (5.3%)	23 (23.5%)	0	
Nodal Status					
pN0	941 (54.0%)	797 (56.1%)	119 (44.2%)	25 (49.0%)	0.005
pN1	528 (30.3%)	409 (28.8%)	104 (38.7%)	15 (29.4%)	
pN2-3	273 (15.7%)	216 (15.2%)	46 (17.1%)	11 (21.6%)	
Grade					
1 or 2	173 (9.9%)	145 (10.2%)	21 (7.8%)	7 (13.7%)	0.176
3	1714 (88.5%)	1258 (88.5%)	241 (89.6%)	42 (82.4%)	
Unknown	28 (1.6%)	19 (1.3%)	7 (2.6%)	2 (3.9%)	
Pathological Stage					
Stage I	420 (24.1%)	364 (25.6%)	45 (16.7%)	11 (21.6%)	0.032
Stage II	1016 (58.3%)	817 (57.5%)	170 (63.2%)	29 (56.8%)	
Stage III	306 (17.6%)	241 (16.9%)	54 (20.1%)	11 (21.6%)	
Locoregional Treatment					
BCS + WBRT	800 (45.9%)	653 (45.9%)	127 (47.2%)	20 (39.2%)	0.369
BCS + PBI	28 (1.6%)	22 (1.6%)	6 (2.2%)	0	
BCS alone	81 (4.7%)	62 (4.4%)	15 (5.6%)	4 (7.8%)	
Mastectomy	430 (24.7%)	361 (25.4%)	55 (20.5%)	14 (27.5%)	
Mastectomy + PMRT	317 (18.2%)	261 (18.4%)	46 (17.1%)	10 (19.6%)	
Unknown	86 (4.9%)	63 (4.4%)	20 (7.4%)	3 (5.9%)	
Disease Event					
Any IDFS Event	345 (19.8%)	281 (19.8%)	55 (20.5%)	9 (17.7%)	0.895
LRR	127 (7.3%)	103 (7.2%)	23 (8.6%)	1 (2.0%)	0.281
DR	223 (12.8%)	185 (13.0%)	29 (10.8%)	9 (17.7%)	0.348
Any death	214 (12.3%)	180 (12.7%)	29 (10.8%)	5 (9.8%)	0.595

Abbreviations Arm A- chemotherapy alone; arm B- chemotherapy with concurrent bevacizumab; arm C- chemotherapy with concurrent and sequential bevacizumab. ECOG Eastern Cooperative Oncology Group. BCS- breast conserving therapy. WBRT- whole breast radiation therapy. PBI – partial breast irradiation. PMRT- post-mastectomy radiation therapy. IDFS - invasive disease-free survival. LRR - locoregional recurrence. DR - distant recurrence

Disease extent, characterized by tumor size and nodal burden, were the primary factors associated with breast cancer events and survival.

Population-based and multi-institutional studies generally suggest an increased incidence of and mortality from TNBC in Black women compared to White women [3, 11–15], while single institutional series are more varied in terms of whether racial disparities are present in survival outcomes of TNBC [16–18]. These studies frequently demonstrate advanced stage of disease at diagnosis, earlier onset of cancer, and more aggressive tumor biology in NHB patients compared to NHW patients [6, 7]. Although biological factors are commonly cited as an explanation for the racial differences in mortality from TNBC, mortality differences are not fully explained by biologic factors alone, and the role of social determinants of health is an increasingly recognized contributing factor to disparities [14, 19].

Several population-based studies have demonstrated that structural racism leading to neighborhood disadvantage contributes to the increased mortality seen in Black women with TNBC [9, 20]. Further, studies have shown that NHB women are more likely to have public or no insurance, diminishing access to care and increasing incidence of and mortality from.

TNBC [5, 8, 21]. Even when NHB women have access to care, they have lower odds of receiving treatment for TNBC compared to their White counterparts, a finding that has been associated with increased mortality [4, 12]. NHB women are also more likely to have delayed initiation of treatment after diagnosis of TNBC [5, 22]. Taken together, the literature suggests that diminished access to care, decreased uptake of and delays in treatment within the NHB population contribute to survival disparities in TNBC.

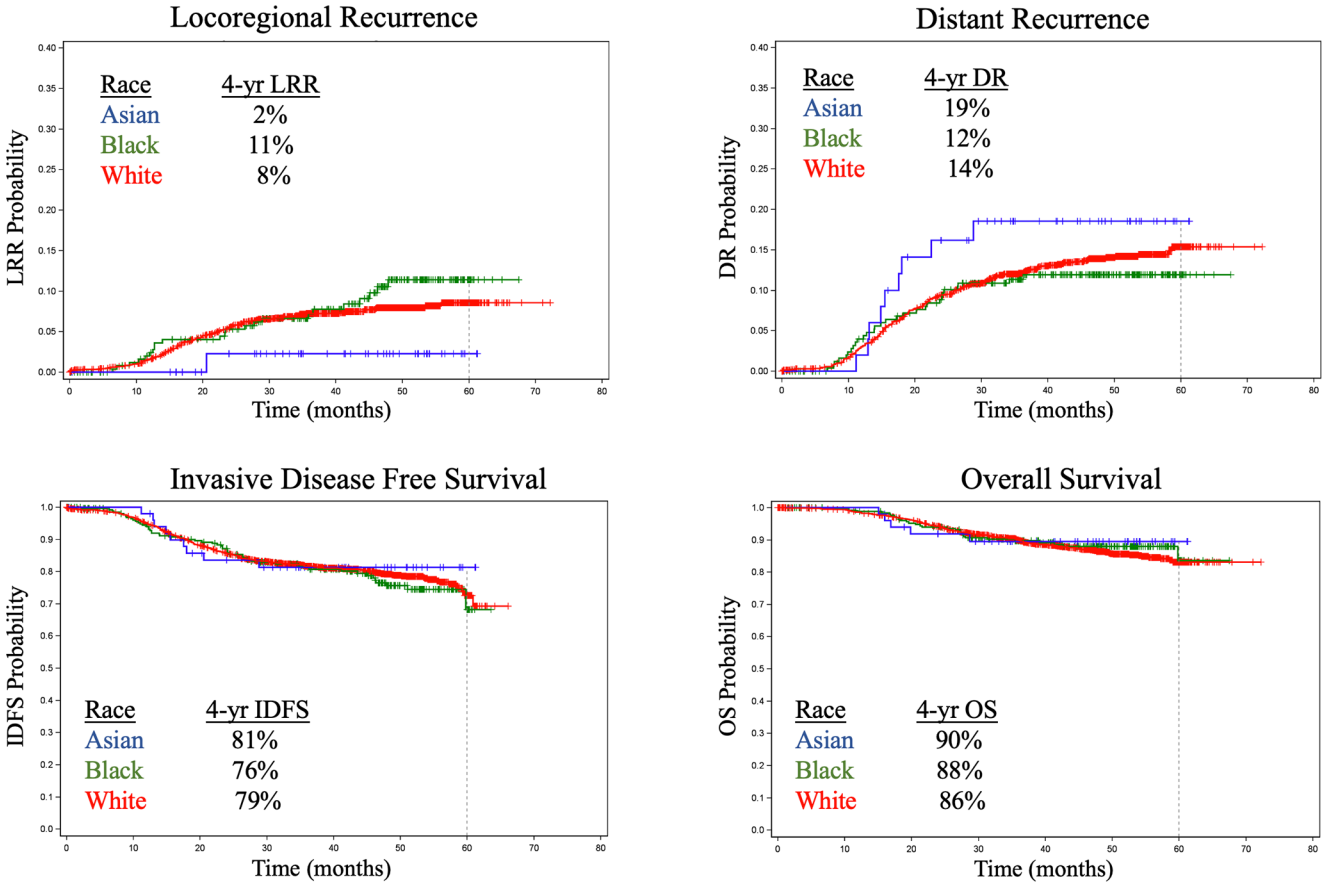

Fig. 2 4-year Kaplan-Meier estimates in disease outcomes for women with triple-negative breast cancer (TNBC) in the E5103 Trial, stratified by race ($n = 1{,}742$). *Abbreviations* LRR – locoregional recurrence. DR- distant recurrence. IDFS – invasive disease-free survival. OS – overall survival

Clinical trial populations represent a select patient population with the support, willingness, and access to participate in clinical trials. Previous work examining inequities in clinical trial populations has suggested that disparities in outcomes by race still exist in hormone-receptor positive breast cancer, while this effect appears to be attenuated in hormone-receptor negative breast cancer [23–26]. In a retrospective analysis of 6676 patients in 35 Southwest Oncology Group trials, post-menopausal Black women with hormone receptor positive breast cancer were found to have higher mortality than other postmenopausal patients, but this difference was not observed in premenopausal patients with hormone receptor-negative breast cancer [23]. Similarly, a pooled analysis of 9702 patients in 8 National Surgical Adjuvant Breast and Bowel Project trials demonstrated that Black race was associated with inferior distant relapse-free survival in hormone receptor-positive breast cancer but not in hormone receptor- negative breast cancer [27]. Within the E1199 randomized clinical trial comparing the efficacy of different taxane regimens in patients with node-positive, stage II-IIIA breast cancer, a secondary analysis of 4817 eligible patients demonstrated that Black patients with hormone receptor- positive breast cancer had worse disease-free and OS compared to non-Black patients, but this was not observed in the subset of patients with TNBC [28]. A previous correlative analysis of the E5103 clinical trial focused on genetic ancestry differences in treatment toxicity and outcomes, also finding a trend of inferior disease-free survival in patients of African ancestry with hormone receptor-positive disease but not in patients with hormone receptor-negative breast cancer [29]. Consistent with these previous analyses in clinical trial populations, our study did not find differences in IDFS or OS in patients with TNBC in the E5103 trial; further, it demonstrated no differences in LRR or DR between racial groups.

It is interesting that racial disparities appear to exist differentially across subtypes of breast cancer, even within clinical trial populations. One possible explanation is that within TNBC, treatment is more standardized to include locoregional therapy and chemotherapy in most patients. In hormone receptor-positive breast cancer, longer-term treatments, including extended duration adjuvant endocrine therapy, allow more opportunities for differential access, adherence, tolerance, duration of treatments, and possibly

Table 2 Adjusted cox-proportional hazards model for each disease outcome

Variable	LRR HR[a] (95% CI)	DR HR [a] (95% CI)	IDFS HR [a] (95% CI)	OS HR [a] (95% CI)
Race				
White	1	1	1	1
Black	1.09 (0.69–1.72)	0.75 (0.51–1.11)	0.96 (0.72–1.29)	0.78 (0.52–1.15)
Asian	0.22 (0.03–1.56)	1.32 (0.70–2.60)	0.81 (0.41–1.58)	0.69 (0.28–1.69)
Age				
< 50	1	1	1	1
≥ 50	0.60 (0.42–0.86)	**0.75 (0.57–0.98)**	0.88 (0.71–1.09)	1.01 (0.77–1.33)
Functional Status				
Fully Active	1	1	1	1
Restricted	0.85 (0.48–1.48)	1.12 (0.77–1.63)	1.10 (0.81–1.49)	1.14 (0.78–1.69)
Locoregional Treatment				
BCS + WBRT	1	1	1	1
BCS + PBI	1.70 (0.52–5.55)	0.83 (0.20–3.41)	1.35 (0.59–3.07)	1.50 (0.47–4.80)
BCS alone	1.14 (0.45–2.86)	1.36 (0.68–2.72)	1.29 (0.74–2.24)	**2.10 (1.10–3.98)**
Mastectomy	1.50 (0.98–2.30)	1.34 (0.94–1.90)	**1.36 (1.03–1.79)**	**1.72 (1.19–2.48)**
Mastectomy + PMRT	**0.57 (0.33–0.99)**	0.78 (0.54–1.13)	0.80 (0.58–1.09)	0.93 (0.64–1.35)
Unknown	1.77 (0.70–4.45)	1.21 (0.53–2.79)	1.61 (0.89–2.92)	1.72 (0.74–3.99)
Tumor Size				
pT1	1	1	1	1
pT2	0.89 (0.61–1.30)	**1.77 (1.28–2.43)**	**1.35 (1.06–1.71)**	**1.84 (1.33–2.56)**
pT3	**2.01 (1.03–3.92)**	**5.08 (3.22–8.01)**	**3.32 (2.26–4.88)**	**4.07 (2.53–6.56)**
Nodal Status				
pN0	1	1	1	1
pN1	**1.87 (1.23–2.84)**	**2.50 (1.77–3.51)**	**1.73 (1.33–2.24)**	**2.40 (1.68–3.43)**
pN2-3	**3.94 (2.40–6.46)**	**5.33 (3.64–7.82)**	**3.38 (2.50–4.58)**	**6.13 (4.14–9.07)**
Grade				
1 or 2	1	1	1	1
3	0.84 (0.48–1.47)	0.88 (0.58–1.34)	0.95 (0.67–1.35)	1.12 (0.71–1.77)
Unknown	1.63 (0.53–5.06)	1.19 (0.45–3.14)	1.02 (0.43–2.45)	0.88 (0.26–2.98)
Study Arm				
Arm A	1	1	1	1
Arm B	1.32 (0.81–2.13)	1.27 (0.88–1.83)	1.03 0.79–1.37)	1.00 (0.70–1.43)
Arm C	0.81 (0.48–1.35)	0.93 (0.63–1.36)	0.78 (0.58–1.04)	0.78 (0.54–1.13)

[a]Adjusted for all listed variables

Bold designates statistical significance

Abbreviations LRR - locoregional recurrence. DR - distant recurrence. IDFS - invasive disease-free survival. OS – overall survival. BCS- breast conserving therapy. WBRT- whole breast radiation therapy. PBI – partial breast irradiation. PMRT – postmastectomy radiation therapy. Arm A- chemotherapy alone; arm B- chemotherapy with concurrent bevacizumab; arm C- chemotherapy with concurrent and sequential bevacizumab

differential endocrine resistance mechanisms, all of which could contribute to disparate outcomes [30–34]. Outside of a clinical trial population, mortality differences may be prevalent across all breast cancer subtypes due to the increased influence of social determinants of health in the general population and disparities across the care continuum [8, 20, 26, 35]. Although our findings for a lack of disparities in the current study are encouraging, the lack of differences in disease outcomes by race may be related to the inherent selection bias of patients willing and able to participate in a clinical trial, which may account for less variation in socioeconomic factors that disproportionately affect Black women with TNBC. This study underscores the importance of accruing diverse patient populations onto clinical trials so that treatment results can be meaningfully generalized to the overall patient population.

Additional studies are warranted to further address the question of whether race-related variation exists in TNBC biology, especially as novel immunotherapy treatments become available. Existing studies demonstrate differences in the immune landscape of breast cancer between Black and White women as well as in TNBC subtypes [36–38]. These differences may become clinically relevant as advances are made in therapeutic manipulation of the tumor microenvironment.

This work has several limitations. Importantly, the trial was not powered for analysis of disease outcomes by race, and small cohorts of NHB and Asian patients limit analyses. As the trial was not designed with LRR and DR in mind, additional adjustment for potential confounding factors such as margin status and germline mutation status were not available. The socioeconomic status of the patients was also unavailable. Lastly, there is an inherent selection bias within clinical trial populations that limits generalizability to the general population. Despite these limitations, the strengths of this study include the use of a large, multicenter, randomized, clinical trial which was open at sites throughout the United States, providing a robust cohort to examine disparities and allows comparison of patients receiving similar treatments.

Conclusions

In this post-hoc analysis of the randomized E5103 clinical trial, there were no racial disparities in LRR, DR, IDFS or OS. Additional data are needed to better understand the disparities observed outside of a clinical trial setting. Our findings for similar outcomes within the context of relatively uniformly treated cohort raise the question of how much of the disparities seen outside of a clinical trial are related to differences in access and treatment.

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Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by O.K., S.L. and A.J. The first draft of the manuscript was written by S.L. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The datasets generated during and/or analyzed during the current study are available on request from the NCTN Data Archive [https://nctn-data-archive.nci.nih.gov/].

Declarations

Competing interests ELM reports consulting roles for Lilly, AstraZeneca, and Novartis. EAM reports compensated service on scientific advisory boards for AstraZeneca, BioNTech, Exact sciences (formerly Genomic Health), Merck, Moderna, Roche/Genentech; uncompensated service on steering committees for Bristol Myers Squibb, Lilly, and Roche/Genentech; speakers honoraria and travel support from Merck Sharp & Dohme; and institutional research support from Roche/Genentech (via SU2C grant) and Gilead. She receives research funding from Susan Komen for the Cure for which she serves as a Scientific Advisor. She also reports uncompensated participation as a member of the American Society of Clinical Oncology Board of Directors. TAK reports speaker honoraria and compensated service on scientific Advisory Board of Exact Sciences. She is also a Senior Associate Editor for Breast Cancer Research and Treatment. MCM reports consulting for Exact Sciences, Pfizer, Roche, Astra Zeneca, Lilly, Novartis, and Abbott; and research support from Novartis and Pfizer. LAN reports research support from Genentech. The remaining authors have no relevant financial or non-financial interests to disclose.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Brigham and Women's Hospital.

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