









Impact of Ethnicity on Breast Cancer Outcome: A Systematic Review and Meta-Analysis of Randomized Phase III Trials of the Last Decade

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ABSTRACT

PURPOSE It remains uncertain whether ethnicity affects the benefit derived from novel breast cancer (BC) treatments. Thus, we conducted a systematic review and meta-analysis to evaluate the heterogeneity of treatment efficacy across different ethnic groups, in both the advanced BC (aBC) setting and the early BC (eBC) setting.

METHODS We systematically searched PubMed, Embase, and Scopus for phase III randomized controlled trials (RCTs) leading to BC drug approval between 2013 and 2023 that had available hazard ratios (HRs) for outcome according to ethnicity. We excluded nonrandomized studies. We compared the three most represented ethnic groups, Whites, Asians, and Blacks, among themselves and with other underrepresented groups (UGs). The pooled HRs and 95% CI in ethnic subgroups were calculated using a random-effects model, and the heterogeneity between the estimates was assessed with an interaction test.

RESULTS Among 23 selected RCTs (14,000 patients) in the aBC setting, 20 provided HRs (95% CI) for progression-free survival (PFS) in the subgroup of Whites, 17 for Asians, four for Blacks, and 23 for non-Asians (Whites + all non-Asian UG) or non-Whites (Asians + all non-Asian UG). Risk of bias was low for all the included RCTs. The HRs for PFS with experimental versus control drugs were 0.62 (95% CI, 0.57 to 0.68) for Whites, 0.54 (95% CI, 0.44 to 0.66) for Asians, and 0.54 (95% CI, 0.34 to 0.85) for Blacks with no significant interethnic difference ($P = .233$ for Whites *v* Asians, $P = .564$ for Whites *v* Blacks, $P = .992$ for Asians *v* Blacks). Similarly, Whites versus non-Whites and Asians versus non-Asians showed no significantly different magnitude of benefit ($P = .406$ and $P = .226$, respectively). No differences were observed in eBC trials either.

CONCLUSION These results offer reassurance for the broader applicability of clinical trial results despite ethnic imbalance.

ACCOMPANYING CONTENT

 [Data Supplement](#)

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INTRODUCTION

A wide variability in breast cancer (BC) risk and outcomes across ethnicities has been described.¹⁻³ Despite the well-documented influence of ethnicity on BC incidence, genomic features, treatment response, and survival, ethnical diversity remains insufficiently addressed in clinical trials, with White population consistently overrepresented.⁴ However, recruitment in clinical trials has increased in Asia over the last decade, with a large patient pool and countries incentives having contributed to this rise.⁵ Therefore, Asian patients have recently become the second most enrolled ethnicity, following Whites. Some pivotal

trials that influenced our daily clinical activity were entirely carried out in Asiatic populations,^{6,7} or enrolled high rates of Asian patients BC.^{8,9}

On the contrary, the trial enrollment of patients of other ethnic backgrounds, such as Black/African Americans or Hispanic/Latinos, is still alarmingly limited.¹⁰ Blacks and Hispanics appear to share a lower incidence of BC compared with Whites.^{11,12} They also display characteristics of increased aggressiveness and a tendency for diagnosis at more advanced stages.^{11,12} In the case of African American women, they also appear to have higher BC mortality rates than White women.^{3,11}

CONTEXT

Key Objective

By analyzing data from randomized phase III clinical trials conducted over the past decade, this study aimed to assess whether certain ethnic subgroups have different magnitudes of benefit from novel breast cancer treatments. This work evaluated treatment efficacy across ethnic groups, including White, Asian, Black, and other underrepresented populations.

Knowledge Generated

The meta-analysis of 23 phase III trials evaluating a wide range of experimental drugs (including cyclin-dependent kinase 4/6 inhibitors, antibody-drug conjugates, and immune checkpoint inhibitors) in the advanced-disease setting found no significant differences in the magnitude of benefit among White, Asian, Black, and other underrepresented ethnic groups. Similarly, the meta-analysis of six trials in early-stage disease showed no differences in treatment benefit across ethnicities.

Relevance

These findings support the broader applicability of clinical trial results across diverse ethnic groups, despite potential imbalances in trial populations. Nonetheless, future efforts should aim for more balanced and ethnically representative enrollment in clinical trials to ensure equitable health care for all ethnic groups.

So far, several studies evaluated the underpinnings of BC variability among ethnicities, depicting a multifaceted panorama.^{1,13,14} Genetic factors, including cancer susceptibility and interethnic variations in drug metabolism and safety profile, might play a critical role.¹⁵ Interethnic differences were also found in microbiota composition and tumor microenvironment.¹⁶ Moreover, circulating estrogen levels, which influence both BC risk and the efficacy of antihormonal therapies, tend to be higher in White and Black women, because of a more abundant intake of dietary fat and higher body adiposity, and lower in Asian and Hispanic women.^{17,18}

Although the most substantial evidence on ethnic differences in drug metabolism, safety, and efficacy to date pertains to chemotherapeutic agents,¹⁹ data regarding newer therapies are emerging. For instance, when considering cyclin-dependent kinase 4/6 inhibitors (CDK4/6is), which have revolutionized the treatment scenarios for patients with hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative BC, ethnicity–treatment interactions were thought to play a relevant role, especially when comparing Asian and non-Asian populations.²⁰ The pharmacogenetic analysis of PALOMA-2/3 trials found different *ABCB1* and *ERCC1* single-nucleotide polymorphism allele frequencies between Asian and non-Asian patients, potentially explaining the higher frequency of palbociclib-induced neutropenia in Asian patients.²¹ Asian patients showed greater magnitude of progression-free survival (PFS) benefit from CDK4/6is when compared with non-Asian patients in a now-outdated meta-analysis.²² However, in a more recent meta-analysis, no difference in the magnitude of benefit from CDK4/6is was found between Asians and non-Asians.²³ Hence, given that the landscape of new available treatments, considering also antibody-drug conjugates (ADCs), poly (ADP-ribose) polymerase inhibitors

(PARPis), and immune checkpoint inhibitors (ICIs), is evolving rapidly, and that universal approval of these new drugs could come from studies with an unbalanced distribution of ethnicities, providing up-to-date evidence on outcomes by ethnicity is of paramount importance.

The aim of the present systematic review and meta-analysis is to evaluate and compare the relative benefit from novel BC therapies for the different ethnic groups in phase III (randomized controlled trials [RCTs]) that brought to drug approval in the last decade.

METHODS

Study Objectives

This study is a systematic review and meta-analysis of phase III RCTs. Its primary objective was to compare the outcomes of different ethnic subgroups enrolled in phase III RCTs that allowed the Food and Drug Administration (FDA) registration of novel BC treatments in the past 10 years.

Search Strategy

The reporting of this study conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 statement (Data Supplement, Tables S1 and S2).²⁴

Novel cancer therapies approved by FDA between January 2013 and December 2023 for the treatment of locally advanced (not amenable to locoregional therapy with curative intent), metastatic or early (ie, that has no spread beyond the breast or the axillary lymph nodes) BC were identified on the FDA website (comprehensive list available in the Data Supplement, Table S3).²⁵ In PubMed, Embase, and Scopus databases, two investigators (E.Z. and L.M.) selected phase

III RCTs that had already been published as full-text articles, which led to FDA approval of these drugs. The terms used were the name of every FDA-approved BC drug (time period 2013–2023), “breast cancer,” and “phase III,” combined with Boolean operators (Data Supplement, Table S4). No restrictions in terms of language were applied. The eligible trials for this analysis were those with the following characteristics: (1) phase III RCTs with published full-text article; (2) conducted in patients with locally advanced, metastatic or early BC; (3) comparing the standard therapy to an experimental cancer drug; (4) available information on PFS in the advanced setting and event-free survival (EFS) or invasive disease-free survival (IDFS) in the early setting; and (5) studies that reported the hazard ratios (HRs) and 95% CIs for outcome in ethnic subgroups. FDA²⁵ and European public assessment reports (EPARs)²⁶ of each experimental drug were also examined, to obtain the HR and 95% CI for ethnic subgroups not reported in the articles. This approach enabled us to expand the available data and enhance the robustness of our analyses.

The studies excluded from this analysis were those with the following characteristics: (1) negative RCTs that did not demonstrate a statistically significant benefit on the primary end point; (2) nonrandomized studies; (3) phase I and phase II clinical trials; (4) studies currently ongoing, not yet published, and for which insufficient results were available at the time of the literature search; and (5) studies reporting the HR for outcome depending on geographic area instead of ethnicity.

Data Extraction

Two investigators (E.D. and A.B.) independently extracted the data from all the full-text articles identified and included in the meta-analysis. In case of multiple reports relating to the same trial, the most recently published results were selected. Two investigators (E.Z. and L.M.) independently assessed the risk of bias for each trial using the Cochrane Risk of Bias tool (version 2) for RCTs.²⁷

Statistical Analysis

HRs and their 95% CI were extracted to explore the differential benefit of experimental and control arms in the ethnic groups. *Q* statistics were used to test for heterogeneity among the studies included in the meta-analyses. The proportion of total variability attributed to interstudy heterogeneity was assessed with the *I*² statistic, a confirmatory test for heterogeneity, with *I*² <25%, 25%–50%, and >50% representing low, moderate, and high degrees of heterogeneity, respectively. The pooled HR estimates were calculated using a random-effect approach, identified as the appropriate. The results were graphically displayed as forest plots, with HR <1.0 indicating better outcome in the experimental arm. The null hypothesis, that the interaction between ethnicity and experimental drug efficacy is equal across subgroups, was tested with a χ^2 test. A funnel plot was used for publication bias assessment.

All reported *P* values are two-sided. Calculations were performed using the Comprehensive Meta-Analysis Software, version v. 2.2.064 (Biostat, Englewood, NJ),²⁸ and R, version 4.2.3.

RESULTS

The database search retrieved 2,962 publications, from which we selected 81 potentially relevant articles for full-text screening (Fig 1). After full article review, 29 RCTs fulfilled the inclusion criteria, being phase III trials that brought to FDA approval of a BC drug. Risk of bias was low for all the included trial (Data Supplement, Table S4). Funnel plot for assessment of the risk of publication bias is available in the Data Supplement (Fig S1).

The drug set was heterogeneous and the distribution of trials by drug type is shown in Figures 2A and 2B: in the advanced setting, most of the included trials tested a CDK4/6i (seven trials) or an anti-HER2 drug (seven trials; Fig 2A); in the early setting, three trials tested three different anti-HER2 treatments, and the other three trials tested a CDK4/6i, a PARPi, and an ICI, respectively (Fig 2B).

The Metastatic Setting

Twenty-three phase III RCTs were identified in the metastatic setting (Table 1).^{8,9,29–50} Of the total 14,000 patients enrolled, the majority (67%) were of White ethnicity, followed by Asian ethnicity (19%; Fig 2C).

The proportion of White patients enrolled varied significantly across trials, ranging from 27% in DESTINY-Breast03 to 85% in MONALEESA-3.^{8,32} Among the 20 RCTs reporting HRs for the White patient subgroup, the experimental treatment arms were associated with a pooled 38% reduction in the risk of disease progression compared with standard arms (HR, 0.62 [95% CI, 0.57 to 0.68]) with high interstudy heterogeneity (*Q* = 43.1; *P* = .001; *I*² = 55.9%; Fig 3A).

Inclusion of Asian patients in the 23 selected RCTs ranged from 3% in the TROPiCS-02 trial to 60% in the DESTINY-Breast-03 trial.^{8,44} Overall, 17 trials provided HR (95% CI) for PFS in the subgroup of Asian patients and were pooled. As expected, Asian patients treated in the experimental arms had a pooled 46% disease progression risk reduction compared with Asian patients treated in the standard arms (HR, 0.54 [95% CI, 0.44 to 0.66]; Fig 3B). The interstudy heterogeneity was high (*Q* = 49.9; *P* < .001; *I*² = 67.9%).

There was no significant difference in the efficacy of the experimental drugs between Asian and White ethnicity (*P* = .233).

Black patients were only 3% of the total (Fig 2C), with the ASCENT trial⁴³ enrolling the highest proportion of Black patients (12% of the total patients included in the trial). Four trials had available HRs for PFS for the experimental versus

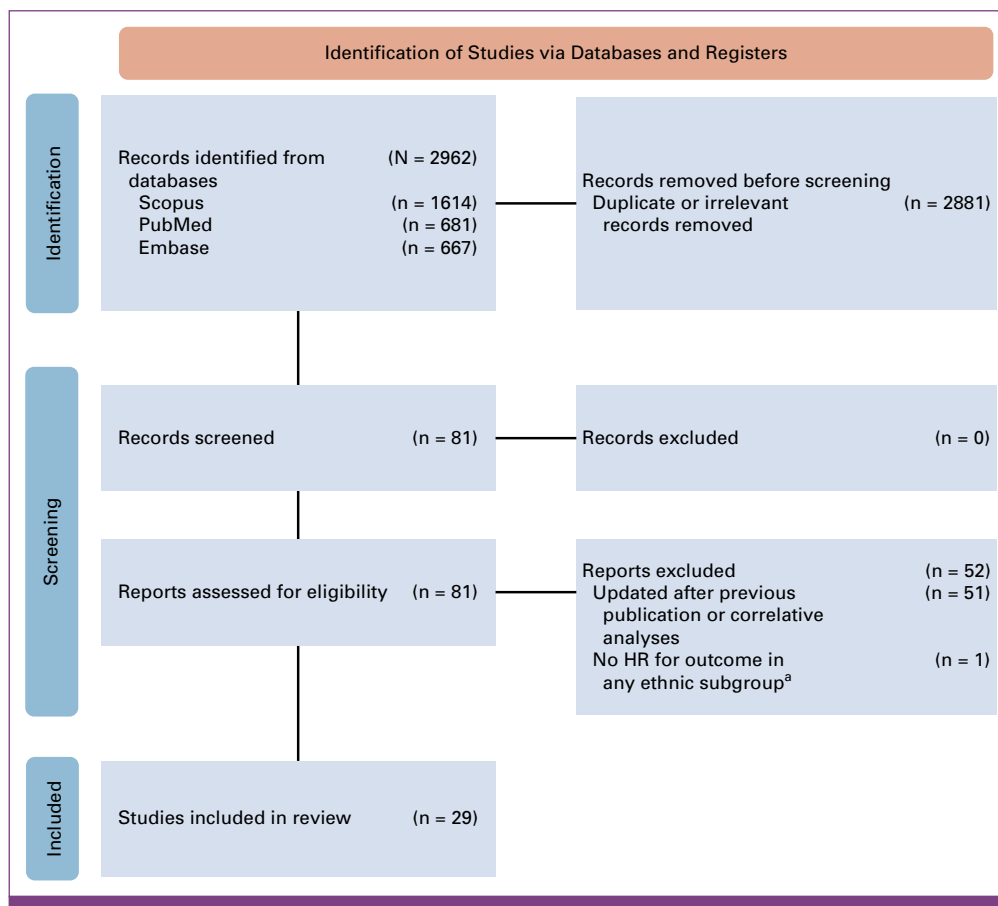


FIG 1. Study selection diagram. ^aDESTINY-Breast02 reported patient ethnic subgroup distribution but no HR for PFS in any ethnic subgroup. HR, hazard ratio; PFS, progression-free survival.

control arms for Black patients (Table 1). Pooled disease progression risk reduction for Black patients treated in the experimental versus standard arms was 4.6% (HR, 0.54 [95% CI, 0.34 to 0.85]). The magnitude of benefit versus other ethnicities was not significantly different ($P = .992$ for Asians ν Blacks; $P = .564$ for Whites ν Blacks). In this analysis, the interstudy heterogeneity was low ($Q = 3.8$; $P = .283$; $I^2 = 21.2\%$).

Furthermore, the aggregation of non-White populations (including Asians, Black, non-White, Hispanic/Latino, or other, when the White category was also presented in the trial) had available HR in 23 RCTs (see Table 1 for the complete categorization). Non-Whites presented a pooled disease progression risk reduction of 4.2% (HR, 0.58 [95% CI, 0.51 to 0.66]), with high heterogeneity ($Q = 78.8$; $P < .001$; $I^2 = 54.3\%$; Data Supplement, Fig S2). No significant difference in the magnitude of benefit from experimental drugs was found between White and non-White ethnicity ($P = .406$).

Moreover, 23 RCTs provided data for non-Asian patients, classified as White, Caucasian, Black, non-Asian, Hispanic/Latino, or other (Table 1). In these diverse non-Asian populations, the meta-analysis showed a pooled risk reduction

for the experimental arms versus the control arms of 4.8% (HR, 0.62 [95% CI, 0.57 to 0.67]), with moderate interstudy heterogeneity ($Q = 50.5$; $P = .001$; $I^2 = 48.6\%$; Data Supplement, Fig S3). In terms of PFS, there was no significant difference in the magnitude of benefit from novel BC drugs between Asian and non-Asian patients ($P = .226$).

Subgroup Analyses

We conducted subgroup analyses by type of experimental drug tested in each trial. Considering only trial groups of more than two trials, we were only able to perform the subgroup analyses for trials testing a CDK4/6i or an anti-HER2 drug. In the pooled analysis of seven trials involving a CDK4/6i, the differences in efficacy among ethnicities were not significant (Data Supplement, Figs S4 and S5). Similarly, in the pooled seven trials testing an anti-HER2 drug, there was no significantly different benefit from experimental drugs among ethnicities (Data Supplement, Figs S6 and S7).

Subgroup analyses limited to first-line trials (Data Supplement, Fig S8) and to trials in subsequent lines of therapy (Data Supplement, Fig S9) similarly showed no differences in efficacy.

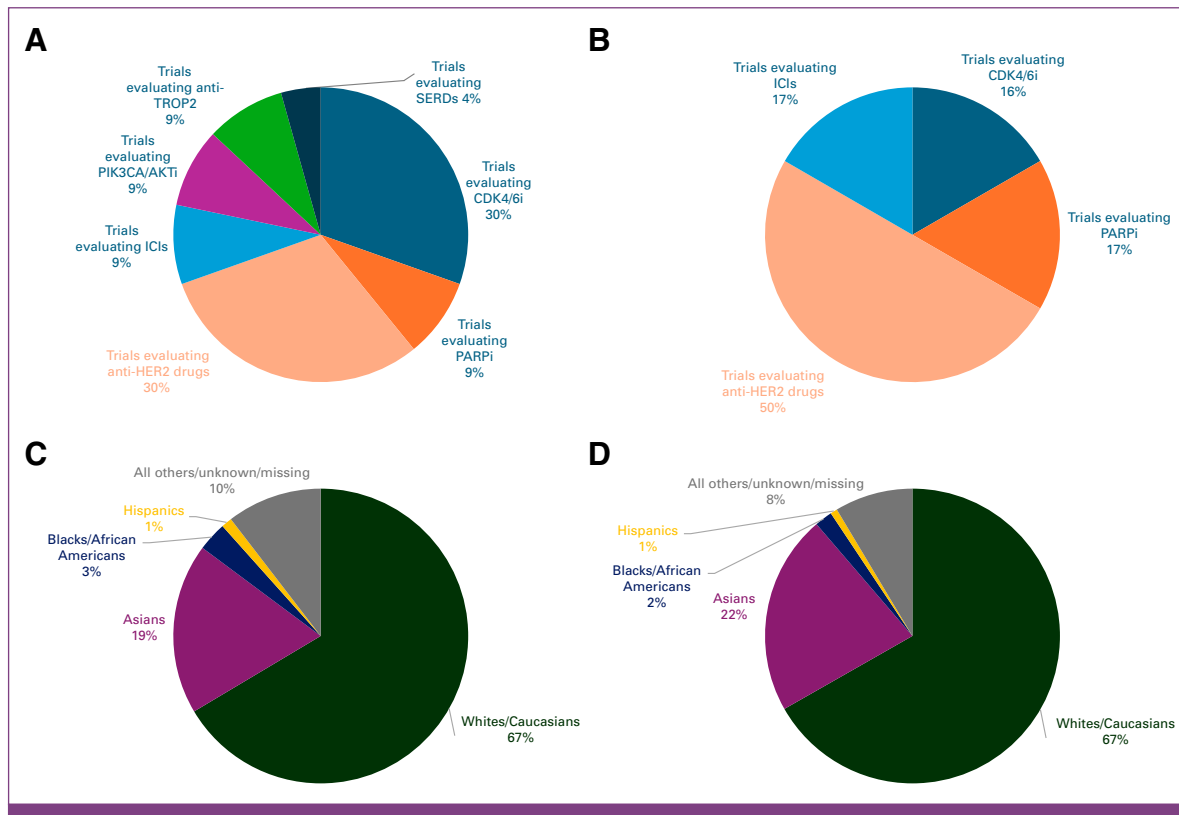


FIG 2. Distribution of included trials by type of drug in the (A) advanced setting and (B) early setting, and by ethnicity in the (C) advanced setting and (D) early setting. anti-HER2, anti-human epidermal growth factor receptor 2; anti-TROP2, anti-trophoblast cell surface antigen 2; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ICI, immune checkpoint inhibitor; PARPi, poly (ADP-ribose) polymerase inhibitor; PIK3CA/AKTi, phosphatidylinositol-3-kinase alpha/AKT inhibitor; SERD, selective estrogen receptor degrader.

The Early Setting

For the early-setting analysis, we selected six phase III RCTs involving more than 16,000 patients, which led to the approval and registration of the respective treatments tested as experimental arms (Table 2).⁵⁴⁻⁵⁶ The most represented patient ethnicity was once again the Whites (67%; Fig 2D). When considering White and Asian patients, HR for IDFS/EFS was available for all studies except KEYNOTE-522.⁵⁶ Pooled risk reduction of an IDFS event was 33% (HR, 0.67 [95% CI, 0.56 to 0.81]) for White patients, with high interstudy heterogeneity ($Q = 9.1$; $P = .060$; $I^2 = 55.9\%$; Fig 4A).

The pooled analysis of the five RCTs reporting on HR (95% CI) for IDFS for Asian patients showed an IDFS advantage of 28% (HR, 0.72 [95% CI, 0.57 to 0.90]) for Asian patients enrolled in the experimental arms compared with the control arms. Interstudy heterogeneity was low ($Q = 2.33$; $P = .675$; $I^2 = 0\%$; Fig 4B).

There was no significant difference in the efficacy of experimental treatment arms between Asian and White ethnicities ($P = .643$).

Black patients were only the 2% of patients enrolled in these early-setting RCTs. HR for IDFS was available only for the KATHERINE⁵³ and APHINITY⁵⁵ trials and was not pooled (Table 2).

When considering non-White patients (Data Supplement, Fig S10), White and non-White subgroups had comparable magnitude of benefit from experimental arms ($P = .690$).

We also performed a pooled analysis for non-Asian patients (Data Supplement, Fig S11). The difference in efficacy of experimental arms for Asian versus non-Asian patients was not significant ($P = .650$).

DISCUSSION

This study demonstrated that novel anticancer drugs approved in the past decade for BC are effective across different ethnic groups. In particular, the benefits were consistent among Asian, White, and, with the limitation of low numbers, Black populations, with no clinically relevant differences in treatment efficacy observed in both the metastatic and early-stage settings. However, since the direct comparison with other ethnicities, such as Hispanics or Pacific

TABLE 1. Ethnic Subgroup Distribution of Patients Enrolled in Phase III Trials Leading to Drug Approvals for Advanced Breast Cancer in the Past Decade (2013-2023)

Study	Line of Treatment for Advanced Disease	Number of Patients for Each Ethnic Group		For PFS for Each Ethnic Group, HR (95% CI)	Meta-Analysis Subgroup Categorization				
					Asian v Non-Asian	Asian v White	White v Non-White	Black	
PALOMA-2 Finn et al ²⁹	1	Palbociclib + letrozole	Placebo + letrozole						
		Total	444	222					
		Asian	65 (14.6%)	30 (13.5%)	0.48 (0.27 to 0.87)	Asian	Asian	Non-White	
		White/Caucasian	344 (77.5%)	172 (77.5%)	0.58 (0.45 to 0.74)	Non-Asian	White	White	
		Black/African American	8 (1.8%)	3 (1.4%)	NA				
		Other	27 (6.1%)	17 (7.7%)	NA				
PALOMA-3 Iwata et al ³⁰	2 ^a	Palbociclib + fulvestrant	Placebo + fulvestrant						
		Total	347	174					
		Asian	74 (21%)	31 (18%)	0.50 (0.31 to 0.82)	Asian	Asian	Non-White	
		White/Caucasian	252 (73%)	133 (76%)	0.50 (0.38 to 0.64)	Non-Asian	White	White	
		Black/African American or other	21 (6%)	10 (6%)	0.56 (0.23 to 1.34)	Non-Asian		Non-White	
		Non-Asian	273 (79%)	143 (82%)	0.45 (0.34 to 0.59)	Non-Asian			
MONALEESA-2 Hortobagyi et al ³¹	1	Ribociclib + letrozole	Placebo + letrozole						
		Total	334	334					
		Asian	28 (8.4%)	23 (6.9%)	0.37 (0.18 to 0.76)	Asian	Asian	Non-White	
		White/Caucasian	269 (80.5%)	280 (83.8%)	NA				
		Black/African American	10 (3%)	7 (2.1%)	NA				
		Other and unknown/missing	27 (8.1%)	24 (7.2%)	NA				
MONALEESA-3 Slamon et al ³²	1, 2	Ribociclib + fulvestrant	Placebo + fulvestrant						
		Total	484	242					
		Asian	45 (9.3%)	18 (7.4%)	1.35 (0.57 to 3.19)	Asian	Asian	Non-White	
		White/Caucasian	406 (83.9%)	213 (88.0%)	0.56 (0.45 to 0.70)	Non-Asian	White	White	
		Other	18 (3.7%)	6 (2.5%)	0.88 (0.20 to 3.91)	Non-Asian		Non-White	
		Unknown/missing	15 (3.1%)	5 (2.1%)	NA				

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TABLE 1. Ethnic Subgroup Distribution of Patients Enrolled in Phase III Trials Leading to Drug Approvals for Advanced Breast Cancer in the Past Decade (2013-2023) (continued)

Study	Line of Treatment for Advanced Disease	Number of Patients for Each Ethnic Group		For PFS for Each Ethnic Group, HR (95% CI)	Meta-Analysis Subgroup Categorization				
					Asian v Non-Asian	Asian v White	White v Non-White	Black	
MONALEESA-7 Tripathy et al ³³	1	Ribociclib + tamoxifen or NSAI + goserelin	Placebo + tamoxifen or NSAI + goserelin						
		Total	335	337					
		Asian	99 (29.6%)	99 (29.4%)	0.40 (0.26 to 0.63)	Asian	Asian	Non-White	
		White/Caucasian	187 (55.8%)	201 (59.6%)	NA				
		Black/African American	10 (3.0%)	9 (2.7%)	NA				
		Other and unknown/missing	39 (11.6%)	28 (8.3%)	NA				
		Non-Asian	200 (59.7%)	213 (63.2%)	0.66 (0.49 to 0.88)	Non-Asian			
MONARCH-2 Sledge et al ³⁴	2 ^a	Abemaciclib + fulvestrant	Placebo + fulvestrant						
		Total	446	223					
		Asian	149 (33.4%)	65 (29.1%)	0.52 (0.36 to 0.74)	Asian	Asian	Non-White	
		White/Caucasian	237 (53.1%)	136 (61.0%)	0.62 (0.47 to 0.81)	Non-Asian	White	White	
		Other	29 (6.5%)	13 (5.8%)	0.31 (0.12 to 0.80)	Non-Asian		Non-White	
		Missing	31 (7.0%)	9 (4.1%)	NA				
MONARCH-3 Goetz et al ³⁵	1	Abemaciclib + letrozole or anastrozole	Placebo + letrozole or anastrozole						
		Total	328	165					
		Asian	103 (31.4%)	45 (27.3%)	0.34 (0.21 to 0.54)	Asian	Asian	Non-White	
		White/Caucasian	186 (56.7%)	102 (61.8%)	0.66 (0.48 to 0.92)	Non-Asian	White	White	
		Other	11 (3.4%)	7 (4.2%)	NA				
		Unknown/missing	28 (8.5%)	11 (6.7%)	NA				
SOLAR-1 André et al ³⁶	2 ^a	Alpelisib + fulvestrant	Placebo + fulvestrant						
		Total	284	288					
		Asian	59 (20.8%)	66 (22.9%)	0.76 (0.43 to 1.35)	Asian	Asian	Non-White	
		White/Caucasian	199 (70%)	178 (61.8%)	0.56 (0.41 to 0.78)	Non-Asian	White	White	
		Black/African American	2 (0.7%)	6 (2.1%)	NA				
		American Indian or Alaska Native	1 (0.4%)	4 (1.4%)	NA				
		Other	9 (3.2%)	17 (5.9%)	0.91 (0.41 to 2.00)	Non-Asian		Non-White	
		Unknown/missing	14 (4.9%)	17 (5.9%)	NA				

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TABLE 1. Ethnic Subgroup Distribution of Patients Enrolled in Phase III Trials Leading to Drug Approvals for Advanced Breast Cancer in the Past Decade (2013-2023) (continued)

Study	Line of Treatment for Advanced Disease	Number of Patients for Each Ethnic Group		For PFS for Each Ethnic Group, HR (95% CI)	Meta-Analysis Subgroup Categorization				
					Asian v Non-Asian	Asian v White	White v Non-White	Black	
OlympiAD Robson et al ³⁷	1, 2, >2	Olaparib		Physician's choice single-agent chemotherapy					
		Total	205	97					
		White/Caucasian	134 (65.4%)	63 (64.9%)	0.67 (0.48 to 0.95)	Non-Asian	White	White	
		Other	71 (34.6%)	34 (35%)	0.51 (0.32 to 0.85)			Non-White	
EMBRACA Litton et al ³⁸ Rugo et al ³⁹	1, 2, >2	Talazoparib		Physician's choice single-agent chemotherapy					
		Total	287	144					
		White/Caucasian	192 (66.9%)	108 (75%)	0.49 (0.35 to 0.68)	Non-Asian	White	White	
		Other	95 (33.1%)	36 (25%)	0.59 (0.34 to 1.00)			Non-White	
HER2CLIMB Murthy et al ⁴⁰	2, >2	Tucatinib + trastuzumab + capecitabine		Placebo + trastuzumab + capecitabine					
		Total	320	160					
		Asian	17 (5.3%)	3 (1.9%)	NA				
		White/Caucasian	225 (70.3%)	125 (78.1%)	0.57 (0.42 to 0.77)	Non-Asian	White	White	
		Black/African American	30 (9.4%)	13 (8.1%)	NA				
		Other and unknown/missing	48 (15.0%)	19 (11.9%)	NA				
		Non-White	95 (29.7%)	35 (21.9%)	0.46 (0.26 to 0.82)			Non-White	
DESTINY-Breast03 Cortés et al ⁸	2, >2	Trastuzumab deruxtecan		Trastuzumab emtansine					
		Total	261	263					
		Asian	152 (58.2%)	162 (61.6%)	0.28 (0.20 to 0.39)	Asian	Asian	Non-White	
		White/Caucasian	71 (27.2%)	72 (27.4%)	0.40 (0.23 to 0.70)	Non-Asian	White	White	
		Black/African American	10 (3.8%)	9 (3.4%)	NA				
Other	28 (10.7%)	20 (7.6%)	0.40 (0.14 to 1.11)	Non-Asian		Non-White			
DESTINY-Breast04 Modi et al ⁹	2, >2	Trastuzumab deruxtecan		Physician's choice chemotherapy					
		Total	373	184					
		Asian	151 (40.5%)	72 (39.1%)	0.38 (0.27 to 0.53)	Asian	Asian	Non-White	
		White/Caucasian	176 (47.2%)	91 (49.5%)	0.63 (0.45 to 0.87)	Non-Asian	White	White	
		Black/African American	7 (1.9%)	3 (1.6%)	NA				
Other	39 (10.5%)	17 (9.2%)	0.78 (0.40 to 1.55)	Non-Asian		Non-White			

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TABLE 1. Ethnic Subgroup Distribution of Patients Enrolled in Phase III Trials Leading to Drug Approvals for Advanced Breast Cancer in the Past Decade (2013-2023) (continued)

Study	Line of Treatment for Advanced Disease	Number of Patients for Each Ethnic Group		For PFS for Each Ethnic Group, HR (95% CI)	Meta-Analysis Subgroup Categorization				
					Asian v Non-Asian	Asian v White	White v Non-White	Black	
IMpassion130 Schmid et al ⁴¹	1	Atezolizumab + nab-paclitaxel		Placebo + nab-paclitaxel					
		Total	451	451					
		Asian	85 (18.8%)	76 (16.9%)	0.76 (0.54 to 1.08)	Non-Asian	Asian	Non-White	
		White/Caucasian	308 (68.3%)	301 (66.7%)	0.78 (0.65 to 0.93)		White	White	
		Black/African American	26 (5.8%)	33 (7.3%)	0.79 (0.44 to 1.42)	Non-Asian		Non-White	Black
		Native American	18 (3.8%)	23 (5.1%)	NA				
		Hawaiian or Other Pacific Islander	1 (0.2%)	0	NA				
		Multiple	2 (0.4%)	3 (0.7%)	NA				
		Unknown/missing	12 (2.7%)	15 (3.3%)	NA				
KEYNOTE-355 Cortés et al ⁴²	1	Pembrolizumab + physician's choice chemotherapy		Placebo + physician's choice chemotherapy					
		Total	566	281					
		Asian	123 (21.7%)	52 (18.5%)	NA				
		White/Caucasian	384 (67.8%)	195 (69.4%)	NA				
		Black/African American	20 (3.5%)	17 (6%)	NA				
		Multiple	11 (1.9%)	8 (2.8%)	NA				
		American Indian or Alaska Native	11 (1.9%)	1 (0.4%)	NA				
		Unknown/missing	17 (3%)	8 (2.8%)	NA				
		Hispanic/Latino	116 (20.5%)	48 (17.1%)	1.25 (0.83 to 1.87)	Non-Asian		Non-White	
Not Hispanic or Latino	423 (74.7%)	218 (77.6%)	0.70 (0.58 to 0.85)						
ASCENT Bardia et al ⁴³	>2	Sacituzumab govitecan		Physician's choice single-agent chemotherapy					
		Total	235	233					
		Asian	9 (4%)	9 (4%)	0.40 (0.08 to 2.08)	Asian	Asian	Non-White	
		White/Caucasian	384 (67.8%)	195 (69.4%)	NA	Non-Asian	White	White	
		Black/African American	28 (12%)	28 (12%)	0.45 (0.24 to 0.86)	Non-Asian		Non-White	Black
		Other	10 (4%)	15 (6%)	NA				

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TABLE 1. Ethnic Subgroup Distribution of Patients Enrolled in Phase III Trials Leading to Drug Approvals for Advanced Breast Cancer in the Past Decade (2013-2023) (continued)

Study	Line of Treatment for Advanced Disease	Number of Patients for Each Ethnic Group		For PFS for Each Ethnic Group, HR (95% CI)	Meta-Analysis Subgroup Categorization					
					Asian v Non-Asian	Asian v White	White v Non-White	Black		
TROPICS-02 Rugo et al ⁴⁴	>2	Sacituzumab govitecan		Physician's choice single-agent chemotherapy						
		Total	272	271						
		Asian	11 (4%)	5 (2%)	NA					
		White/Caucasian	384 (67.8%)	195 (69.4%)	NA					
		Black/African American	8 (3%)	13 (5%)	NA					
		Others	0	5 (2%)	NA					
		Unknown/missing	69 (25%)	70 (26%)	NA					
		Non-White	19 (6.7%)	23 (8.5%)	1.23 (0.55 to 2.75)		Non-White			
EMERALD Bidard et al ⁴⁵	2, >2	Elaeestrant		Standard-of-care endocrine monotherapy						
		Total	239 ^a	238 ^a						
		Asian	16 (8.4%)	16 (8.2%)	1.09 (0.46 to 2.64)		Asian	Asian	Non-White	
		White/Caucasian	384 (67.8%)	195 (69.4%)	NA		Non-Asian	White	White	
		Black/African American	5 (2.6%)	7 (3.6%)	NA					
		Hispanic	19 (7.9%)	18 (7.6%)	NA					
		Other	1 (0.5%)	1 (0.5%)	NA					
		Unknown/missing	30 (12.6%)	27 (11.3%)	NA					
CLEOPATRA Swain et al ⁴⁶	1	Pertuzumab + trastuzumab + docetaxel		Placebo + trastuzumab + docetaxel						
		Total	408	406						
		Asian	128 (31.4%)	133 (32.8%)	0.77 (0.58 to 1.03)		Asian	Asian	Non-White	
		White/Caucasian	384 (67.8%)	195 (69.4%)	NA		Non-Asian	White	White	
		Black/African American	10 (2.5%)	20 (4.9%)	0.54 (0.19 to 1.51)		Non-Asian		Non-White Black	
		Other	19 (4.7%)	18 (4.4%)	0.45 (0.20 to 1.01)		Non-Asian		Non-White	
		Unknown/missing	6 (1.3%)	0	NA					

(continued on following page)

TABLE 1. Ethnic Subgroup Distribution of Patients Enrolled in Phase III Trials Leading to Drug Approvals for Advanced Breast Cancer in the Past Decade (2013-2023) (continued)

Study	Line of Treatment for Advanced Disease	Number of Patients for Each Ethnic Group		For PFS for Each Ethnic Group, HR (95% CI)	Meta-Analysis Subgroup Categorization				
					Asian v Non-Asian	Asian v White	White v Non-White	Black	
EMILIA Diéras et al ⁴⁷	2, >2	Trastuzumab emtansine		Lapatinib + capecitabine					
		Total	496	495					
		Asian	86 (17%)	94 (19%)	0.82 (0.57 to 1.18)	Asian	Asian	Non-White	
		White/Caucasian	384 (67.8%)	195 (69.4%)	NA	Non-Asian	White	White	
		Black/African American	21 (4%)	29 (6%)	NA				
		Other	10 (2%)	7 (1%)	0.59 (0.31 to 1.11)	Non-Asian		Non-White	
		Unknown/missing	5 (1%)	7 (1%)	NA				
NALA Saura et al ⁴⁸	>2	Neratinib + capecitabine		Lapatinib + capecitabine					
		Total	210	223					
		Asian, Black/African American or other	85 (40.5%)	106 (47.5%)	0.63 (0.47 to 0.85)			Non-White	
		White/Caucasian	384 (67.8%)	195 (69.4%)	NA	Non-Asian	White	White	
SOPHIA Rugo et al ⁴⁹	>2	Margetuximab + physician's choice chemotherapy		Trastuzumab + physician's choice chemotherapy					
		Total	266	270					
		Asian	20 (7.5%)	14 (5.2%)	0.40 (0.15 to 1.05)	Asian	Asian	Non-White	
		White/Caucasian	384 (67.8%)	195 (69.4%)	NA	Non-Asian	White	White	
		Black/African American	16 (6.0%)	12 (4.4%)	0.18 (0.04 to 0.91)	Non-Asian		Non-White	Black
		Other	25 (9.4%)	22 (8.1%)	0.62 (0.28 to 1.36)	Non-Asian		Non-White	
CAPitello-291 Turner et al ⁵⁰	2 ^a , >2	Capiwasertib + fulvestrant		Placebo + fulvestrant					
		Total	355	353					
		Asian	95 (26.8%)	94 (26.6%)	0.62 (0.44 to 0.86)	Asian	Asian	Non-White	
		White/Caucasian	384 (67.8%)	195 (69.4%)	NA	Non-Asian	White	White	
		Black/African American	4 (1.1%)	4 (1.1%)	NA				
		Other	55 (15.5%)	49 (13.9%)	0.63 (0.42 to 0.96)	Non-Asian		Non-White	

Abbreviations: BC, breast cancer; HR, hazard ratio; NA, not available; NSAI, nonsteroidal aromatase inhibitor; PFS, progression-free survival; v, versus.

^aFirst-line for endocrine resistance advanced BC.

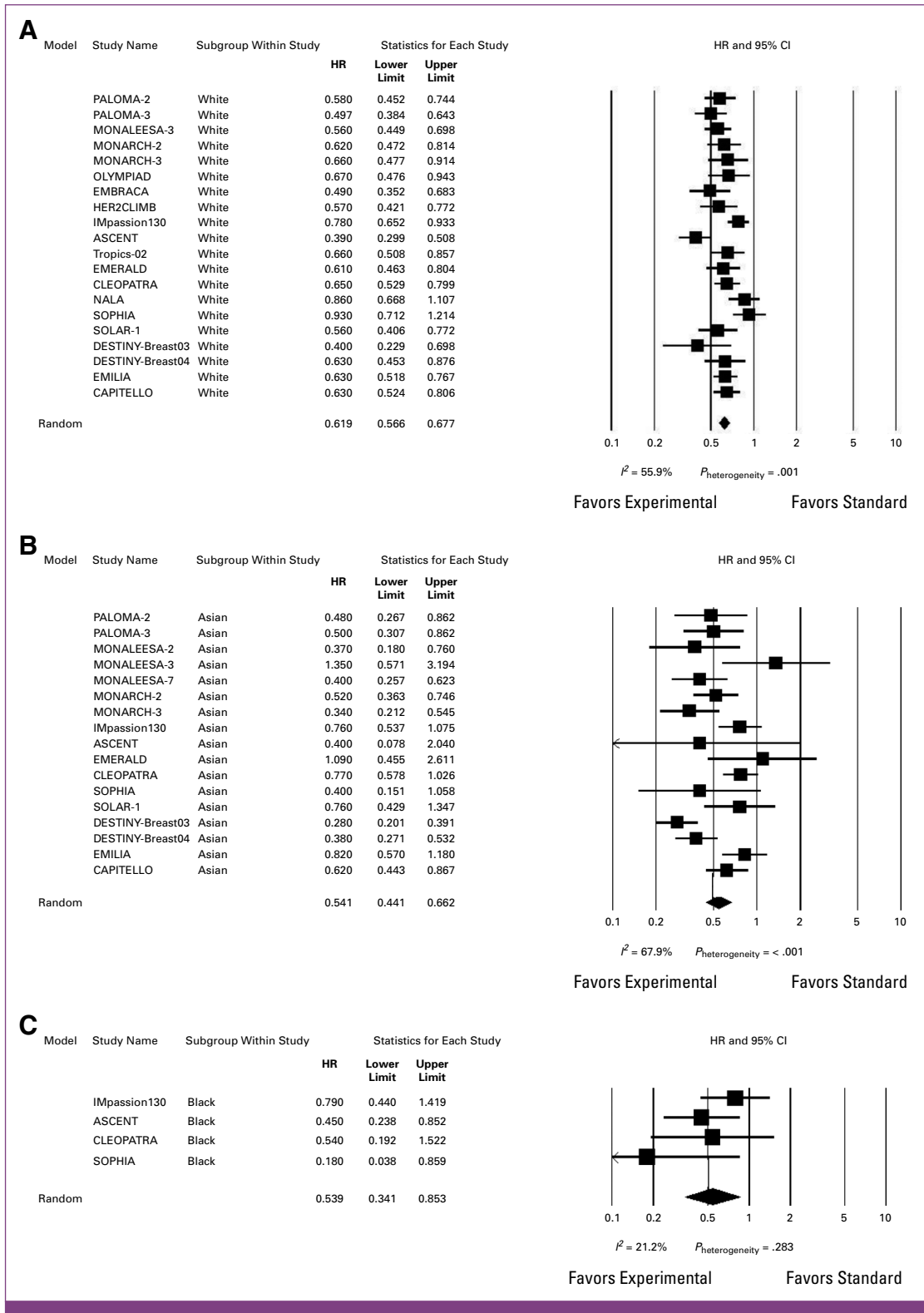


FIG 3. Forest plot of HRs for PFS for the experimental drug versus the standard drug in (A) White, (B) Asian, and (C) Black subgroups. Squares represent trial-specific HRs. Horizontal lines indicate the 95% CIs. Diamonds indicate the meta-analytic pooled HRs, calculated through random-effects model. HRs, hazard ratios; PFS, progression-free survival.

TABLE 2. Ethnic Subgroup Distribution of Patients Enrolled in Phase III Trials Leading to Drug Approvals for Early Breast Cancer in the Past Decade (2013-2023)

Study	Line of Treatment in the Early Setting (end point considered)	Number of Patients for Each Ethnic Group		HR (95% CI) for IDFS/EFS for Each Ethnic Group	Meta-Analysis Subgroup Categorization				
					Asian v Non-Asian	Asian v White	White v Non-White	Black	
MonarchE Johnston et al ⁵¹	Adjuvant (IDFS)	Abemaciclib + ET		Placebo + ET					
		Total		2,808		2,829			
		Asian		675 (24.0%)		669 (23.6%)		0.82 (0.51 to 1.33)	
		White/Caucasian		384 (67.8%)		195 (69.4%)		NA	
		Other		146 (5.2%)		140 (4.9%)		1.04 (0.45 to 2.40)	
ExteNET Martin et al ⁵²	Adjuvant (IDFS)	Neratinib		Placebo					
		Total		1,420		1,420			
		Asian		188 (13.2%)		197 (13.9%)		0.55 (0.28 to 1.04)	
		White/Caucasian		384 (67.8%)		195 (69.4%)		NA	
		Black/African American or other		67 (4.7%)		88 (6.2%)		0.61 (0.13 to 2.21)	
KATHERINE von Minckwitz et al ⁵³	Adjuvant (IDFS)	Trastuzumab emtansine		Trastuzumab					
		Total		743		743			
		Asian		65 (8.7%)		64 (8.6%)		0.65 (0.32 to 1.32)	
		White/Caucasian		384 (67.8%)		195 (69.4%)		NA	
		Black/African American		21 (2.8%)		19 (2.6%)		0.13 (0.02 to 1.10)	
OlympiA Tutt et al ⁵⁴	Adjuvant (IDFS)	Olaparib		Placebo					
		Total		921		915			
		Asian		259 (28.1%)		272 (29.7%)		0.59 (0.36, 0.95)	
		White/Caucasian		384 (67.8%)		195 (69.4%)		NA	
		Black/African American		19 (2.1%)		29 (3.2%)		NA	
APHINITY von Minckwitz et al ⁵⁵	Adjuvant (IDFS)	Pertuzumab + trastuzumab + chemotherapy		Placebo + trastuzumab + chemotherapy					
		Total		2,400		2,404			
		Asian		590 (24.6%)		598 (24.9%)		0.85 (0.57 to 1.26)	
		White/Caucasian		384 (67.8%)		195 (69.4%)		NA	
		Black/African American		32 (1.3%)		41 (1.7%)		0.77 (0.07 to 8.49)	
Other		66 (2.8%)		69 (2.9%)		0.52 (0.19 to 1.38)			

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TABLE 2. Ethnic Subgroup Distribution of Patients Enrolled in Phase III Trials Leading to Drug Approvals for Early Breast Cancer in the Past Decade (2013-2023) (continued)

Study	Line of Treatment in the Early Setting (end point considered)	Number of Patients for Each Ethnic Group		HR (95% CI) for IDFS/EFS for Each Ethnic Group	Meta-Analysis Subgroup Categorization				
					Asian v Non-Asian	Asian v White	White v Non-White	Black	
KEYNOTE-522 Schmid et al ⁵⁶	Neoadjuvant (EFS)	Pembrolizumab + chemotherapy							
		Placebo + chemotherapy							
		Total	784	390					
		Hispanic	86 (11.0%)	39 (10.0%)	0.74 (0.38 to 1.45)	Non-Asian		Non-White	
		Non-Hispanic	615 (78.4%)	307 (78.7%)	0.58 (0.42 to 0.80)				
Other	NA	NA	NA						

Abbreviations: EFS, event-free survival; ET, endocrine therapy; HR, hazard ratio; IDFS, invasive disease-free survival; NA, not available; v, versus.

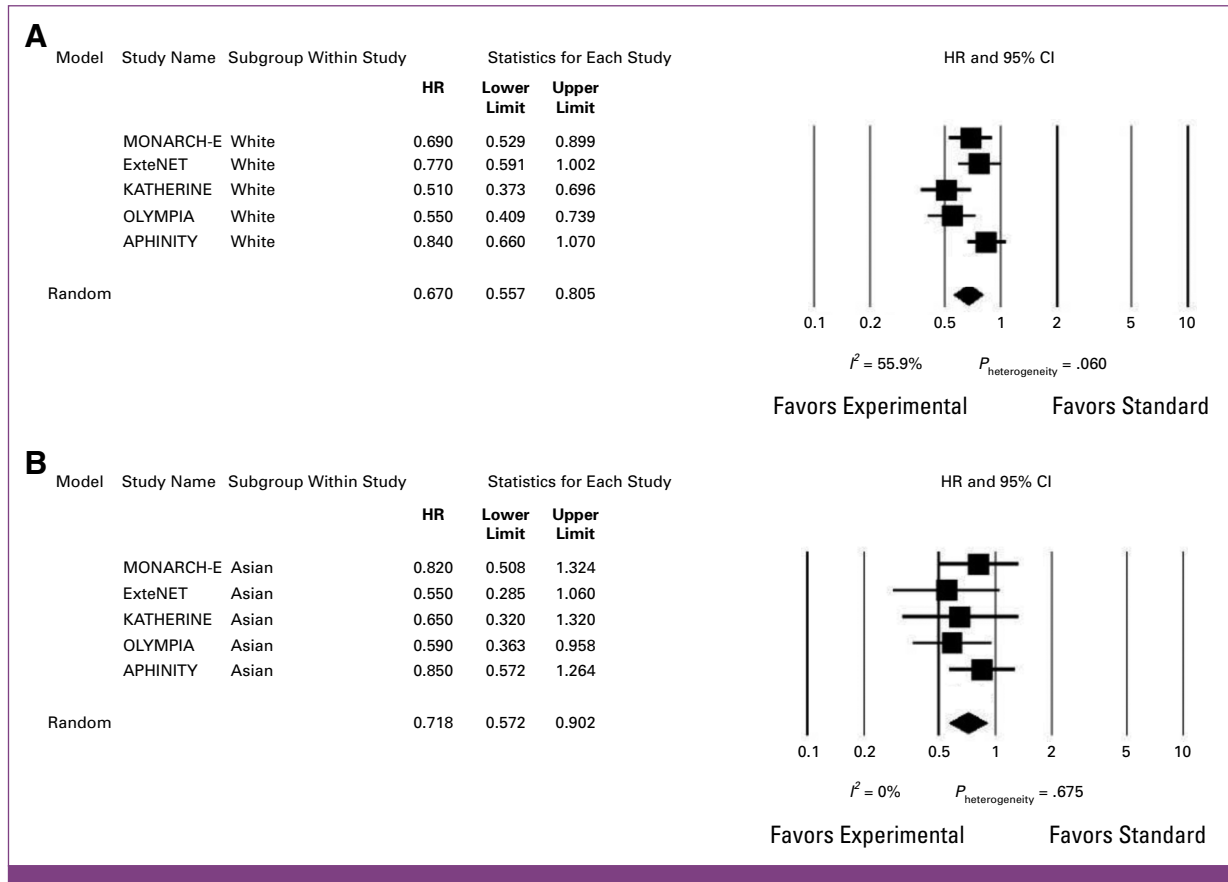


FIG 4. Forest plot of HRs for IDFS for the experimental drug versus the standard drug in (A) White and (B) Asian subgroups. Squares represent trial-specific HRs. Horizontal lines indicate the 95% CIs. Diamonds indicate the meta-analytic pooled HRs, calculated through random-effects model. HRs, hazard ratios; IDFS, invasive disease-free survival.

Islanders, is still hardly feasible today because of their underrepresentation in RCTs, in the present meta-analysis, we constituted the heterogeneous groupings of non-Asian and non-White patients. We observed no differences in the magnitude of benefit from novel BC drugs when comparing Asians versus non-Asians or Whites versus non-Whites.

Evaluating whether the effectiveness of novel therapies varies across ethnic groups is an important step toward understanding the disparities in BC survival. Compared with White women, Asian women tend to have better BC survival, whereas Black women consistently show the lowest survival rates.³ Hispanics, Native Hawaiians, and Native Americans generally exhibit intermediate outcomes, better than those of Black women but not as favorable as those of Asian and White women.³

To the best of our knowledge, existing studies on ethnic disparities in novel BC therapies have primarily focused on CDK4/6is, ICIs, and anti-HER2 agents, whereas data regarding ADCs, PARPis, selective estrogen receptor degraders, and phosphatidylinositol-3-kinase alpha/AKT inhibitors are still lacking.

Several previous studies reported a larger benefit from novel BC drugs, including CDK4/6is and ICIs, for Asian versus White patients.^{21,22,56-58} In the case of ICIs, higher efficacy in Asians patients was found also in other cancer types.^{59,60} Asian patients with BC harbor more immune-activated tumor microenvironment than White patients.¹⁶ This might partly explain the higher efficacy not only of ICIs, but also of CDK4/6is, which exert their activity by promoting anticancer immune responses.²⁰ In the case of anti-HER2 drugs, Asian patients exhibited a higher risk of developing grade 3 or 4 thrombocytopenia related to trastuzumab emtansine, a toxicity that may lead to dose delays and potentially reduced treatment efficacy.⁶¹

By contrast, emerging evidence suggests that Black patients and other underrepresented groups might experience a smaller survival benefit from novel anticancer drugs for BC. In a real-world study comparing patient outcomes before and after the introduction of CDK4/6is, overall survival improved for White women, but not for Black or Hispanic women.⁶² On the contrary, ICIs demonstrated comparable efficacy in White and Black patients.⁶³ Anti-HER2 BC drugs were associated with higher cardiotoxicity in Black patients

compared with other ethnic groups, leading to treatment discontinuation and reduced efficacy.⁶⁴

Therefore, given the growing body of research on interethnic biological variability, a differential benefit from novel BC treatments was expected. However, our study found no difference in the benefit across ethnicities both in the advanced setting and in the early-disease setting.

The relevance of our findings is strengthened by their consistency across all the comparisons, including Whites versus non-Whites, Asians versus non-Asians, and Whites or Asians versus Blacks, and the subanalyses for drug type and line of therapy.

Even after accounting for interethnic biological variability, certain factors may attenuate the expected differences and help close the gap in BC across ethnicities.

The increasing global adoption of a Western lifestyle, characterized by high-fat diets, physical inactivity, delayed or absent childbearing, and alcohol consumption, has been strongly associated with rising BC incidence worldwide.^{65,66} Environmental exposures may also contribute to narrowing the interethnic gap. Urbanization and industrialization in regions such as Asia have increased exposure to estrogenic pollutants, potentially raising endogenous estrogen levels and aligning risk profiles with those of Western populations.^{3,67} Moreover, clinical trial data suggest that interethnic pharmacokinetic differences may not significantly affect the dosing of novel therapeutic agents. A review of phase I/II studies found that recommended doses for 17 molecular-targeted therapies were largely consistent across Asian and Caucasian populations.⁶⁸ Although ethnic variability remains relevant, particularly for certain chemotherapeutic agents,⁴⁹ it may be less impactful for newer drug classes such as targeted therapies and ICIs as those that we considered in this study.

A strength of this work is the quality of evidence available and used in the meta-analysis. Data were obtained from 29 large and global phase III RCTs, including more than 30,000 patients, and results are based on the well-defined and validated end points of PFS, in the advanced-disease setting, and IDFS/EFS, in the early-disease setting. Despite the large

number of enrolled patients and having included RCTs developed on a global scale, the majority of the enrolled patients were White, whereas Black and Hispanic individuals represented at most 2%. Moreover, several RCTs had partially missing ethnicity data, with TROPiCS-02, for instance, not providing ethnic information for 25% of enrolled patients.⁴³

The possible limitations of our meta-analysis are the following: the meta-analysis relies on published trial (or FDA/EPAR registries) results rather than on individual patient's data; heterogeneous treatments (CDK4/6is, ADCs, ICIs, and others) were included; the study did not include data on differences in safety and tolerability of the drugs among ethnicities; ethnic groups are intrinsically heterogeneous and likely encompass significant biological diversity within themselves (eg, between Eastern Asia and Western Asia patients); the underrepresentation of ethnic subgroups other than White or Asian limits the generalizability of our results to populations outside these two groups; and variables other than ethnicity, such as tumor features or socioeconomic variables, which could affect the response to treatments, might have been distributed differently between ethnicities, and these variables might have influenced our results.

In conclusion, this meta-analysis attempted to answer two fundamental questions in current clinical research, on one side if different ethnicities, implying different BC biology and patterns of response to cancer treatments, affect clinical trial results. On the other side, if data from clinical trials with heterogeneous populations are generalizable to every patient. The emerging data are reassuringly suggesting that ethnicity does not affect the magnitude of benefit of anti-cancer drugs approved for BC treatment in the past decade. However, the marked underrepresentation of ethnic groups beyond White and Asian populations limits the ability to draw robust and generalizable conclusions for underrepresented populations. This study highlights the urgent need for future research efforts that prioritize equitable and inclusive trial designs, ensuring broader representation across all ethnic groups. Greater diversity in clinical trial enrollment is a critical step toward achieving equity in cancer care and producing evidence that meaningfully reflects all the populations affected.

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All data were extracted from indexed manuscripts or FDA or EPAR registries.

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Administrative support: Massimo Dominici

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Final approval of manuscript: All authors

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