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

Emma Zattarin, MD[1,2]; Luca Moscetti, MD[1,3]; Elisa D'Agostino, MD[1]; Alberto Bertolotti, MD[1]; Isabella Sperduti, MS[4]; Chiara Chiavelli, PhD, MS[1,2]; Fabio Canino, MD[1,2]; Federico Piacentini, MD, PhD[1,2]; Laura Cortesi, MD[1]; Massimo Dominici, MD[1,2]; and Angela Toss, MD, PhD[1,2]

DOI https://doi.org/10.1200/GO-25-00139

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

Accepted April 30, 2025
Published July 1, 2025

JCO Global Oncol 11:e2500139

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. FDA[25] 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 trial[43] 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

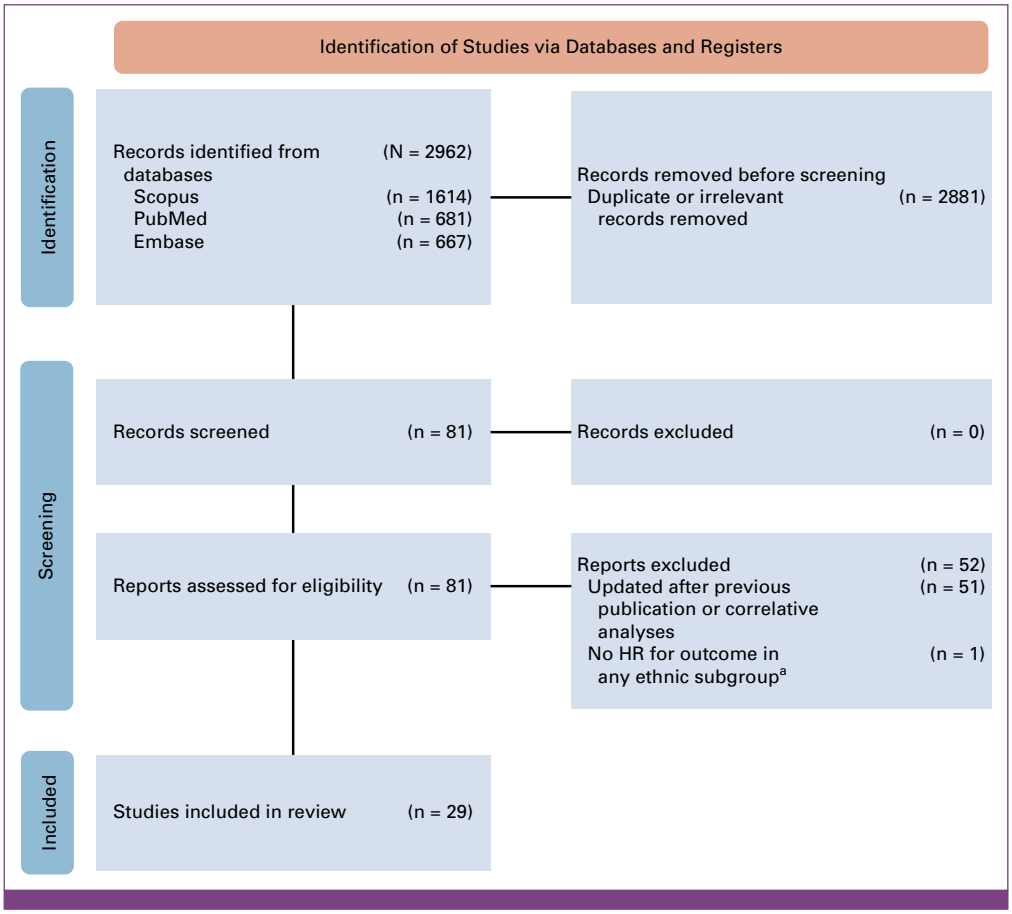

FIG 1. Study selection diagram. [a]DESTINY-Breast02 reported patient ethnic subgroup distribution but no HR for PFS in any ethnic subgroup. HR, hazard ratio; PFS, progression-free survival.

control arms for Black patients (Table 1). Pooled disease progression risk reduction for Black patients treated in the experimental versus standard arms was 46% (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 *v* Blacks; P = .564 for Whites *v* 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 42% (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 48% (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.

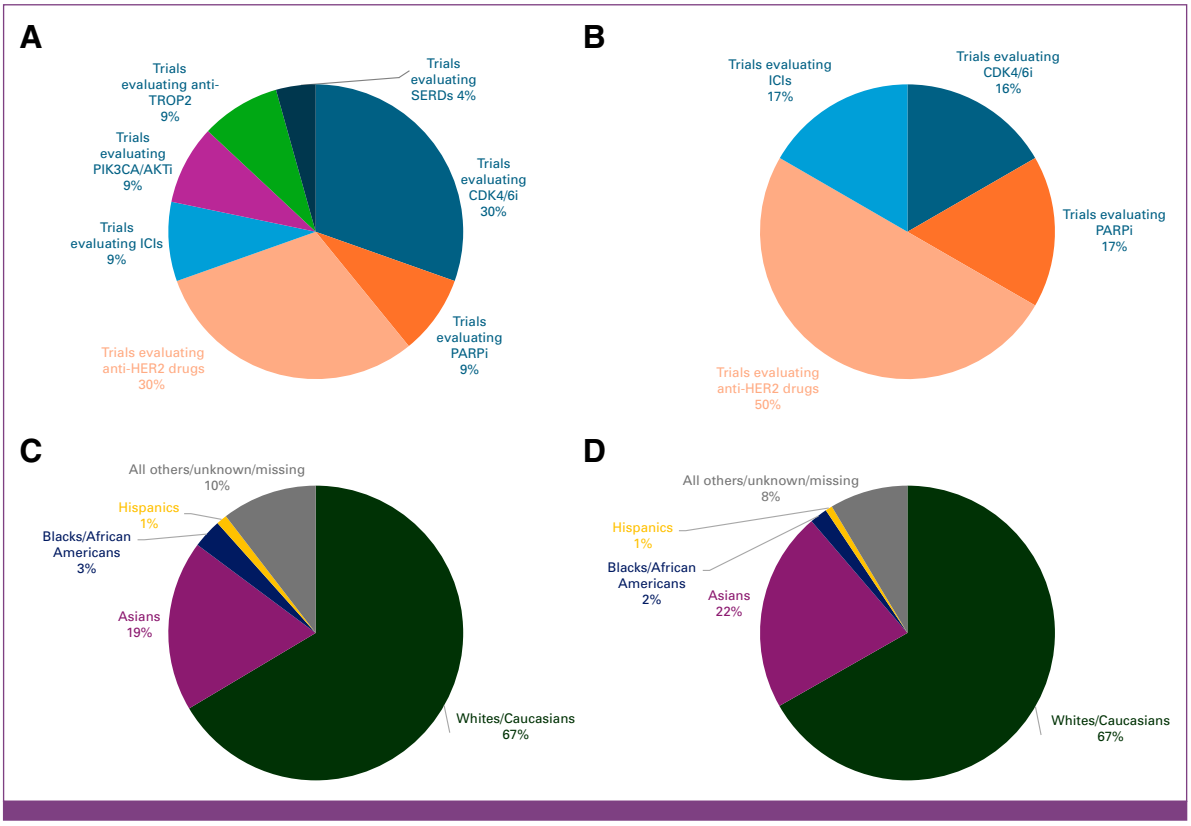

FIG 2. Distribution of included trials by type of drug in the (A) advanced setting and (B) early setting, and by ethnicity in the (C) advanced setting and (D) early setting. anti-HER2, anti–human epidermal growth factor receptor 2; anti-TROP2, anti–trophoblast cell surface antigen 2; CDK4/6i, cyclin-dependent 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).[51-56] 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 KATHERINE[53] and APHINITY[55] 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			
		Non-Asian	281 (84.1%)	287 (85.9%)	0.61 (0.49 to 0.78)	Non-Asian		
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			

(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
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			

(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
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

(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
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				

(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
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	Non-Asian	White	White	
	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	Elacestrant	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	Capivasertib + 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.
[a]First-line for endocrine resistance advanced BC.

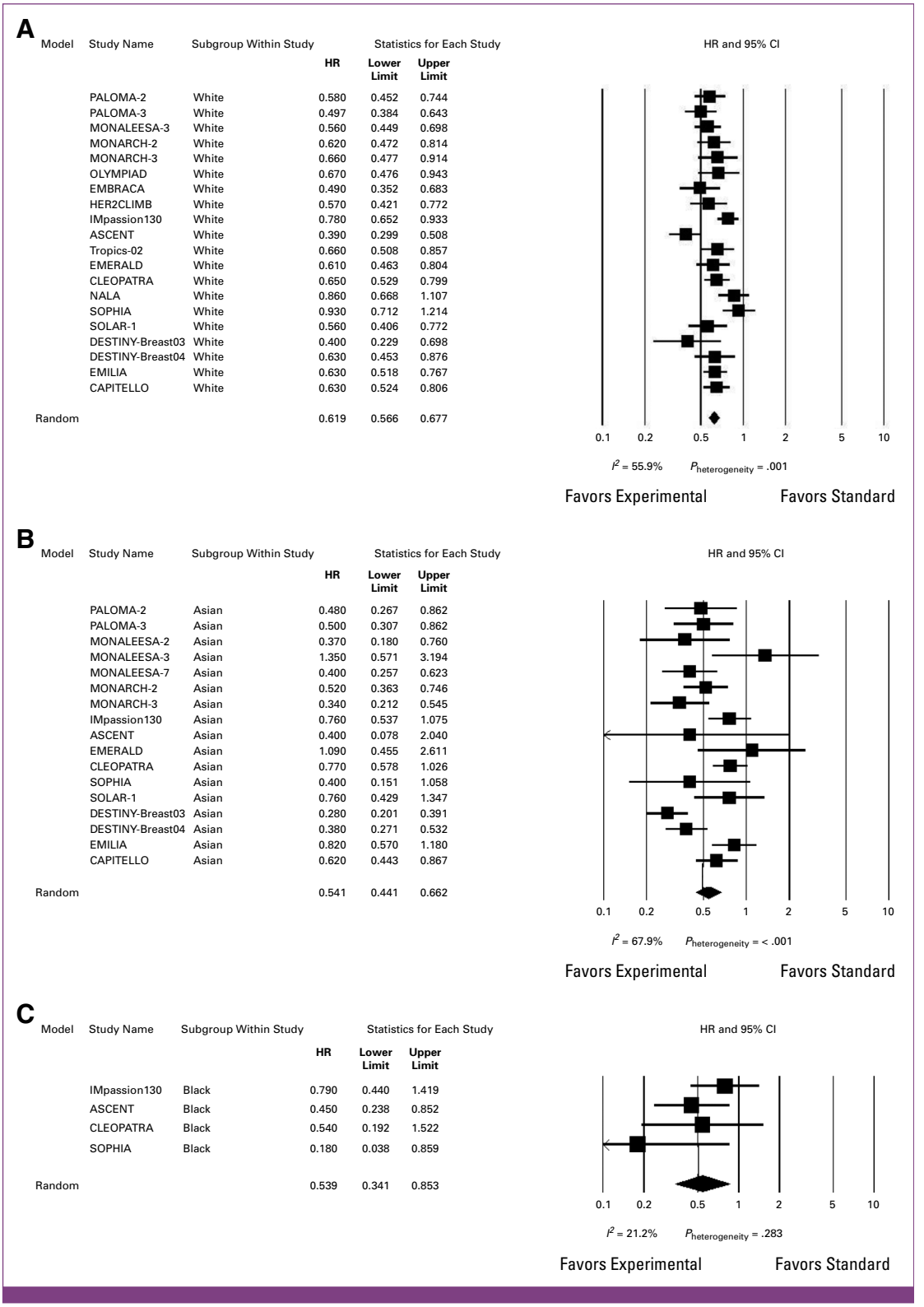

FIG 3. Forest plot of HRs for PFS for the experimental drug versus the standard drug in (A) White, (B) Asian, and (C) Black subgroups. Squares represent trial-specific HRs. Horizontal lines indicate the 95% CIs. Diamonds indicate the meta-analytic pooled HRs, calculated through random-effects model. 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)	Asian	Asian	Non-White	
		White/Caucasian	384 (67.8%)	195 (69.4%)	NA	Non-Asian	White	White	
		Other	146 (5.2%)	140 (4.9%)	1.04 (0.45 to 2.40)	Non-Asian		Non-White	
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)	Asian	Asian	Non-White	
		White/Caucasian	384 (67.8%)	195 (69.4%)	NA	Non-Asian	White	White	
		Black/African American or other	67 (4.7%)	88 (6.2%)	0.61 (0.13 to 2.21)	Non-Asian		Non-White	
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)	Asian	Asian	Non-White	
		White/Caucasian	384 (67.8%)	195 (69.4%)	NA	Non-Asian	White	White	
		Black/African American	21 (2.8%)	19 (2.6%)	0.13 (0.02 to 1.10)	Non-Asian		Non-White	Black
		American Indian or Alaska Native	36 (4.8%)	50 (6.7%)	0.44 (0.18 to 1.03)	Non-Asian		Non-White	
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)	Asian	Asian	Non-White	
		White/Caucasian	384 (67.8%)	195 (69.4%)	NA	Non-Asian	White	White	
		Black/African American	19 (2.1%)	29 (3.2%)	NA	Non-Asian		Non-White	
		Other	17 (1.8%)	15 (1.6%)	NA	Non-Asian		Non-White	
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)	Asian	Asian	Non-White	
		White/Caucasian	384 (67.8%)	195 (69.4%)	NA	\Asian	White	White	
		Black/African American	32 (1.3%)	41 (1.7%)	0.77 (0.07 to 8.49)	Non-Asian		Non-White	Black
		Other	66 (2.8%)	69 (2.9%)	0.52 (0.19 to 1.38)	Non-Asian		Non-White	

(continued on following page)

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.

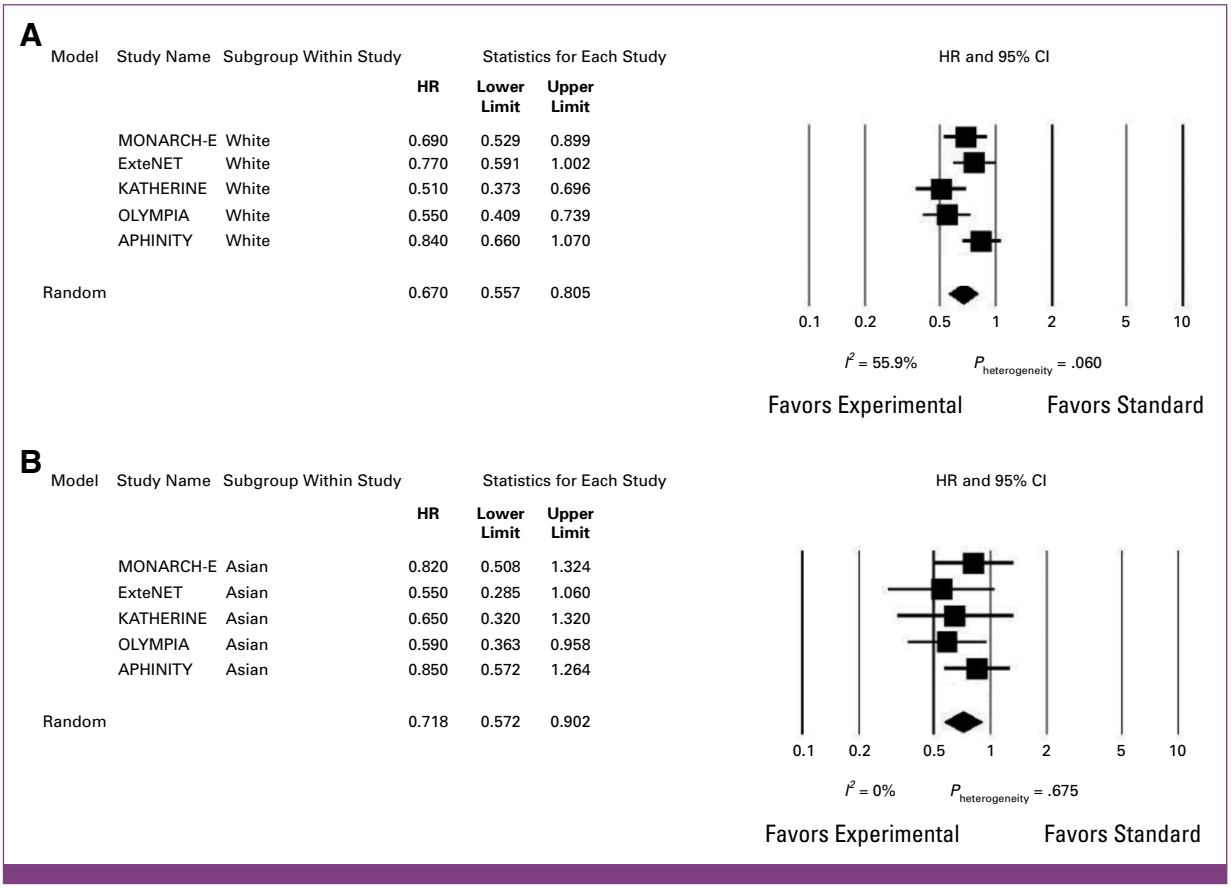

FIG 4. Forest plot of HRs for IDFS for the experimental drug versus the standard drug in (A) White and (B) Asian subgroups. Squares represent trial-specific HRs. Horizontal lines indicate the 95% CIs. Diamonds indicate the meta-analytic pooled HRs, calculated through random-effects model. HRs, hazard 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,[19] 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 had been distributed differently between ethnicities, and these variables might had 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 anticancer 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.

AFFILIATIONS

[1]Department of Oncology and Hematology, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy
[2]Department of Medical and Surgical Sciences, University of Modena and Reggio Emilia, Modena, Italy
[3]Gruppo Oncologico Italiano per la Ricerca Clinica (GOIRC), Parma, Italy
[4]Biostatistical Unit—Clinical Trials Center, IRCCS Regina Elena National Cancer Institute, Rome, Italy

CORRESPONDING AUTHOR

Angela Toss, MD, PhD; e-mail: angela.toss@unimore.it.

EQUAL CONTRIBUTION

E.Z. and L.M. contributed equally to the paper.

PRIOR PRESENTATION

Presented in part at the San Antonio Breast Cancer Symposium (SABCS) 2024, San Antonio, TX, December 10-13, 2024.

DATA SHARING STATEMENT

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

AUTHOR CONTRIBUTIONS

Conception and design: Emma Zattarin, Luca Moscetti, Angela Toss
Financial support: Massimo Dominici, Angela Toss
Administrative support: Massimo Dominici
Provision of study materials or patients: Federico Piacentini
Collection and assembly of data: Emma Zattarin, Alberto Bertolotti, Elisa D'Agostino, Fabio Canino, Federico Piacentini, Laura Cortesi, Angela Toss
Data analysis and interpretation: Emma Zattarin, Luca Moscetti, Isabella Sperduti, Chiara Chiavelli, Massimo Dominici, Angela Toss
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/go/authors/author-center.
Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Emma Zattarin
Honoraria: Lilly
Travel, Accommodations, Expenses: Merck

Luca Moscetti
Honoraria: Gilead Sciences, Roche/Genentech, Lilly
Consulting or Advisory Role: Roche, Seagen, AstraZeneca
Travel, Accommodations, Expenses: Lilly, Pfizer

Federico Piacentini
Consulting or Advisory Role: Roche, Seagen, Daiichi Sankyo/AstraZeneca
Expert Testimony: Gilead Sciences
Travel, Accommodations, Expenses: Novartis, AstraZeneca/Daiichi Sankyo, Roche
Other Relationship: Pfizer

Laura Cortesi
Honoraria: AstraZeneca, Pfizer, Novartis, MSD, Gilead Sciences, Daiichi Sankyo Europe GmbH, Roche/Genentech
Consulting or Advisory Role: Pfizer, Novartis, MSD
Speakers' Bureau: AstraZeneca, MSD Oncology, Novartis, Gilead Sciences
Travel, Accommodations, Expenses: AstraZeneca, Gilead Sciences, Daiichi Sankyo Europe GmbH

Massimo Dominici
Stock and Other Ownership Interests: Eir Biotherapies
Consulting or Advisory Role: Eir Biotherapies
Patents, Royalties, Other Intellectual Property: Several patents in cell and gene therapies, not related with the topics of the current manuscript

Angela Toss
Honoraria: Lilly, Pfizer, Novartis, Gilead Sciences, Seagen, MSD Oncology, AstraZeneca
Consulting or Advisory Role: Lilly, Novartis, MSD/AstraZeneca, Daiichi Sankyo/AstraZeneca, Pfizer, Seagen
Travel, Accommodations, Expenses: Daiichi Sankyo/AstraZeneca, Gilead Sciences

No other potential conflicts of interest were reported.

ACKNOWLEDGMENT

The authors are particularly grateful to the Angela Serra Association for Cancer Research and Gruppo Oncologico Italiano per la Ricerca Clinica (GOIRC) for their support.

REFERENCES

1. Yap YS: Outcomes in breast cancer-does ethnicity matter? ESMO Open 8:101564, 2023
2. Lin CH, Yap YS, Lee KH, et al: Contrasting epidemiology and clinicopathology of female breast cancer in Asians vs the US population. J Natl Cancer Inst 111:1298-1306, 2019
3. Maskarinec G, Sen C, Koga K, et al: Ethnic differences in breast cancer survival: Status and determinants. Womens Health (Lond) 7:677-687, 2011
4. García-Cárdenas JM, Indacochea A, Pesantez-Coronel D, et al: Toward equitable precision oncology: Monitoring racial and ethnic inclusion in genomics and clinical trials. JCO Precis Oncol 10.1200/PO.23.00398
5. Yap YS, Lu YS, Tamura K, et al: Insights into breast cancer in the east vs the west: A review. JAMA Oncol 5:1489-1496, 2019
6. Masuda N, Lee SJ, Ohtani S, et al: Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med 376:2147-2159, 2017
7. Lu YS, Mahidin EIBM, Azim H, et al: Final results of RIGHT choice: Ribociclib plus endocrine therapy versus combination chemotherapy in premenopausal women with clinically aggressive hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer. J Clin Oncol 42:2812-2821, 2024
8. Cortés J, Kim SB, Chung WP, et al: Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. N Engl J Med 386:1143-1154, 2022
9. Modi S, Jacot W, Yamashita T, et al: Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. N Engl J Med 387:9-20, 2022
10. Nazha B, Mishra M, Pentz R, et al: Enrollment of racial minorities in clinical trials: Old problem assumes new urgency in the age of immunotherapy. Am Soc Clin Oncol Educ Book 39:3-10, 2019
11. Williams DR, Mohammed SA, Shields AE: Understanding and effectively addressing breast cancer in African American women: Unpacking the social context. Cancer 122:2138-2149, 2016
12. Giaquinto AN, Sung H, Newman LA, et al: Breast cancer statistics 2024. CA Cancer J Clin 74:477-495, 2024
13. Hoskins KF, Danciu OC, Ko NY, et al: Association of race/ethnicity and the 21-gene recurrence score with breast cancer-specific mortality among US women. JAMA Oncol 7:370-378, 2021
14. Shi Y, Steppi A, Cao Y, et al: Integrative comparison of mRNA expression patterns in breast cancers from Caucasian and Asian Americans with implications for precision medicine. Cancer Res 77:423-433, 2017
15. Yadav S, LaDuca H, Polley EC, et al: Racial and ethnic differences in multigene hereditary cancer panel test results for women with breast cancer. J Natl Cancer Inst 113:1429-1433, 2021
16. Kan Z, Ding Y, Kim J, et al: Multi-omics profiling of younger Asian breast cancers reveals distinctive molecular signatures. Nat Commun 9:1725, 2018
17. Pinheiro SP, Holmes MD, Pollak MN, et al: Racial differences in premenopausal endogenous hormones. Cancer Epidemiol Biomarkers Prev 14:2147-2153, 2005
18. Moore SC, Matthews CE, Ou Shu X, et al: Endogenous estrogens, estrogen metabolites, and breast cancer risk in postmenopausal Chinese women. J Natl Cancer Inst 108:djw103, 2016
19. Pathak S, Zajac KK, Annaji M, et al: Clinical outcomes of chemotherapy in cancer patients with different ethnicities. Cancer Rep (Hoboken) 6:e1830, 2023 (suppl 1)
20. Pala L, Conforti F, Goldhirsch A: Ethnicity-based differences in breast cancer features and responsiveness to CDK4/6 inhibitors combined with endocrine therapy. Lancet Oncol 21:e130, 2020
21. Iwata H, Umeyama Y, Liu Y, et al: Evaluation of the association of polymorphisms with palbociclib-induced neutropenia: Pharmacogenetic analysis of PALOMA-2/-3. Oncologist 26:e1143-e1155, 2021
22. Lee KWC, Lord S, Finn RS, et al: The impact of ethnicity on efficacy and toxicity of cyclin D kinase 4/6 inhibitors in advanced breast cancer: A meta-analysis. Breast Cancer Res Treat 174:271-278, 2019
23. Buonaiuto R, Caltavituro A, Tafuro M, et al: Influence of ethnicity on cyclin-dependent kinase inhibitor efficacy and toxicity: A systematic review and meta-analysis. Breast 79:103833, 2025
24. Page MJ, McKenzie JE, Bossuyt PM, et al: The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 372:n71, 2021
25. U.S. Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
26. European Medicines Agency. Medicines. https://www.ema.europa.eu/en/medicines
27. Sterne JAC, Savović J, Page MJ, et al: RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ 366:l4898, 2019
28. van Houwelingen HC, Arends LR, Stijnen T: Advanced methods in meta-analysis: Multivariate approach and meta-regression. Stat Med 21:589-624, 2002

29. Finn RS, Martin M, Rugo HS, et al: Palbociclib and letrozole in advanced breast cancer. N Engl J Med 375:1925-1936, 2016
30. Iwata H, Im SA, Masuda N, et al: PALOMA-3: Phase III trial of fulvestrant with or without palbociclib in premenopausal and postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer that progressed on prior endocrine therapy-safety and efficacy in Asian patients. JCO Glob Oncol 10.1200/JGO.2016.008318
31. Hortobagyi GN, Stemmer SM, Burris HA, et al: Ribociclib as first-line therapy for HR-positive, advanced breast cancer. N Engl J Med 375:1738-1748, 2016
32. Slamon DJ, Neven P, Chia S, et al: Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. J Clin Oncol 36:2465-2472, 2018
33. Tripathy D, Im SA, Colleoni M, et al: Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): A randomised phase 3 trial. Lancet Oncol 19:904-915, 2018
34. Sledge GW Jr, Toi M, Neven P, et al: MONARCH 2: Abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. J Clin Oncol 35:2875-2884, 2017
35. Goetz MP, Toi M, Campone M, et al: MONARCH 3: Abemaciclib as initial therapy for advanced breast cancer. J Clin Oncol 35:3638-3646, 2017
36. André F, Ciruelos E, Rubovszky G, et al: Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. N Engl J Med 380:1929-1940, 2019
37. Robson M, Im SA, Senkus E, et al: Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med 377:523-533, 2017
38. Litton JK, Rugo HS, Ettl J, et al: Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. N Engl J Med 379:753-763, 2018
39. Rugo HS, Ettl J, Hurvitz SA, et al: Outcomes in clinically relevant patient subgroups from the EMBRACA study: Talazoparib vs physician's choice standard-of-care chemotherapy. JNCI Cancer Spectr 4:pkz085, 2020
40. Murthy RK, Loi S, Okines A, et al: Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. N Engl J Med 382:597-609, 2020
41. Schmid P, Adams S, Rugo HS, et al: Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med 379:2108-2121, 2018
42. Cortes J, Rugo HS, Cescon DW, et al: Pembrolizumab plus chemotherapy in advanced triple-negative breast cancer. N Engl J Med 387:217-226, 2022
43. Bardia A, Hurvitz SA, Tolaney SM, et al: Sacituzumab govitecan in metastatic triple-negative breast cancer. N Engl J Med 384:1529-1541, 2021
44. Rugo HS, Bardia A, Marmé F, et al: Overall survival with sacituzumab govitecan in hormone receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer (TROPiCS-02): A randomised, open-label, multicentre, phase 3 trial. Lancet 402:1423-1433, 2023
45. Bidard FC, Kaklamani VG, Neven P, et al: Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: Results from the randomized phase III EMERALD trial. J Clin Oncol 40:3246-3256, 2022
46. Swain SM, Miles D, Kim SB, et al: Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): End-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. Lancet Oncol 21:519-530, 2020
47. Diéras V, Miles D, Verma S, et al: Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): A descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. Lancet Oncol 18:732-742, 2017
48. Saura C, Oliveira M, Feng YH, et al: Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with ≥2 HER2-directed regimens: Phase III NALA trial. J Clin Oncol 38:3138-3149, 2020
49. Rugo HS, Im SA, Cardoso F, et al: Margetuximab versus trastuzumab in patients with previously treated HER2-positive advanced breast cancer (SOPHIA): Final overall survival results from a randomized phase 3 trial. J Clin Oncol 41:198-205, 2023
50. Turner NC, Oliveira M, Howell SJ, et al: Capivasertib in hormone receptor-positive advanced breast cancer. N Engl J Med 388:2058-2070, 2023
51. Johnston SRD, Harbeck N, Hegg R, et al: Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2-node-positive, high-risk, early breast cancer (monarchE). J Clin Oncol 38:3987-3998, 2020
52. Martin M, Holmes FA, Ejlertsen B, et al: Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 18:1688-1700, 2017
53. von Minckwitz G, Huang CS, Mano MS, et al: Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med 380:617-628, 2019
54. Tutt ANJ, Garber JE, Kaufman B, et al: Adjuvant olaparib for patients with BRCA1- or BRCA2-mutated breast cancer. N Engl J Med 384:2394-2405, 2021
55. von Minckwitz G, Procter M, de Azambuja E, et al: Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. N Engl J Med 377:122-131, 2017
56. Schmid P, Cortes J, Dent R, et al: Event-free survival with pembrolizumab in early triple-negative breast cancer. N Engl J Med 386:556-567, 2022
57. Inoue K, Masuda N, Iwata H, et al: Japanese subpopulation analysis of MONARCH 2: Phase 3 study of abemaciclib plus fulvestrant for treatment of hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer that progressed on endocrine therapy. Breast Cancer 28:1038-1050, 2021
58. Mukai H, Shimizu C, Masuda N, et al: Palbociclib in combination with letrozole in patients with estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: PALOMA-2 subgroup analysis of Japanese patients. Int J Clin Oncol 24:274-287, 2019
59. Xu RC, Wang L, Lin Y, et al: Immunotherapy and its racial specificity for breast cancer treatment in Asia: A narrative review. Lancet Reg Health West Pac 57:101180, 2024
60. Tan AR, Im SA, Mattar EZ, et al: Primary results from DAWNA-1: A phase III, randomized, double-blind study of dalpiciclib plus fulvestrant versus placebo plus fulvestrant in HR-positive, HER2-negative advanced breast cancer. J Clin Oncol 41, 2023 (suppl 17; abstr LBA1000)
61. Zhang P, Yin Y, Mo H, et al: Dalpiciclib plus letrozole as first-line treatment for HR-positive, HER2-negative advanced breast cancer: DAWNA-2, a randomized, double-blind, phase 3 trial. Lancet Oncol 24:62-73, 2023
62. Alvarez A, Bernal AM, Anampa J: Racial disparities in overall survival after the introduction of cyclin-dependent kinase 4/6 inhibitors for patients with hormone receptor-positive, HER2-negative metastatic breast cancer. Breast Cancer Res Treat 198:75-88, 2023
63. Miller S, Jiang R, Schipper M, et al: Effectiveness and safety of immune checkpoint inhibitors in Black patients versus White patients in a US national health system: A retrospective cohort study. Lancet Oncol 25:1666-1676, 2024
64. Litvak A, Batukbhai B, Russell SD, et al: Racial disparities in the rate of cardiotoxicity of HER2-targeted therapies among women with early breast cancer. Cancer 124:1904-1911, 2018
65. Konieczna J, Perez-Cornago A, Schlesinger S, et al: Adulthood dietary and lifestyle patterns and risk of breast cancer: Global Cancer Update Programme (CUP Global) systematic literature review. Am J Clin Nutr 121:14-31, 2024
66. Gathani T, Ali R, Balkwill A, et al: Ethnic differences in breast cancer incidence in England are due to differences in known risk factors for the disease: Prospective study. Br J Cancer 110:224-229, 2014
67. Lu YY, Chen ML, Sung FC, et al: Daily intake of 4-nonylphenol in Taiwanese. Environ Int 33:903-910, 2007
68. Yokota T, Bendell J, LoRusso P, et al: Impact of race on dose selection of molecular-targeted agents in early-phase oncology trials. Br J Cancer 118:1571-1579, 2018