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REVIEW ARTICLE

An Overview of the Treatment Efficacy and Side Effect Profile of Pharmacological Therapies in Asian Patients with Breast Cancer

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Abstract

Breast cancer (BC) among Asians accounts for ~ 40% of the global BC burden. Differences in BC risk, presentation, tumor biology, and response to treatment exist between Asian and non-Asian patients; however, Asian patients are often underrepresented in clinical trials. This narrative review summarizes the efficacy and safety of pharmacological therapies for BC in Asian populations, with a focus on outcomes in Asian versus non-Asian patients treated with chemotherapy, hormone therapy, anti-human epidermal growth factor receptor-2 targeted therapies, cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, mammalian target of rapamycin inhibitors, bone-targeted therapies, poly-ADP ribose polymerase, phosphoinositide 3-kinase, and checkpoint inhibitors. While most therapies have demonstrated comparable efficacy and safety in Asian and non-Asian patients with BC, differences that are largely attributed to pharmacogenetic variations between populations exist. Pharmacogenetic differences may contribute to a reduced clinical benefit of tamoxifen, whereas improved clinical outcomes have been reported with tyrosine kinase inhibitors and CDK4/6 inhibitors in Asian versus non-Asian patients with BC. In particular, Asian patients have an increased incidence of hematological toxicities, including neutropenia, although adverse events can be effectively managed using dose adjustments. Recent trials with CDK4/6 inhibitors have increased efforts to include Asians within study subsets. Future clinical trials enrolling higher numbers of Asian patients, and an increased understanding of differences in patient and tumor genetics between Asians and non-Asians, have the potential to incrementally improve the management of BC in Asian patients.

Key Points

Data suggest important differences in tumor biology, treatment response, and metabolism of anticancer drugs between Asians and non-Asians with breast cancer (BC), yet the majority of clinical trials are conducted in Western settings.

A review of the literature suggests that while many treatments for Asians and non-Asians with BC often have similar efficacy and safety, important differences have been reported, particularly regarding hematological toxicities.

There is a need for future studies to enroll a higher proportion of Asian patients, and for further research into the reasons behind the differences seen between Asians and non-Asians with BC, in order to improve the management of Asian patients with this disease.

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1 Introduction

Breast cancer (BC) in Asian women accounts for ~ 40% of the global BC incidence [1], and is rising [2–5]. Age-standardized incidence rates in Asia vary considerably across the continent, but are lower than in Western countries. Mortality rates are substantially higher compared with Western populations, although there also are large variations in BC mortality rates across Asia [1–3]. Furthermore, BC in Asia typically affects a younger population at a more advanced stage [1, 4, 5].

Patients in Asian and non-Asian countries share several risk factors contributing to BC development, including early menarche, late menopause, older age at first pregnancy, and absence of breastfeeding [1, 4, 5]. In contrast, dietary and lifestyle factors, including lower alcohol consumption, less hormone replacement therapy, lower body mass index (BMI), and increased consumption of soy-based products reduce the risk of BC in Asian women [5]. Although an increasingly Westernized lifestyle accounts for rapidly rising BC incidence among East Asian women, a recent study demonstrated significant differences in secular trends with age-specific incidences of female BC in Asians versus a USA-based population [6]. Furthermore, the age-specific pathological features of BC in East Asian countries were distinct from the USA, but similar to Asian Americans, thereby suggesting ethnic differences in its etiology and biology [6].

Genetic differences between Asians and non-Asians may also contribute to differences in tumor biology, response to treatment, and metabolism of anticancer drugs [3–5, 7]. Initial speculations focusing on early onset of BC in Asians suggested a higher frequency of the basal-like subtype BC, characterized by poor differentiation, resulting in a relatively poor prognosis [8, 9]. However, recent studies in Taiwan and Japan indicated that women aged < 50 years have a higher probability of hormone receptor-positive disease and lower probability of triple-negative BC than those ≥ 50 years of age [8–10]. Evidence also suggests that pharmacogenetic differences contribute to chemotherapy having poorer tolerability and higher toxicity among Asians [3]. The majority of clinical trials are conducted in Western settings, limiting the applicability of their data to Asian populations.

In this review, we provide an overview of the efficacy and safety of pharmacological therapies for BC in Asians, with a focus on comparing outcomes in Asian versus non-Asian patients.

2 Search Strategy

This article is a narrative review. A series of free-text searches in PubMed for papers published between January 2000 and June 2021 were conducted using various combinations of keywords, including: breast cancer; anastrozole, letrozole, goserelin, tamoxifen, fulvestrant, lapatinib, pertuzumab, neratinib, ribociclib, abemaciclib, palbociclib, everolimus, denosumab, zoledronic acid, talazoparib, veliparib, olaparib, rucaparib, niraparib, Talzenna, AZD-281, MK-7339, Lynparza, pembrolizumab, atezolizumab, tislelizumab, avelumab, durvalumab, alpelisib, BYL719, idelalisib, copanlisib, duvelisib, taselisib, buparlisib, BMK120, and umbralisib; and Asian, Japan, Japanese, China, Chinese, Taiwan, Taiwanese, Korea, Korean, and ethnicity. In addition, a search of key congresses was undertaken, the reference lists of papers found in the search were examined for relevant studies, and key papers were included based on the authors' clinical experience and knowledge of the field.

3 Chemotherapy

The efficacy of chemotherapy in Asians is generally comparable to that observed in Caucasians, based on a retrospective comparison of East Asian and global studies using paclitaxel and gemcitabine [11]. Slightly higher response rates (44.6–50.0% vs. 41.4%), 12-month overall survival (OS) (78.6–86.5% vs. 71.1%), and progression-free survival (PFS) (7.6–7.7 months vs. 5.9 months) were observed in East Asians receiving paclitaxel–gemcitabine therapy for metastatic BC compared with the global population [11]. Of note, these findings are based on a limited number of studies with relatively small sample sizes that were subject to high censoring rates, and the global studies included more patients with worse performance status [11]. Despite this, several differences were observed in the pharmacological properties of chemotherapy in Asians compared with other races. East Asian patients are generally more susceptible to chemotherapeutic side effects compared with patients in Western countries [12]. A larger population of Japanese patients had grade 4 neutropenia with carboplatin-paclitaxel combination therapy, a long-standing doublet regimen that was well tolerated in patients with lung and ovarian cancers in the USA [13, 14].

Hematological toxicities are key areas of difference between Asians and other races. Several studies have reported a higher prevalence of neutropenia in Asian versus non-Asian patients administered chemotherapy, despite lower dosage in some Asian countries [11, 15]. For example, > 30% of Asians treated with four cycles of adjuvant docetaxel–cyclophosphamide experienced grade ≥ 3 neutropenia compared with < 5% of Caucasians [16]. Increased hematological toxicity was reported in Asians administered taxane-based therapy [11, 17]. Notably, increased risk of docetaxel-related hematological adverse events (AEs) is associated with a lower clearance rate of docetaxel in Asians [18]. An increased incidence of edema, myalgia, nail

disorder, febrile neutropenia, upper respiratory tract infection, reduced appetite, and rash were reported for Asians treated with either trastuzumab or pertuzumab and trastuzumab, in combination with docetaxel [19]. These AEs led to 47% of docetaxel dose reductions in Asians versus 13% in non-Asians, though a similar number of treatment cycles were administered in both groups and treatment efficacy was not significantly affected [19]. Cyclophosphamide in combination with doxorubicin was also linked to higher rates of hematological toxicity [20, 21]. In particular, low BMI may be a risk factor for hematological toxicities in Asians, although the risk may be effectively managed using a dose adjustment or titration strategy [20–23]. Potential interactions related to co-exposure with traditional medicine and chemotherapy remain largely unknown [20].

Despite the absence of relevant differences in clinical antitumor activity, regional disparity exists in tolerability profiles and phenotypic characteristics of some cytotoxic agents among Asians and non-Asians [24, 25]. Asians are known to metabolize capecitabine faster than Caucasians, and hence are more likely to tolerate higher doses, without influencing efficacy [26]. Patients from the USA were ~ 3.5 times more susceptible to developing grades 3 and 4 gastrointestinal toxicities compared with Asians when receiving fluoropyrimidine treatment [24]. In contrast, no clinically relevant differences in pharmacokinetics, efficacy, or safety were observed with gemcitabine, paclitaxel, or vinorelbine [11, 23, 27, 28].

4 Hormone Therapy

The efficacy, safety, and pharmacokinetic characteristics of hormone therapy are generally comparable between Asian and Caucasian patients with early or advanced BC [29–42]. For example, a subgroup analysis of the FALCON study showed that the treatment effects of fulvestrant versus anastrozole were generally consistent between the Asian and non-Asian populations (Table 1) [38]. However, differences in the clinical benefit and toxicity profile of some hormone therapies exist among non-Caucasians.

Pharmacogenetic differences may contribute to a reduced clinical benefit of tamoxifen therapy in Asians with BC [34, 35]. Tamoxifen is metabolized to its highly potent active metabolites endoxifen and 4-hydroxytamoxifen. Several cytochrome P450 (CYP) enzymes, including CYP2D6, perform an important step in the bioactivation process [43–45]. Furthermore, the *CYP2D6* gene is highly polymorphic, leading to altered enzyme expression and function [45]. Accordingly, clinically relevant variations in CYP2D6 phenotype frequency between individuals and races could impact the efficacy of tamoxifen therapy [33, 34, 46]. The *CYP2D6**10 variant, associated with reduced enzyme activity, is more common in Asians, and this results in significantly lower plasma concentrations of endoxifen and 4-hydroxytamoxifen, and poorer clinical outcomes for Asians with metastatic BC [34]. A meta-analysis investigating the effect of *CYP2D6**10 polymorphisms on clinical outcomes in 1,794 Asian patients with BC across 15 retrospective studies concluded that the *CYP2D6**10 variant reduces the efficacy of tamoxifen treatment, as illustrated by lower disease-free survival (DFS) and higher recurrence rates [35, 36].

Letrozole, an aromatase inhibitor, has been shown to be better tolerated by Black, Hispanic, Asian, Pacific Island, and native North American/Alaskan women, who reported a significantly lower incidence of hot flashes (49% vs. 58%; $p = 0.02$), fatigue (29% vs. 39%; $p = 0.005$), diarrhea (3% vs. 7%; $p = 0.033$), and arthritis (2% vs. 7%; $p = 0.006$) than Caucasians; these women did not achieve the same improvement in DFS [36]. This variability in letrozole efficacy and safety in Asians has been attributed to pharmacokinetic differences, poorer treatment adherence, and divergent menopausal experiences between races [36]. These results need confirmation in other trials of aromatase inhibitors, given the heterogeneity of the non-Caucasian cohort and the limited number of Asian patients.

5 Anti-Human Epidermal Growth Factor Receptor 2 (HER2)-Targeted Therapies

The recommended dosages of molecular targeted therapies are not based on body mass or surface area. In general, the pharmacokinetics, efficacy, and safety profiles of targeted therapies such as tyrosine kinase inhibitors (TKIs), monoclonal antibodies, and antibody–drug conjugates are comparable across races in patients with advanced BC (Table 1) [19, 47–54]. However, several studies have reported superior clinical outcomes with TKIs among Asians.

A numerically improved objective response rate (ORR; 66.4% vs. 51.3%), clinical benefit rate (CBR; 70.2% vs. 60.2%), and PFS [55.6 (95% confidence interval (CI) 44.1–64.0) vs. 36.1 (95% CI 32.1–40.0) weeks] have been observed in Asian patients with advanced disease who were administered neratinib-based therapy compared with non-Asians [53], which correlates with similar or greater invasive DFS in early BC [52, 53]. Likewise, disease control with lapatinib in combination with capecitabine is considerably higher in Asian than Caucasian populations (58–59% vs. 27–29%) [51, 54], but these outcomes may not be entirely attributable to racial differences because Asian patients exhibited greater treatment adherence and a longer duration of treatment [52, 53]. In addition, whether the improved efficacy was a result of the epidermal growth factor receptor inhibitor or the partner drug capecitabine could not be determined. A subgroup analysis of the DESTINY-Breast01 study

Table 1 Clinical studies of hormone therapies and HER2-targeted therapies in advanced breast cancer with data available for an Asian subgroup

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, n	Age, years	Menopausal status	Race	Stage	HR status	HER2 status
Hormone therapies												
Fulvestrant												
Noguchi et al. (2018) [38] FALCON study subgroup analysis	PFS was comparable between Asian and non-Asian subgroups: In the Asian subgroup median PFS was 16.6 vs. 15.9 months for fulvestrant and anastrozole therapy, respectively (HR 0.81; 95% CI 0.44–1.50) In the non-Asian subgroup, median PFS was 16.5 vs. 13.8 months for fulvestrant and anastrozole therapy, respectively (HR 0.79; 95% CI 0.62–1.01)	*Asian subgroup:* ORR: 56.7 and 41.4% in the fulvestrant and anastrozole arms, respectively CBR: 79.4 and 75.8% in the fulvestrant and anastrozole arms, respectively Median DOR: 20.0 months with fulvestrant vs. 11.1 months with anastrozole Median DOCB: 25.4 months with fulvestrant vs. 16.6 months with anastrozole *Non-Asian subgroup:* ORR: 44.2 and 45.5% in the fulvestrant and anastrozole arms, respectively CBR: 78.1 and 73.9% in the fulvestrant and anastrozole arms, respectively Median DOR: 21.6 months with fulvestrant vs. 13.7 months with anastrozole Median DOCB: 22.1 months with fulvestrant vs. 19.1 months with anastrozole AE profiles were similar for Asian and non-Asian subgroups	20 countries across Europe, North America, South America, South Africa, and Asia [39]	Fulvestrant 500 mg IM on days 0, 14, 28 of a 28-day cycle	Anastrozole 1 mg/day PO	67 (Asian subgroup) 395 (non-Asian subgroup)	*Asian subgroup* Median age: 63.0 years (range 47–84) *Non-Asian subgroup* Median age: 62.0 years (range 36–90)	Postmenopausal	*Asian subgroup* ($n = 67$; 14.5%; included only patients enrolled at centers in Japan ($n = 31$) China ($n = 25$) Taiwan ($n = 11$), not patients of Asian ethnicity enrolled in non-Asian countries) *Non-Asian subgroup* ($n = 395$; 85.5%) including White ($n = 349$), Black ($n = 8$), Pacific Islander/American Indian/Alaskan native ($n = 6$)	Locally advanced or metastatic	*Asian subgroup* 82% ER+/PR+ ($n = 55$) 18% ER+/PR- ($n = 12$) *Non-Asian subgroup* 76% ER+/PR+ ($n = 299$) 19% ER+/PR- ($n = 75$) 4% ER+/PR unknown ($n = 17$) 1% ER-/PR+ ($n = 4$)	–

Table 1 (continued)

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, n	Age, years	Menopausal status	Race	Stage	HR status	HER2 status
HER2-targeted therapies												
Pertuzumab												
Swain et al. (2014) [19] CLEOPATRA regional subgroup analysis	Adding pertuzumab to trastuzumab–docetaxel therapy improved PFS and OS to a similar extent in patients from Asia and other regions, and the ITT population: *PFS* Asia: HR = 0.68 (95% CI 0.48–0.95) Other regions: HR = 0.61 (95% CI 0.48–0.76) *OS* Asia: HR = 0.64 (95% CI 0.41–1.00) Other regions: HR = 0.66 (95% CI 0.50–0.89)	In patients from Asia: Incidence of febrile neutropenia and mucosal inflammation 2-fold higher in the pertuzumab treatment arm Incidence of edema, myalgia, nail disorder, febrile neutropenia, upper respiratory tract infection, rash and decreased appetite was twofold higher across treatment arms compared with patients from other regions	25 countries across Asia, Europe, North America, and South America [47]	Pertuzumab 840 mg IV loading dose, followed by 420 mg every 3 weeks Trastuzumab 8 mg/kg IV loading dose, followed by 6 mg/kg every 3 weeks Docetaxel 75 mg/m^2 IV every 3 weeks	Trastuzumab 8 mg/kg IV loading dose, followed by 6 mg/kg every 3 weeks Docetaxel 75 mg/m^2 IV every 3 weeks	804	*Patients from Asia* Median age: 53.0 years (range 28–81) *Patients outside Asia* Median age: 54.0 years (range 22–89)	–	Patients from Asian region (n = 253; 31.5%) Patients from non-Asian region (n = 551; 68.5%)	Locally recurrent, unresected or metastatic	–	HER2+

Table 1 (continued)

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, n	Age, years	Menopausal status	Race	Stage	HR status	HER2 status
Neratinib												
ExteNET study												
Chan et al. (2016) [49] ExteNET study	Neratinib therapy for 12 months significantly improved 2-year invasive DFS (HR 0.67; 95% CI 0.50–0.91; $p = 0.009$)	In patients administered neratinib: DFS was significantly improved (93.9% vs. 91.6%; HR, 0.63; 95% CI 0.46–0.84; $p = 0.002$) Most common grade 3/4 AE were diarrhea, vomiting and nausea	495 centers across Europe, Asia, Australasia, North America, and South America	Neratinib 240 mg/day PO for 12 months	Placebo	2840	Median age: 52.0 years (range 45–60)	47% Premenopausal ($n = 1327$) 53% Postmenopausal ($n = 1513$)	81% White ($n = 2300$) 3% Black ($n = 74$) 14% Asian ($n = 385$) 3% Other ($n = 81$)	Locally invasive early-stage breast cancer	57% ER+ and/or PR+ ($n = 1631$) 43% ER−/PR− ($n = 1209$)	HER2+
Chan et al. (2021) [130] ExteNET study final efficacy results	In patients who initiated treatment ≤ 1 and > 1 year post-trastuzumab, invasive DFS was improved by neratinib at 5 years (HR 0.58; 95% CI 0.41–0.82 and 0.74; 0.29–1.84, respectively)	Neratinib was associated with a numerical improvement in OS at 8 years in the ≤ 1 year and post-trastuzumab group (HR 0.79; 95% CI 0.55–1.13)	–	–	–	–	–	–	–	–	–	–
Iwata et al. (2018) [52, 131] ExteNET study subgroup	In patients from Asia, neratinib therapy for 12 months improved 5-year invasive DFS (HR 0.54; 95% CI 0.26–1.08; $p = 0.085$)	In patients from Asia treated with neratinib: Incidence of grade 3/4 diarrhea was higher than in the ITT population	–	Neratinib 240 mg/day PO for 12 months	Placebo	2840	*Patients from Asia* Median age: 53.0 years	47% Premenopausal ($n = 1327$) 53% Postmenopausal ($n = 1513$)	12% of patients from Asia ($n = 341$) 88% of patients from other regions ($n = 2499$)	Locally invasive early-stage	*Patients from Asia* 48% HR+	HER2+

Table 1 (continued)

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, n	Age, years	Menopausal status	Race	Stage	HR status	HER2 status
Other studies												
Xu et al. (2018) [53] Pooled analysis of six Phase 1/2 studies	In patients from Asia receiving neratinib therapy: ORR and CBR were higher than in patients from other regions (ORR 66.4% vs. 51.3%; CBR 72.0% vs. 60.2%) Median PFS was prolonged (55.6 vs. 36.1 weeks; $p < 0.0001$)	Incidence of grade 3/4 hematological AEs (neutropenia, leukopenia) were higher among patients from Asia	Asia region included China, Hong Kong, Japan, Korea, Malaysia, Singapore, Thailand, and Taiwan Other regions included Europe, Australasia, India, and North and South America	Neratinib 240 mg/day (all studies) Neratinib combined with one of the following in all but one study: Trastuzumab 4 mg/kg loading dose, then 2 mg/kg weekly Paclitaxel 80 mg/m^2 on days 1, 8, and 15 of a 28-day schedule Vinorelbine 25 mg/m^2 on days 1 and 8 of a 21-day schedule Capecitabine 1500 mg/m^2/day on days 1–14 of a 21-day schedule Capecitabine 2000 mg/m^2/day on days 1–14 of a 21-day schedule Trastuzumab 4 mg/kg loading dose, then 2 mg/kg weekly + paclitaxel 80 mg/m^2 on days 1, 8, and 15 of a 28-day schedule	–	1199 (98% female)	*Patients from Asia* Median age: 52.0 years (range 20–83) *Patients from other regions* Median age: 53.0 years (range 26–83)	–	34% of patients from Asia ($n = 407$) 66% of patients from other regions ($n = 792$)	Metastatic	*Patients from Asia* 48% HR+ ($n = 195$) 50% HR− ($n = 204$) 2% unknown ($n = 8$) *Patients from other regions* 48% HR+ ($n = 379$) 48% HR− ($n = 377$) 4.5% unknown ($n = 36$)	HER2+

AE adverse event, *CBR* clinical benefit rate, *CI* confidence interval, *DFS* disease-free survival, *DOCB* duration of clinical benefit, *DOR* duration of response, *ER* estrogen receptor, *HR* hazard ratio, *IM* intramuscular, *ITT* intention to treat, *IV* intravenous, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *PR* progesterone receptor

showed that race (Asian vs. non-Asian) did not impact the efficacy of trastuzumab deruxtecan in patients with HER2-positive metastatic BC previously treated with trastuzumab emtansine [55].

Data regarding the safety profiles of targeted therapies are conflicting. For example, Asians treated with trastuzumab demonstrate fewer instances of cardiac toxicity compared with non-Asians [56], but patients treated with neratinib have higher rates of grade 3/4 diarrhea and hematological events [52, 53]. Similarly, trastuzumab emtansine (T-DM1) poses a greater risk of thrombocytopenia among Asians [57].

6 Cyclin-Dependent Kinase (CDK) 4/6 Inhibitors

The more recently conducted trials on CDK4/6 inhibitors have demonstrated increased effort to include Asians within the study subsets, especially for premenopausal patients. In the first-line setting for patients with advanced BC, consistent data have shown Asians deriving greater benefit from CDK4/6 inhibitors than their non-Asian counterparts or the overall intent-to-treat population (Table 2) [58–74]. For example, ~ 70% of East Asian patients with measurable disease [PFS hazard ratio (HR) 0.33 (95% CI 0.20–0.56)] responded to abemaciclib–anastrozole therapy versus 59% of the overall population [PFS HR 0.54 (95% CI 0.42–0.70)] in the MONARCH-3 study, although interactions between race/geographical location and outcomes for Asians were not formally tested [60, 73]. The PFS HR in Asians treated with palbociclib in combination with letrozole was 0.48 (95% CI 0.27–0.87) while that of non-Asians was 0.58 (95% CI 0.45–0.74) in the PALOMA-2 study (Table 2) [59]. The MONALEESA-2 study of ribociclib and letrozole combination therapy also demonstrated clinically meaningful PFS in Asians [HR 0.30 (95% CI 0.13–0.66)] compared with the non-Asians [HR 0.60 (95% CI 0.46–0.79)] [74]. Asians treated with ribociclib in the MONALEESA-7 study had greater benefits when compared with the non-Asians; the PFS HR in Asians was 0.41 (95% CI 0.26–0.66) versus 0.66 (95% CI 0.48–0.92) in non-Asians. Higher ORR and CBR was also achieved with ribociclib in Asians compared with non-Asians (ORR 59% vs. 47%; CBR 86% vs. 80%) [61]. Furthermore, the HR for OS in Asians was 0.40 (95% CI 0.22–0.72) versus 0.91 (95% CI 0.64–1.30) in non-Asians [75]. A recent meta-analysis confirmed that ethnicity influences efficacy of CDK4/6 inhibitor therapies (abemaciclib, palbociclib, ribociclib) as first-line treatment options in patients with advanced BC [76]. Specifically, among Asians ($n = 492$), the HR for PFS was 0.39 (95% CI 0.29–0.51; $p < 0.0001$) for combination CDK4/6 inhibitor–endocrine therapy compared with endocrine monotherapy, while in non-Asians ($n = 2007$) the HR for PFS for combination CDK4/6 inhibitor–endocrine therapy versus endocrine monotherapy was 0.62 (95% CI 0.54–0.71; $p < 0.0001$), demonstrating a significant interaction between ethnicity and treatment effect on PFS ($p = 0.002$) [76].

In the second-line and beyond setting in advanced BC, the benefits of adding a CDK4/6 inhibitor to fulvestrant in Asian patients were less apparent compared with benefits seen in Caucasian patients. While the MONARCH-2 study demonstrated the addition of abemaciclib led to comparable outcomes between East Asians versus the overall population in terms of PFS HR [0.52 (95% CI 0.36–0.74) vs. 0.55 (95% CI 0.45–0.68)] [70, 71] and OS HR [0.80 (95% CI 0.52–1.24) vs. 0.76 (95% CI 0.61–0.95)] [77], results from the PALOMA-3 and MONALEESA-3 studies did not show similar findings [78]. These results may be limited by the small number of Asians being included in the trials and subtle differences in eligibility criteria used in each study. The median PFS and OS HRs for the Asian population in the MONALEESA-3 study were 1.35 (95% CI 0.57–3.19) and 1.42 (95% CI 0.46–4.33), respectively [68, 79]. In the PALOMA-3 study, OS HR was 1.04 (95% CI 0.57–1.93) in Asian patients versus 0.78 (95% CI 0.60–1.01) in Caucasian patients, despite a similar PFS HR between Asian and non-Asian patients [Asian 0.49 (95% CI 0.27–0.87); non-Asian 0.45 (95% CI 0.34–0.59)] [63, 78]. In the monarchE study, Asian patients with high-risk early BC had clinically meaningful improvements in invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS) with abemaciclib plus endocrine therapy versus endocrine therapy alone [80]. There was a 22.3% reduction in the risk of developing invasive disease with abemaciclib plus endocrine therapy versus endocrine therapy alone, while 2-year IDFS rates were 93.2% versus 90.1%, and 2-year DRFS rates were 94.4% versus 91.7%. The benefits seen in Asian patients in monarchE were consistent with those seen in the overall population [80].

Although CDK4/6 inhibitors are generally well tolerated and exhibited an acceptable safety profile that is comparable between Asians and non-Asians [61, 74], ethnic variation in AE profiles has been observed. For palbociclib, compared with non-Asians, a reduced rate of fatigue (19% vs. 44%), but increased incidence of neutropenia (92% vs. 78%), stomatitis (41% vs. 24%), rash (32% vs. 11%), and nasopharyngitis (21% vs. 10%) have been reported for Asians [63]. In the PALOMA-3 study, Asian ethnicity was significantly associated with an increased chance of developing grade 3/4 neutropenia with palbociclib [81]. A similar finding was observed in the PALOMA-2 study, and the investigation of pharmacokinetics showed that geometric mean palbociclib C_{trough} values were higher in Asians relative to non-Asians (93.8 vs. 61.7 ng/mL), which indicated greater palbociclib exposure in Asians [82]. Pharmacogenetic analyses of the PALOMA-2 and PALOMA-3 studies have suggested an

association of drug-related polymorphisms with palbociclib-related neutropenia [83, 84]. Compared with the global study population, a higher rate of neutropenia was also seen among East Asian patients treated with abemaciclib for metastatic or recurrent BC, along with a greater incidence of leukopenia, alopecia, and increased alanine aminotransferase and aspartate aminotransferase levels [73]. In PALOMA-2 dose reductions were used to manage tolerability issues, and Asian patients had dose reductions more frequently than non-Asian patients [82], which has the potential to affect efficacy; however, an exposure-response analysis showed that palbociclib exposure had no impact on PFS [85].

For ribociclib, a higher rate of grade 3/4 QT-interval prolongation occurs among Asians than non-Asians (3.8% vs. 0.6%) [61]. The low number of Asians enrolled across studies greatly limits the ability to make formal inter-ethnic comparisons. A meta-analysis assessing the influence of ethnicity on toxicity associated with combination CDK4/6 inhibitor and endocrine therapy reported that the addition of a CDK4/6 inhibitor resulted in a higher incidence of neutropenia in Asians when compared with non-Asians (91% vs. 75%; *p*-value between groups 0.00001; *p*-value for ethnicity interaction 0.07) [76]. Likewise, Asians tended to experience lower rates of diarrhea compared with non-Asians, although the interaction was not statistically significant (15% vs. 32%; *p*-value between groups 0.003; *p*-value for ethnicity interaction 0.35) [76]. While Asian ethnicity was generally associated with a significantly lower risk of nausea (*p*-value for ethnicity interaction 0.007), the difference was not significant (39.4% vs. 42.4%; *p*-value between groups 0.76) [76]. Interstitial lung disease (ILD) is another class of AE noted in the Asian population, especially in Japan [86]. Differences in genetic sensitivity and variation in reporting ILD as an adverse drug reaction may play a prominent role in the higher incidence rates, although further studies are warranted for validation [86, 87].

Overall, neutropenia appears to be the most common treatment-related AE in Asians treated with a CDK4/6 inhibitor. This is usually manageable through dose reduction or delay and does not affect treatment efficacy, or increase the incidence of neutropenic fever [61, 63, 73, 76, 88, 89]. The generally lower body mass in Asians under a recommended flat dose of CDK 4/6 inhibitors has been proposed as a possible factor that leads to higher toxicities [25]. Genetic factors also play a role, with a Phase 1b study finding that the maximum tolerated dose of ribociclib was 300 mg in Japanese patients versus 600 mg in non-Japanese Asians [90]. Drug exposure seems relatively similar among Asian and non-Asian patients according to the pharmacokinetic profiles [63, 91].

7 Mammalian Target of Rapamycin (mTOR) Inhibitors

Few studies have explored racial differences in the efficacy and safety of mTOR inhibitors in patients with BC, but currently available data suggest similar efficacy and safety profiles for Asian and non-Asian patients with advanced BC (Table 3) [92–95]. Specifically, the addition of everolimus to exemestane treatment produces similar benefits in survival among Asian (Chinese and Japanese) and non-Asian patients, with a median PFS of 8.5 months versus 7.3 months [93]. The addition of everolimus is associated with more toxicity compared with hormone therapy alone, resulting in a higher proportion of dose reductions and treatment discontinuations [96]. Although everolimus treatment is considered to be well tolerated and safe to use in Asians, some AEs are more common among Asians when compared with non-Asians, such as dysgeusia (31% vs. 20%), pneumonitis (23% vs. 15%), nail disorder (22% vs. 5%), increased lactate dehydrogenase (14% vs. 4%), ILD (13% vs. < 2%), and stomatitis (80% vs. 54%) [93]. These AEs can generally be managed through early intervention and dose modification [93].

8 Bone-Targeted Therapies

Due to an increased risk of bone metastases and treatment-related bone loss, patients with BC are often treated with denosumab or bisphosphonates to prevent and treat skeletal-related events [97–99]. Several studies have demonstrated comparable efficacy, safety, and pharmacokinetics for denosumab and zoledronic acid in Asian (predominantly Japanese) cohorts (Table 4) [97, 98, 100] and non-Asian cohorts [101–104]. For example, Japanese women with BC-related bone metastases show similar baseline levels of the bone turnover marker urinary N-telopeptide corrected for creatinine (uNTx/Cr) to non-Japanese (White and Hispanic) patients following denosumab treatment, along with comparable sustained suppression of uNTx/Cr [97]. Similarly, zoledronic acid is effective for preventing aromatase inhibitor-associated bone loss in postmenopausal Japanese women [98], and has been shown to significantly reduce skeletal complications by 39% in Japanese women with BC and bone metastases [100]. While higher rates of low-grade pyrexia, fatigue, abdominal pain, and hypocalcemia have been reported in Japanese women with zoledronic acid compared with placebo, zoledronic acid is generally well tolerated [100].

Table 2 Phase 3 randomized studies of CDK4/6 inhibitors in advanced breast cancer with data available for an Asian subgroup

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, *n*	Age (years)	Menopausal status	Race	Stage	HR status	HER2 status
Ribociclib												
Yap et al. (2016) [74] MONALEESA-2 subgroup analysis	PFS was significantly prolonged in patients treated in Asia (HR 0.30; 95% CI 0.13–0.66) and outside Asia (HR 0.60; 95% CI 0.46–0.79)	Acceptable AE profile; comparable between treatment groups	29 countries	Ribociclib 600 mg/day PO on 3-weeks-on, 1-week-off schedule Letrozole 2.5 mg/day PO	Letrozole 2.5 mg/day PO	668	Median age (ribociclib arm): 62.0 years (range 23–91)	Postmenopausal	10% of patients from Asia[a] ($n = 68$) 90% of patients from non-Asia region[a] ($n = 600$)	Recurrent or metastatic	99.6% ER+ ($n = 665$) 82.2% PR+ ($n = 549$)	99% HER2− ($n = 664$)
Im et al. (2018) [61] MONALEESA-7 subgroup analysis[b]	In Asian patients, ribociclib prolonged PFS compared with 11 months in the placebo group (HR 0.41; 95% CI 0.26–0.66; $p < 0.001$; median PFS not reached in the ribociclib group) In non-Asian patients, ribociclib prolonged PFS from 16.5 to 23.8 months (HR 0.66; 95% CI 0.48–0.92; $p = 0.001$)	In Asian patients: ORR of 58.5 and 34.2% in ribociclib and placebo treatment groups CBR of 86.2 and 63.2% in ribociclib and placebo treatment groups In non-Asian patients: ORR of 46.5 and 37.4% in ribociclib and placebo treatment groups CBR of 79.5 and 64.2% in ribociclib and placebo treatment groups Ribociclib-associated AEs were consistent with prior studies, though the incidence of any-grade neutropenia, leukopenia, lymphopenia, hot flush, nausea, fatigue, and vomiting were slightly lower, and decreased neutrophil and white blood cell counts slightly higher among Asian patients	30 countries	Ribociclib 600 mg/day PO on 3-weeks-on, 1-week-off schedule Goserelin 3.6 mg SC on day 1 of every 28-day cycle	Goserelin 3.6 mg SC on day 1 of every 28-day cycle	495 (excluded patients receiving tamoxifen therapy, analyzing only patients receiving ribociclib/placebo + goserelin + letrozole/anastrozole)	*Asian* Median age: 44.0 years (range 27–58) *Non-Asian* Median age: 44.0 years (range 25–55)	Premenopausal or perimenopausal	66% Non-Asian ($n = 329$) 34% Asian ($n = 166$)	Locoregionally recurrent or metastatic	–	HER2−

Table 2 (continued)

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, *n*	Age (years)	Menopausal status	Race	Stage	HR status	HER2 status
Slamon et al. (2018) [68] MONALEESA-3	The median PFS HR for the Asian population in the MONALEESA-3 study was 1.35 (95% CI 0.57–3.19); White population was 0.56 (95% CI 0.45–0.70); and Others, 0.88 (95% CI 0.20–3.91) PFS HR for the overall patient population was 0.59 (95% CI 0.48–0.73)	ORR of 32.4 and 21.5% in ribociclib-fulvestrant and placebo-fulvestrant treatment groups CBR was 70.2 and 62.8% in ribociclib-fulvestrant and placebo-fulvestrant treatment groups Most common all-grade AEs in either arm were neutropenia, nausea, and fatigue. Most common grade 3 AEs were neutropenia and leukopenia	30 countries	Ribociclib 600 mg PO per day; 3 weeks on, 1 week off Fulvestrant 500 mg IM on day 1 of each 28-day cycle, with an additional dose on day 15 of cycle 1	Fulvestrant 500 mg IM on day 1 of each 28-day cycle, with an additional dose on day 15 of cycle 1	726 patients randomly assigned at a 2:1 ratio to ribociclib-fulvestrant ($n = 484$) or placebo-fulvestrant ($n = 242$)	Median age: 63.0 years (range 31–89) for ribociclib-fulvestrant treatment group 63.0 years (range 34–86) for placebo-fulvestrant treatment group	Postmenopausal	For ribociclib-fulvestrant 83.9% White ($n = 406$) 9.3% Asian ($n = 45$) 1.0% Native American ($n = 5$) 0.6% Black ($n = 3$) 3.1% Unknown ($n = 15$) 2.1% Other ($n = 10$) For placebo-fulvestrant 88.0% White ($n = 213$) 7.4% Asian ($n = 18$) 0.4% Native American ($n = 1$) 0.8% Black ($n = 2$) 2.1% Unknown ($n = 5$) 1.2% Other ($n = 3$)	Advanced (metastatic or loco regionally recurrent disease not amenable to curative treatment	ER+ 99.4% ($n = 481$) for ribociclib-fulvestrant and 99.6% ($n = 241$) for placebo-fulvestrant PR+ 72.9% ($n = 353$) for ribociclib-fulvestrant and 69.0% ($n = 167$) for placebo-fulvestrant	HER2−
Abemaciclib												
Sledge et al. (2017) [70] MONARCH-2	The addition of abemaciclib to fulvestrant treatment prolonged PFS from 9.3 to 16.4 months (HR 0.55; 95% CI 0.45–0.68, $p < 0.001$)	ORR of 48.1 and 21.3% in abemaciclib–fulvestrant and fulvestrant-alone treatment groups CBR was 72.2 and 56.1% in abemaciclib–fulvestrant and fulvestrant monotherapy groups Abemaciclib treatment associated with a higher rate of diarrhea, neutropenia, nausea, and fatigue	19 countries	Abemaciclib 150 mg twice daily Fulvestrant 500 mg IM on day 1 and 15 of the 1st cycle and day 1 of subsequent 28-day cycles	Fulvestrant 500 mg IM on day 1 and 15 of 1st cycle and day 1 of subsequent cycles	669	Median age: 61.0 years (range 32–91)	17% pre- or peri-menopausal ($n = 114$) 82% post-menopausal ($n = 551$)	56% Caucasian ($n = 373$) 32% Asian ($n = 214$) 6% Other ($n = 42$)	Advanced	76% PR+ ($n = 510$)	HER2−

Table 2 (continued)

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, *n*	Age (years)	Menopausal status	Race	Stage	HR status	HER2 status
Sledge et al. (2020) [69] MONARCH-2 final OS results	–	There was a statistically significant increase in OS with abemaciclib-fulvestrant vs. fulvestrant alone (HR 0.757; 95% CI 0.606–0.945; $p = 0.01$) Median OS was 46.7 vs. 37.3 months with abemaciclib-fulvestrant vs. fulvestrant alone Improvements in OS were consistent between regional subgroups: North America: HR 0.596 (95% CI 0.39–0.90); Europe: HR, 0.848 (95% CI 0.61–1.17); Asia: 0.798 (95% CI 0.52–1.24)	–	–	–	–	–	–	–	–	–	–
Toi et al. (2017) [71] MONARCH-2 subgroup analysis	In Asian patients, the addition of abemaciclib to fulvestrant treatment prolonged PFS from 11.6 to 22.8 months (HR 0.52; 95% CI 0.36–0.74, $p < 0.001$)	ORR of 48 and 23% in abemaciclib–fulvestrant and fulvestrant-alone treatment groups Abemaciclib treatment associated with a higher rate of diarrhea, neutropenia, nausea, and fatigue	–	Abemaciclib 150 mg twice daily Fulvestrant 500 mg IM on day 1 and 15 of the 1st cycle and day 1 of subsequent 28-day cycles	Fulvestrant 500 mg IM on day 1 and 15 of 1st cycle and day 1 of subsequent cycles	214	Median age: 61.0 years (range 32–91)	Pre- and post-menopausal	Asian	Advanced	HR+	HER2−

Table 2 (continued)

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, *n*	Age (years)	Menopausal status	Race	Stage	HR status	HER2 status
Inoue et al. (2021) [62] MONARCH-2 Japanese subgroup analysis	Abemaciclib-fulvestrant vs. fulvestrant alone, median PFS: 21.2 vs. 14.3 months; HR, 0.67 (95% CI 0.38–1.19)	ORR of 37.5% with abemaciclib-fulvestrant, vs. 12.9% with fulvestrant alone Abemaciclib treatment associated with a higher rate of diarrhea, neutropenia, and leukopenia	Japan	Abemaciclib 150 mg twice daily Fulvestrant 500 mg IM on day 1 and 15 of the 1st cycle and day 1 of subsequent 28-day cycles	Fulvestrant 500 mg IM on day 1 and 15 of 1st cycle and day 1 of subsequent cycles	95	Median age Abemaciclib group: 56.5 (range 32–76) Placebo group: 58.0 (range 32–81)	Pre- and post-menopausal	Asian	Advanced	HR+	HER2−
Goetz et al. (2017) [60] MONARCH-3	Median PFS was prolonged by the addition of abemaciclib (HR 0.54; 95% CI 0.41–0.72; $p < 0.0001$)	ORR was 59.2 and 43.8% in abemaciclib–fulvestrant and anastrozole/letrozole-alone treatment groups CBR was 78.0 and 71.5% in abemaciclib–fulvestrant and anastrozole/letrozole-alone treatment groups Median DOR was not reached in the abemaciclib arm and was 14.1 months in the anastrozole/letrozole monotherapy arm Most common AE with abemaciclib treatment was diarrhea (predominantly grade 1) Abemaciclib treatment was associated with a higher incidence of grade 3/4 neutropenia, diarrhea, and leukopenia	22 countries (East Asian countries included Japan, South Korea, and Taiwan)	Abemaciclib 150 mg twice daily Anastrozole 1 mg/day *or* letrozole 2.5 mg/day	Anastrozole 1 g/day *or* letrozole 2.5 mg/day	493	Median age: 63.0 years (range 32–88)	Postmenopausal	58% White ($n = 288$) 30% Asian ($n = 148$) 4% Other ($n = 18$)	Advanced	77% PR+ ($n = 382$)	HER2−

Table 2 (continued)

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, *n*	Age (years)	Menopausal status	Race	Stage	HR status	HER2 status
Johnston et al. (2019) [64] MONARCH-3 final PFS results	Median investigator-assessed PFS was 28.2 vs. 14.8 months with abemaciclib vs. placebo (HR 0.54; 95% CI 0.42–0.70; $p = 0.000002$) When groups were stratified by Caucasian vs. Asian, HR (95% CI) was 0.664 (0.48–0.92) and 0.338 (0.21–0.54), respectively	–	–	–	–	–	–	–	–	–	–	–
Tokunaga et al. (2018) [73] MONARCH-3 subgroup analysis	In East Asian patients, the addition of abemaciclib to anastrozole or letrozole treatment significantly prolonged PFS from 12.8 months; median PFS not reached in the combination therapy group (HR 0.33; 95% CI 0.20–0.56; $p < 0.0001$)	In East Asian patients: ORR was 69.8 and 45.9% in abemaciclib–fulvestrant and anastrozole/letrozole-alone treatment groups CBR was 88.4 and 70.3% in abemaciclib–fulvestrant and anastrozole/letrozole-alone treatment groups Higher incidence of neutropenia and increased transaminases in East Asian patients	22 countries (East Asian countries included Japan, South Korea, and Taiwan)	Abemaciclib 150 mg twice daily Anastrozole 1 mg/day *or* letrozole 2.5 mg/day	Anastrozole 1 mg/day *or* letrozole 2.5 mg/day	144	*East Asian patients* Median age: 61.0 years (range 45–85)	Postmenopausal	East Asian: 37% Japanese; 22% Taiwanese; 41% South Korean	Advanced	*In East Asian patients* 75% PR+ ($n = 108$)	HER2−

Table 2 (continued)

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, *n*	Age (years)	Menopausal status	Race	Stage	HR status	HER2 status
Toi et al. (2021) [72] MONARCH-2 and -3 East Asian subgroup analysis	Median PFS MONARCH-2, abemaciclib-fulvestrant vs. fulvestrant alone 21.2 vs. 11.6 months (HR 0.520; 95% CI 0.36–0.75; $p < 0.001$) MONARCH-3, abemaciclib-vs. placebo Not reached vs. 12.8 months (HR 0.326; 95% CI 0.20–0.53; $p < 0.001$)	MONARCH-2, abemaciclib-fulvestrant vs. fulvestrant alone ORR for patients with measurable disease was 47.5% vs. 23.4% CBR was 76.2% vs. 75.4% MONARCH-3, abemaciclib vs. placebo ORR for patients with measurable disease was 69.8% vs. 45.9% CBR was 87.3% vs. 73.8% The most common AE of any grade reported in both studies was diarrhea, followed by neutropenia	Japan, Korea, and Taiwan	MONARCH-2 Abemaciclib 150 mg twice daily Fulvestrant 500 mg IM on day 1 and 15 of the 1st cycle and day 1 of subsequent 28-day cycles MONARCH-3 Abemaciclib 150 mg twice daily Anastrozole 1 mg/day *or* letrozole 2.5 mg/day	MONARCH-2 Fulvestrant 500 mg IM on day 1 and 15 of 1st cycle and day 1 of subsequent cycles MONARCH-3 Anastrozole 1 mg/day *or* letrozole 2.5 mg/day	MONARCH-2, $n = 212$ MONARCH-3, $n = 144$	Median age MONARCH-2 Abemaciclib-fulvestrant and fulvestrant alone 55 (range 32–76) and 56 (32–81) MONARCH-3 Abemaciclib and placebo 60 (45–78) and 62 (46–85)	Pre- and postmenopausal	Asian	Advanced	–	HER2−
Palbociclib												
Finn et al. (2016) [59] PALOMA-2	Palbociclib significantly prolonged PFS from 14.5 to 24.8 months (HR 0.58; 95% CI 0.46–0.72, $p < 0.001$) Analysis by race showed PFS favored Palbociclib-letrozole in both Asians (HR 0.48; 95% CI 0.27–0.87) and non-Asians (HR 0.58; 95% CI 0.45–0.74)	ORR was 55.3 and 44.4% in palbociclib–letrozole and letrozole-alone treatment groups CBR was 84.9 and 70.3% in palbociclib–letrozole and letrozole monotherapy groups Palbociclib–letrozole treatment associated with higher rates of neutropenia, leukopenia, alopecia, anemia, thrombocytopenia, diarrhea, cough, and stomatitis	17 countries	Palbociclib 125 mg/day PO on 3-weeks-on, 1-week-off schedule Letrozole 2.5 mg/day PO	Letrozole 2.5 mg/day PO	666	Median age 61.5 years (range 28–89)	Postmenopausal	78% White ($n = 516$) 14% Asian ($n = 95$) < 2% Black ($n = 11$) 7% Other ($n = 44$)	Advanced	ER+	HER2−

Table 2 (continued)

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, *n*	Age (years)	Menopausal status	Race	Stage	HR status	HER2 status
Dieras et al. (2019) [58] PALOMA-2	Asian ethnicity carries a higher risk of developing grade 3/4 neutropenia ($p < 0.001$) but is manageable with dose reduction	Dose reduction to manage neutropenia does not affect PFS	17 countries	Palbociclib 125 mg/day PO on 3-weeks-on, 1-week-off schedule Letrozole 2.5 mg/day PO	Letrozole 2.5 mg/day PO	–	Median age: 62.0 years (range 30–89)	Postmenopausal	–	Advanced	ER+	HER2−
Mukai et al. (2019) [67] PALOMA-2 Japanese subgroup analysis	Among Japanese patients, median PFS was 22.2 months with palbociclib–letrozole vs. 13.8 months with letrozole alone (HR 0.59; 95% CI 0.26–1.34; $p = 0.103$)	Confirmed ORR was numerically higher with palbociclib–letrozole vs. letrozole alone (46.4% [27.5–66.1] vs. 38.5% [13.9–68.4]) in patients with measurable disease Hematologic AEs were more frequent in Japanese patients vs. the overall population: (neutropenia: 93.8% vs. 79.5%; leukopenia: 62.5% vs. 39.0%). Palbociclib dose reductions were more common in Japanese patients (62.5% vs. 36.0%)	Japan	Palbociclib 125 mg/day PO on 3-weeks-on, 1-week-off schedule Letrozole 2.5 mg/day PO	Letrozole 2.5 mg/day PO	46	Median age Palbociclib-letrozole, 67 (range 44–88) Letrozole, 61 (range 51–88)	Postmenopausal	Asian	Advanced	ER+	HER2−

Table 2 (continued)

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, *n*	Age (years)	Menopausal status	Race	Stage	HR status	HER2 status
Iwata et al. (2017) [63] PALOMA-3 subgroup analysis	In Asian patients, adding palbociclib to fulvestrant therapy significantly prolonged PFS from 5.8 months; median PFS not reached in the palbociclib arm (HR 0.49; 95% CI 0.27–0.87; $p = 0.0065$) In non-Asian patients, PFS was 9.5 and 3.8 months in palbociclib and placebo arms, respectively (HR 0.45; 95% CI 0.34–0.59; $p < 0.001$)	In Asian patients, ORR and CBR were similar to those in non-Asians: ORR was 19 and 13% in palbociclib–fulvestrant and fulvestrant-alone treatment groups CBR was 70 and 52% in palbociclib–fulvestrant and fulvestrant-alone treatment groups The incidence of neutropenia, stomatitis, nasopharyngitis were higher, but the incidence of fatigue lower, among Asian patients Pharmacokinetic analysis indicated similar palbociclib exposure in Asian and non-Asian patients (mean steady state plasma concentrations of 85.7 and 74.8 ng/mL, respectively) In Asian patients, QoL similar between treatment arms	17 countries Asian subgroup analysis included study sites from Japan, Korea, Taiwan, and other patients self-identified as Asian race	Palbociclib 125 mg/day PO on 3-weeks-on, 1-week-off schedule Fulvestrant 500 mg IM every 14 days for the first three doses, then every 28 days	Fulvestrant 500 mg IM every 14 days for the first three doses, then every 28 days	521	*Asian* Median age: 54.0 years (range 34–82) *Non-Asian* Median age: 58.0 years (range 29–88)	*Asian* 42% Pre- or peri-menopausal ($n = 44$) 58% Post-menopausal ($n = 61$) *Non-Asian* 15% Pre- or peri-menopausal ($n = 64$) 85% Post-menopausal ($n = 352$)	20% of patients were Asian ($n = 105$) 80% of patients were non-Asian ($n = 416$)	Advanced	67% ER+/PR+ ($n = 349$) 27% ER+/PR- ($n = 139$)	HER2−

Table 2 (continued)

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, *n*	Age (years)	Menopausal status	Race	Stage	HR status	HER2 status
Masuda et al. (2019) [66] PALOMA-3 Japanese subgroup analysis	Median PFS for palbociclib–vs. placebo was 13.6 months vs. 11.2 months (HR 0.82; $p = 0.339$)	ORR was 24% with palbociclib and 25% with placebo ($p = 0.72$) CBR rates were 71 and 88% in the palbociclib and placebo groups, respectively ($p = 0.93$) Neutropenia, leukopenia, and thrombocytopenia were more common in Japanese patients than the overall population (93% vs. 79%; 74% vs. 46%; and 37% vs. 19%)	Japan	Palbociclib 125 mg/day PO on 3-weeks-on, 1-week-off schedule Fulvestrant 500 mg IM every 14 days for the first three doses, then every 28 days	Fulvestrant 500 mg IM every 14 days for the first three doses, then every 28 days	35	Median age Palbociclib, 53 (range 36–77) Placebo, 57 (range 39–79)	49% Pre- or perimenopausal ($n = 17$) 51% Postmenopausal ($n = 18$)	Asian	Advanced	–	HER2–
Kim et al. (2021) [65] PALOMA-3 Korean subgroup analysis	Median PFS was significantly longer with palbociclib vs. placebo [12.3 vs. 5.4 months; HR 0.40 (95% CI 0.19–0.83); $p = 0.005$]	Confirmed ORR was 21.1% with palbociclib and 11.8% with placebo Neutropenia was the most common AE	Korea	Palbociclib 125 mg/day PO on 3-weeks-on, 1-week-off schedule Fulvestrant 500 mg IM every 14 days for the first three doses, then every 28 days	Fulvestrant 500 mg IM every 14 days for the first three doses, then every 28 days	43	Median age Palbociclib, 51.5 years Placebo, 49.0 years	42% Pre- or perimenopausal ($n = 18$) 58% Postmenopausal ($n = 25$)	Asian	Advanced	–	HER2–

AE adverse event, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *CBR* clinical benefit rate, *CI* confidence interval, *DOR* duration of response, *ER* estrogen receptor, *HR* hazard ratio for progression or death, *HR status* hormone receptor status, *IM* intramuscular, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival, *PO* orally, *PR* progesterone receptor, *QoL* quality of life, *SC* subcutaneous

[a]Subgroup analysis is based on geographical region and not race

[b]In MONALEESA-7, patients also received treatment with tamoxifen or a non-steroidal aromatase inhibitor (letrozole or anastrozole). The Asian subgroup analysis included only patients receiving letrozole or anastrozole

Table 3 Clinical studies of mTOR inhibitors in patients with advanced breast cancer with data available for an Asian subgroup

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, *n*	Age (years)	Menopausal status	Race	Stage	HR status	HER2 status
Everolimus												
Toi et al. (2017) [94] BOLERO-1 subgroup analysis	In Asian patients with HR- disease, addition of everolimus to the trastuzumab–paclitaxel regimen prolonged PFS from 14.5 to 25.5 months (HR 0.48; 95% CI 0.29–0.79) In non-Asian patients with HR- disease, median PFS was 16.2 vs. 12.3 months in the everolimus and placebo arms, respectively (HR 0.76; 95% CI 0.51–1.15)	In Asian patients with HR- disease: ORR and CBR were similar between treatment arms (ORR 69.2% vs. 79.9%; CBR 80.8% vs. 82.9%) In non-Asian patients with HR- disease: ORR and CBR were lower in the everolimus arm (ORR 65.6% vs. 68.7%; CBR 72.3% vs. 79.9%) Most common non-hematologic AE were stomatitis, diarrhea, and rash. Most common hematologic AE were neutropenia, decreased neutrophil count, and leukopenia Hematologic AE were more common than in non-Asian patients (leukopenia, decreased neutrophil count)	28 countries	Everolimus 10 mg/day PO Trastuzumab 4 mg/kg IV loading dose on day 1, then 2 mg/kg weekly on a 4-week cycle Paclitaxel 80 mg/m^2 IV on days 1, 8, and 15 of each 4-week cycle	Trastuzumab 4 mg/kg IV loading dose on day 1, then 2 mg/kg weekly on a 4-week cycle Paclitaxel 80 mg/m^2 IV on days 1, 8, and 15 of each 4-week cycle	719	*Asian patients* Median age: 52.0 years (range 23–82) *Non-Asian patients* Median age: 53.5 years (range 19–86)	Postmenopausal	*Asian* (n = 303; 42%) 73% Chinese (n = 220); 14% Japanese (n = 42); < 1% Indian (n = 1); 13% Other Asian (n = 40) *Non-Asian* (n = 416, 58%);27% Hispanic /Latino (n = 112); 73% Other non-Asian (n = 304)	Metastatic or locally recurrent invasive	*Asian patients* 56% ER+/PR+ (n = 169) 44% ER−/PR− (n = 132) *Non-Asian patients* 57% ER+/PR+ (n = 237) 43% ER−/PR− (n = 179)	HER2+

Table 3 (continued)

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, *n*	Age (years)	Menopausal status	Race	Stage	HR status	HER2 status
Noguchi et al. (2014) [93] BOLERO-2 study subgroup analysis	In Asian patients, median PFS was 8.5 months for everolimus plus exemestane vs. 4.1 months for exemestane-alone (HR 0.62; 95% CI 0.41–0.94) In non-Asian patients, median PFS was 7.3 months for combination therapy vs. 2.8 months for exemestane monotherapy	CBR and ORR were greater among Asian patients following combination therapy and exemestane-alone (CBR, 58% vs. 29%; ORR, 19% vs. 0%) compared with non-Asian patients (CBR, 50% vs. 26%; ORR, 11% vs. 2%) Asian patients reported higher rate of stomatitis, rash, dysgeusia, pneumonitis, nail disorder, increased LDH, nasopharyngitis, and interstitial lung disease	24 countries, including Asia, Europe, and North America regions	Everolimus 10 mg/day PO and exemestane 25 mg/day PO	Exemestane 25 mg/day PO	724	*Asian* Median age: 60.0 years (range 28–79) *Non-Asian* Median age: 62.0 years (range 34–93)	Postmenopausal	20% of patients were Asian ($n = 143$) Of these, 74% ($n = 106$) were of Japanese origin 80% of patients were non-Asian ($n = 581$)	Metastatic or locally advanced disease that had progressed or recurred during or after treatment with letrozole or anastrozole therapy	All patients' tumors ER+ 72% PR+	HER2−

Table 3 (continued)

Study or subgroup	Primary end-point	Secondary end-points	Countries	Intervention	Comparator	Patients, *n*	Age (years)	Menopausal status	Race	Stage	HR status	HER2 status
Toyama et al. (2017) [95] BOLERO-4 study subgroup analysis	Median PFS was 20.3 months (95% CI 14.8–26.0) and 22 months (95% CI, 17.1–25.7) for Asian and non-Asian patients, respectively	Overall, AE more common among Asian patients, particularly stomatitis, decreased weight, anemia, hyperglycemia, reduced appetite, rash, and nasopharyngitis	13 countries	*First-line treatment* Everolimus 10 mg/day PO Letrozole 2.5 mg/day PO	–	202	Median age: 64.0 years	Postmenopausal	22% of patients were Asian ($n = 44$) 78% of patients were non-Asian ($n = 158$)	Metastatic or locally advanced	ER+	HER2–

AE adverse event, *CBR* clinical benefit rate, *CI* confidence interval, *ECOG* Eastern Cooperative Oncology Group performance status, *ER* estrogen receptor, *HR* hazard ratio for progression or death, *HR status* hormone receptor status, *IV* intravenously, *LDH* lactate dehydrogenase, *mTOR* mammalian target of rapamycin, *ns* not significant, *ORR* objective response rate, *PFS* progression-free survival, *PO* orally, *PR* progesterone receptor, *QoL* quality of life

9 Poly-ADP Ribose Polymerase (PARP), Phosphoinositide 3-Kinase (PI3K), and Checkpoint Inhibitors

Of the PARP inhibitors under investigation for the treatment of locally advanced/metastatic BC, olaparib and talazoparib have data available for both overall populations and Asian subgroups (Table 5), which generally show that efficacy in Asian subgroups was similar to that in the overall population [105–110]. The OlympiAD study investigated olaparib versus physician's choice of chemotherapy, and while the study was not powered to detect differences between races, the Asian subgroup analysis found that similar to the overall population, there was a greater clinical benefit with olaparib than with chemotherapy with regard to PFS and response rates [106]. Olaparib was well tolerated in Asian patients, having a lower rate of grade ≥ 3 AEs than chemotherapy [106]. The number of Asian patients in the EMBRACA studies of talazoparib versus chemotherapy was limited ($n = 33$; Table 5); however, both efficacy (as measured by PFS and response rates) and AEs were all consistent with the overall population [110].

The SOLAR-1 study showed that the PI3K inhibitor alpelisib plus fulvestrant prolonged PFS versus placebo plus fulvestrant in patients with PI3K-mutated, hormone-receptor positive, HER2-negative breast cancer who have previously received endocrine therapy (Table 5) [111–113]. An analysis of the SOLAR-1 results according to geographic region showed that in Asia, median PFS and response rates were improved with alpelisib plus fulvestrant versus placebo plus fulvestrant, consistent with the overall population; notably, the ORR in Asia was numerically higher than the ORRs seen in other regions (46.7% vs. 21.1% and 21.4% in North America and Latin America, respectively) [113]. The most common AEs of any grade in the Asian subgroup were hyperglycemia and decreased appetite (75 and 58%, respectively) [113]; these occurred in the alpelisib group of the main cohort at a frequency of 64 and 36% [111].

The checkpoint inhibitor atezolizumab was investigated in patients with advanced triple-negative BC in the IMpassion130 study (Table 5) [114–116]. In IMpassion130, the White and Asian subgroups had similar median PFS [115], and a subgroup analysis of the 65 Japanese patients participating in IMpassion130 showed consistent results to those in the overall population [114]. Fewer Japanese patients withdrew from IMpassion130 because of AEs compared with the overall population, and generally no new safety signals were observed in this subgroup [114]. Another checkpoint inhibitor that is being investigated in patients with BC is pembrolizumab, in the KEYNOTE studies (Table 5). To date, much of the KEYNOTE data in Asian patients are available only in abstract form; all abstracts reported a benefit

Table 4 Clinical studies of bone-targeted therapies in Japanese patients with breast cancer

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Adjuvant therapy	Intervention	Comparator	Patients, *n*	Age, years	Menopausal status	Race	Stage	HR status	Baseline LS and TH BMD score
Denosumab													
Yonemori et al. (2008) [97]	Predominantly mild (grade ≤ 2) AE associated with denosumab Laboratory findings similar between groups	Denosumab pharmacokinetics were approximately dose-linear At day 141: uNTx (corrected for creatinine) was suppressed by median 63% sCTX was reduced by median 80% BSAP was reduced by median 53% Osteocalcin was reduced by median 42%	Japan	Concurrent chemotherapy and hormonal therapy allowed if unchanged within 13 days of study	Dose-ascending study involving three cohorts: 1. Denosumab 60 mg SC (single dose) 2. Denosumab 180 mg SC (single dose) 3. Denosumab 180 mg SC every 4 weeks (3 doses total)	–	18	Median age: 57.0 years (range 28–67)	–	Japanese	Metastatic	72% of patients HR+ ($n = 13$)	–

Table 4 (continued)

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Adjuvant therapy	Intervention	Comparator	Patients, *n*	Age, years	Menopausal status	Race	Stage	HR status	Baseline LS and TH BMD score
Zoledronic acid													
Takahashi et al. (2012) [98]	LS BMD increased 4.9% at 12 months	After 12 months: TH BMD increased 4.4% Mean serum NTX reduced 24% Mean serum BSAP reduced 39% AE similar between groups	Japan	–	Upfront treatment with zoledronic acid 4 mg (or an adjusted dose based on renal function) IV over 15 min every 6 months for 5 years	Delayed treatment with zoledronic acid 4 mg (or an adjusted dose based on renal function) IV over 15 min every 6 months for 5 years	204	Median age: 60.0 years (range 46–82)	Postmenopausal	Japanese	Early	All patients ER+ ($n = 194$) PR+ ($n = 140$)	YAM ≥ -2.0
Kohno et al. (2005) [100]	Rate of SRE reduced 39% at 12 months (SRE ratio = 0.61)	At 12 months: Percent of patients with at least 1 SRE reduced by 20% Delayed time-to-first SRE 41% reduced risk of SRE	Japan	Antineoplastic or hormonal therapy allowed	Zoledronic acid 4 mg IV over 15 min every 4 weeks for 12 months	Placebo	228	Median age: 53.0 years	–	Japanese	Metastatic	–	–

AE adverse events, *BMD* bone mineral density, *BSAP* bone-specific alkaline phosphatase, *CI* confidence interval, *ER* estrogen receptor, *HR* hazard ratio, *HR status* hormone receptor status, *IV* intravenously, *LS* lumbar spine, *NTx* N-telopeptide, *PR* progesterone receptor, *SC* subcutaneously, *sCTX* serum type 1 collagen cross-link C-telopeptide, *SRE* skeletal-related event, *TH* total hip, *uNTx* urinary N-telopeptide, *Z-FAST* Zometa-Femara Adjuvant Synergy Trial, *YAM* young adult mean

of pembrolizumab versus comparator (placebo or standard therapy) that was consistent with the overall population [117–119]. Pembrolizumab was well tolerated, with AEs consistent with the known safety profile [117, 118].

10 Future Directions

Asians are often under-represented in clinical trials of BC therapies, limiting conclusions regarding the efficacy and safety of different therapies for this population [3, 120]. While subgroup analyses comparing Asian versus non-Asian populations have been performed in some large international studies, regional and local studies are often required to confirm outcomes in Asian populations. For example, China's National Medical Products Administration requires large international trials that include at least 100 Chinese patients per intervention, in addition to local pharmacokinetic studies [3]. Similarly, Japan's Ministry of Health, Labor, and Welfare and Pharmaceuticals and Medical Devices Agency regulatory review requires pharmacokinetic, efficacy, safety, and medical data for Japanese subjects, which leads to initiation of additional clinical trials in Japan [121]. This approval system has been criticized for requiring data from only a small number of Japanese patients that may be inadequate to detect ethnic differences in efficacy and safety [121]. Hence, pharmacovigilance programs in Asian countries play a critical role in post-approval safety monitoring and reporting of AEs [122].

A clear, stage-specific, survival gap remains among different ethnicities despite significant improvement in overall BC outcomes, suggesting the need for inclusion of non-biologic factors, including treatment differences, to explain observed outcome disparities [123]. A lack of understanding of racial and ethnic differences in patient response to pharmacological interventions also has downstream effects for patients by limiting their access to more effective or safer treatments. Likewise, the social, cultural, and economic settings represent challenges in applying the results and recommendations from studies enrolling largely non-Asian populations [1, 3]. Future studies can help to overcome these challenges by actively engaging clinical trial centers in Asia to facilitate greater recruitment of Asians into clinical trials and more robust subgroup analyses of outcomes in Asians [3].

The field of genomics is also providing greater insight in tumor biology, enabling molecularly defined prognostic staging, which could have important implications for Asians with BC [3, 7, 124, 125]. Currently, prognostic staging based on multigene analysis draws from a predominantly Caucasian dataset, offering limited usefulness for risk stratification and therapy selection in Asians, for whom these tests have not yet been validated [3, 124]. Genomics provides an opportunity to establish the molecular profiles and biomarkers for subtypes of BCs that are more prevalent in Asian populations, which can guide treatment selection, and may be used to guide dosing strategies and inform cost-benefit analyses [122, 124]. Used together, tumor genomics and patient pharmacogenetics may facilitate more effective, safer, highly personalized treatments for Asians [125].

11 Conclusions

Asian and non-Asian patients with BC have different risk profiles and tumor biology, in addition to possible race-related differences in pharmacogenetics and environmental factors [122, 124], which can influence the extent to which interventions and treatments validated in Western populations can be generalized and applied to Asian settings.

The efficacy of most BC chemotherapies and hormonal therapies appears to be broadly similar in Asian and non-Asian populations, with the exception of tamoxifen in patients with a *CYP2D6**10 polymorphism, which is more common in Asians [29, 32, 35, 37, 38, 41, 42, 126–128]. Similarly, comparable efficacy is seen between Asian and non-Asian patients treated with anti-HER2-targeted therapies.

In contrast, the first-line studies with CDK4/6 inhibitors suggest potential race-related differences in the efficacy of these agents [76]. In particular, Asians appear to derive greater benefit from CDK4/6 inhibitor therapy than non-Asians [73, 76], which may be driven by variations in pharmacodynamics given the limited differences in pharmacokinetics [63, 129].

Furthermore, small Asian populations in clinical trials may limit insight into ethnic differences in efficacy and safety profiles of treatments for BC. Notably, differences in efficacy between Asian and overall populations have generally only been found in subgroup analyses with higher numbers of Asians, which has limited statistical validity and would be expected to increase the likelihood of any differences being observed [61, 63, 73]. In addition, the use of varying definitions of Asian race or ethnicity and combination therapies in studies of CDK4/6 inhibitors make it difficult to develop a clear understanding of the relative clinical profile of CDK4/6 inhibitors in Asian versus non-Asian patients [76]. Therefore, further studies are necessary to elucidate any race-related variation in response to CDK4/6 inhibitors and underlying mechanisms.

Asians experience a higher rate of hematological toxicity, particularly neutropenia, following administration of chemotherapy, targeted therapies, and possibly CDK4/6 inhibitors. The underlying mechanisms resulting in these outcomes are not well understood, but these AEs can generally be

Table 5 Phase 3 randomized studies of PARP, PI3K, and checkpoint inhibitors in breast cancer with data available for an Asian subgroup

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, *n*	Age (years)	Menopausal status	Race	Stage	HR status	HER2 status
PARP inhibitors												
Olaparib												
Robson et al. 2017 [105] OlympiAD	PFS or death from any cause Median PFS, Olaparib vs. standard therapy: 7.0 vs. 4.2 months HR for disease progression or death: 0.58 (95% CI 0.43–0.80); $p < 0.001$	OS, HR for death, olaparib vs. standard therapy: 0.90 (95% CI 0.63–1.29); $p = 0.57$ Time from randomization to second progression or death after first progression, olaparib vs. standard therapy: 13.2 vs. 9.3 months; HR 0.57 (95% CI 0.40–0.83); $p = 0.003$ ORR, olaparib vs. standard therapy: 59.9% vs. 28.8% HRQoL (mean change from baseline in QLQ-C30), olaparib vs. standard therapy: 3.9 ± 1.2 vs. -3.6 ± 2.2; $p = 0.004$ Safety: most AEs with olaparib were grade 1/2. Rate of grade ≥ 3 events, olaparib vs. standard therapy: 36.6% vs. 50.5%	19 countries	Olaparib 300 mg BID PO	Standard chemotherapy with capecitabine, eribulin or vinorelbine	302	Median (range): olaparib, 44 (22–76) years; standard therapy, 45 (24–68) years	–	White: 65.2% ($n = 197$) Asian: 31.1% ($n = 94$) Other: 3.6% ($n = 11$)	Metastatic	Triple negative: 49.7% ($n = 150$) HR+: 50.4% ($n = 152$)	HER2−

Table 5 (continued)

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, *n*	Age (years)	Menopausal status	Race	Stage	HR status	HER2 status
Robson et al. 2019 [107] OlympiAD final OS and tolerability results		Median OS, olaparib vs. standard therapy: 19.3 vs. 17.1 months; HR, 0.90 (95% CI 0.66–1.23); $p = 0.513$ Olaparib vs. standard therapy: 6-month OS, 93.1% vs. 85.8%; 12-month OS, 72.7% vs. 69.2%; 18-month OS, 54.1% vs. 48.0% ORR, olaparib vs. standard therapy: 57.6% vs. 22.2% No new safety signals were reported										
Im et al. 2020[106] OlympiAD Asian subgroup	PFS by blinded review, olaparib vs. standard therapy: 5.7 vs. 4.2 months; HR), 0.53 (95% CI 0.29–0.97)	OS, olaparib vs. standard therapy: 20.5 vs. 20.9 months; HR, 0.98 (95% CI 0.54–1.78) ORR, olaparib vs. standard therapy: 63.6% vs. 38.1% DoR, median (IQR), olaparib vs. standard therapy: 4.2 (2.8–8.2) vs. 2.8 months (2.1–12.2) The incidence of grade ≥ 3 AEs, olaparib vs. standard therapy Asian patients: 45.8% vs. 59.3% Global OlympiAD study population: 38.0% vs. 49.5%	China, Japan, Korea, and Taiwan	–	–	87	Median (range): olaparib, 46 (28–74) years; standard therapy, 47 (24–66) years	–	Asian	Metastatic	Triple negative: 51.7% ($n = 45$) HR+: 48.3% ($n = 42$)	Negative

Table 5 (continued)

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, *n*	Age (years)	Menopausal status	Race	Stage	HR status	HER2 status
Talazoparib												
Litton et al. 2018 [109] EMBRACA	Radiologic PFS Talazoparib vs. standard therapy, median (95% CI): 8.6 (7.2–9.3) vs. 5.6 (4.2–6.7) months HR for disease progression or death: 0.54 (95% CI 0.41–0.71); $p<0.001$	Interim OS, talazoparib vs. standard therapy, median (95% CI): 22.3 (18.1–26.2) vs. 19.5 (16.3–22.4) months; HR for death: 0.76 (95% CI 0.55–1.06); $p = 0.11$ Investigator-assessed ORR, talazoparib vs. standard therapy: 62.6% vs. 27.2%; $p<0.001$ Clinical benefit at 24 weeks, talazoparib vs. standard therapy: 68.6% vs. 36.1%; $p<0.001$ DoR, talazoparib vs. standard therapy, median (IQR): 5.4 (2.8–11.2) vs. 3.1 (2.4–6.7)	Australia, Belgium, Brazil, France, Germany, Ireland, Israel, Italy, Korea, Poland, Russia, Spain, Taiwan, Ukraine, UK, and USA	Continuous oral talazoparib 1 mg/day	Protocol-specified, single-agent chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) in continuous 21-day cycles, as per the treating institution's guidelines	431	Median (range): talazoparib, 45 (27–84) years; standard therapy, 50 (24–88) years	–	–	Locally advanced/metastatic	Triple negative: 44.1% ($n = 190$) HR+: 55.9% ($n = 241$)	HER2−
Litton et al. 2020[108] EMBRACA final OS results		Final OS, talazoparib vs. standard therapy, median (95% CI): 19.3 (16.6–22.5) vs. 19.5 (17.4–22.4) months; HR 0.85 (95% CI, 0.67–1.07); $p = 0.17$ Talazoparib vs. standard therapy: 1-year OS, 71% vs. 74%; 2-year OS, 42% vs. 38%; 3-year OS, 27% vs. 21%	–	–	–	–	–	–	–	–	–	–

Table 5 (continued)

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, *n*	Age (years)	Menopausal status	Race	Stage	HR status	HER2 status
Lee et al. 2019 [110] EMBRACA Asian subgroup analysis	PFS by blinded review Talazoparib vs. standard therapy, median: 9.0 vs. 7.1 months; HR 0.74 (95% CI 0.22–2.44)	ORR, talazoparib vs. standard therapy: 62.5% vs. 25.0%; OR 1.88 (95% CI 0.07–117.85) DoR, talazoparib vs. standard therapy: 9.5 vs. 5.2 months	Korea, Taiwan	–	–	33	Median: talazoparib, 41 years; standard therapy, 45 years	–	Asian	Locally advanced/metastatic	Triple negative: 42.4% HR+: 57.6%	HER2−
PI3K inhibitors												
Alpelisib												
Andre et al. 2019 [111] SOLAR-1	Alpelisib-fulvestrant vs. placebo-fulvestrant Investigator-assessed PFS in cohort with PI3K mutation, median (95% CI), 11.0 (7.5–14.5) vs. 5.7 (3.7–7.4) months HR for progression or death: 0.65 (95% CI 0.50–0.85), $p < 0.001$ 12-month PFS in cohort with PI3K mutation, 46.3% vs. 32.9%	Alpelisib vs. placebo OS in cohort with PI3K mutation PFS in cohort without PI3K mutation, median (95% CI), 7.4 (5.4–9.3) vs. 5.6 (3.9–9.1); HR for progression or death, 0.85 (95% CI 0.58–1.25) 12-month PFS in cohort without PI3K mutation, 28.4% vs. 22.2% ORR in cohort with PI3 mutation: 26.6% vs. 12.8% Clinical benefit in cohort with PI3 mutation: 61.5% vs. 45.3%	34 countries	Alpelisib 300 mg/day PO + fulvestrant 500 mg IM on days 1 and 15 on cycle 1 and day 1 of subsequent cycles	Placebo + fulvestrant 500 mg on days 1 and 15 on cycle 1 and day 1 of subsequent cycles	572 PI3K mutation: 341 No PI3K mutation: 231	PI3K mutation, median (range), alpelisib/fulvestrant: 63 (25–87); placebo/fulvestrant: 64 (38–92) No PI3K mutation, median (range), alpelisib/fulvestrant: 62 (39–82); placebo/fulvestrant: 63 (32–88)	Postmenopausal	–	Advanced	All HR+ (specific percentage NR)	HER2−

Table 5 (continued)

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, *n*	Age (years)	Menopausal status	Race	Stage	HR status	HER2 status
Andre Ann Oncol 2021 [112] SOLAR-1 final OS results	–	Alpelisib-fulvestrant vs. placebo-fulvestrant Median (95% CI) OS in cohort with PI3K mutation, 39.3 (34.1–44.9) vs. 31.4 (26.8–41.3) months; HR, 0.86 (95% CI 0.64–1.15); $p = 0.15$ Median (95% CI) OS in cohort with PI3K mutation detected by ctDNA, 34.4 (28.7–44.9) vs. 25.2 (20.7–29.6) months; HR, 0.74 (95% CI 0.51–1.08)	–	–	–	–	–	–	–	–	–	–
Loibl et al. 2019 [113] SOLAR-1 subgroup analysis by geographic region	Asian mutant PI3K cohort, alpelisib-fulvestrant vs. placebo-fulvestrant Median PFS, 14.5 vs. 9.0 months; HR 0.55 (95% CI 0.20–1.51)	Asian mutant PI3K cohort, alpelisib-fulvestrant vs. placebo-fulvestrant ORR, 46.7% vs. 10.5%	Hong Kong, India, Korea, Taiwan, and Thailand (Japan was excluded from the Asian subgroup and analyzed separately)	–	–	34	–	–	Asian	–	–	–

Table 5 (continued)

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, *n*	Age (years)	Menopausal status	Race	Stage	HR status	HER2 status
Checkpoint inhibitors												
Atezolizumab												
Schmid et al. 2018 [115] IMpassion130	ITT and PD-L1 positive populations, atezolizumab/nab-paclitaxel vs. placebo/nab-paclitaxel ITT—investigator-assessed median PFS, 7.2 vs. 5.5 months; stratified HR for progression or death, 0.80 (95% CI 0.69–0.92); $p = 0.002$ Median PFS, White subgroup, 7.2 vs. 5.5 months; HR 0.78 (95% CI 0.65–0.93) Median PFS, Asian subgroup. 7.2 vs. 5.5 months; HR 0.76 (95% CI 0.54–1.08) PD-L1 positive—investigator-assessed median PFS, 7.5 vs. 5.0 months; stratified HR for progression or death, 0.62 (95% CI 0.49–0.78); $p = 0.001$ Median PFS, White subgroup, 7.5 vs. 5.0 months; HR 0.61 (95% CI 0.46–0.80) Median PFS, Asian subgroup. 7.4 vs. 5.3 months; HR 0.72 (95% CI 0.41–1.27) ITT—investigator-assessed median OS, 21.3 vs. 17.6 months; stratified HR for death, 0.84 (95% CI, 0.69–1.02); $p = 0.08$ PD-L1—investigator-assessed median OS, 25.0 vs. 15.5 months; stratified HR for death, 0.62 95% CI, (0.45–0.86)	ITT and PD-L1 positive populations, atezolizumab/nab-paclitaxel vs. placebo/nab-paclitaxel ITT—ORR, 56.0% vs. 45.9% PD-L1 positive—ORR, 58.9% vs. 42.6% ITT—median DoR, 7.4 vs. 5.6 months PD-L1 positive—median DoR, 8.5 vs. 5.5 months	41 countries	Atezolizumab 840 mg IV on days 1 and 15 plus nab-paclitaxel 100 mg/m^2 IV BSA on days 1, 8, and 15 of each cycle	IV placebo plus IV nab-paclitaxel 100 mg/m^2 BSA on days 1, 8, and 15 of each cycle	ITT, $n = 902$ PD-L1 positive, $n = 369$	Atezolizumab/nab-paclitaxel, median (range), 55 (20–82) years Placebo/nab-paclitaxel, median (range), 56 (26–86) years	–	ITT population White 67.5% ($n = 609$) Asian 17.9% ($n = 161$) Black 6.5% ($n = 59$) Native American 4.4% ($n = 40$) Other 0.7% ($n = 6$) Unknown 3.0% ($n = 27$) PD-L1 positive White 68.8% ($n = 254$) Asian 17.9% ($n = 66$) Black 6.2% ($n = 23$) Native American 4.6% ($n = 17$) Other 0% ($n = 0$) Unknown 2.4% ($n = 9$)	Metastatic or unresectable locally advanced	100% triple negative	HER2−

Table 5 (continued)

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, *n*	Age (years)	Menopausal status	Race	Stage	HR status	HER2 status
Schmid et al. 2020 [116] IMpassion130 updated efficacy results	ITT and PD-L1 positive populations, atezolizumab/nab-paclitaxel vs. placebo/nab-paclitaxel ITT—investigator-assessed median OS, 21.0 vs. 18.7 months; stratified HR for OS, 0.86 (95% CI 0.72–1.02); $p = 0.08$ Median OS, White subgroup, 21.0 vs. 17.6 months; HR, 0.80 (95% CI 0.65–0.98) Median OS, Asian subgroup. 29.4 vs. 30.3 months; HR 1.17 (95% CI 0.74–1.87) 24-month OS, 42.4% vs. 38.7% PD-L1—investigator-assessed median OS, 25.0 vs. 18.0 months; stratified HR for death, 0.71 (95% CI 0.54–0.94) Median OS, White subgroup, 23.4 vs. 16.5 months; HR, 0.71 (95% CI 0.52–0.98) Median OS, Asian subgroup. 30.3 vs. NE months; HR 1.04 (95% CI 0.49–2.17) 24-month OS, 50.7% vs. 36.9%	–	–	–	–	–	–	–	–	–	–	–

Table 5 (continued)

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, *n*	Age (years)	Menopausal status	Race	Stage	HR status	HER2 status
Iwata et al. 2019 [114] IMpassion130 Japanese subgroup analysis	ITT and PD-L1 positive populations, atezolizumab/nab-paclitaxel vs. placebo/nab-paclitaxel ITT—investigator-assessed median PFS, 7.4 vs. 4.6 months; HR, 0.47 (95% CI 0.25–0.90 Median OS, NE vs. 16.8 months; HR 0.44 (95% CI 0.16–1.24) PD-L1—investigator-assessed median PFS, 10.8 vs. 3.8 months; HR 0.04 (95% CI < 0.01–0.35) Median OS, NE vs. 13.3 months; HR (95% CI). 0.12 (95% CI 0.01–0.99)	ITT and PD-L1 positive populations, atezolizumab/nab-paclitaxel vs. placebo/nab-paclitaxel ITT—ORR, 67.6% vs. 51.6% PD-L1 positive—ORR, 75.0% vs. 53.8% ITT—median DoR, 5.6 vs. 3.7 months PD-L1 positive—median DoR, 9.1 vs. 3.7 months	Japan	–	–	ITT, *n* = 65 PD-L1 positive, *n* = 25	Atezolizumab/nab-paclitaxel, median (range), 55 (31–82) years Placebo/nab-paclitaxel, median (range), 64 (37–77) years	–	Asian	–	–	–
Pembrolizumab												
Cortes et al. 2019 [132] KEYNOTE-119	Pembrolizumab vs. standard therapy, median OS 9.9 vs. 10.8 months; HR, 0.97 (95% CI 0.82–1.15)	Pembrolizumab vs. standard therapy Median PFS, 2.1 vs. 3.3 months; HR 1.60 (95% CI 1.33–1.92) ORR, 9.6% vs. 10.6% Median DoR, 12.2 vs. 8.3 months DCR, 12.2% vs. 18.7%	NR	Pembrolizumab 200 mg Q3W	Standard therapy (physician's choice of capecitabine, eribulin, gemcitabine, or vinorelbine)	622	–	–	–	Metastatic breast cancer	Triple negative, 100%	Negative

Table 5 (continued)

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, *n*	Age (years)	Menopausal status	Race	Stage	HR status	HER2 status
Im et al. 2020. [118] KEYNOTE-119 Asia-Pacific subgroup analysis	Pembrolizumab vs. standard therapy Median OS, 11.6 vs. 13.8 months	Pembrolizumab vs. standard therapy Median PFS, 2.1 vs. 4.1 months ORR, 12% vs. 13% Median DoR, 13.4 vs. 8.4 months	Asia-Pacific	–	–	181	–	–	–	–	–	–
Cortes et al. 2020 [133] KEYNOTE-355 (part 2 results)	Pembrolizumab/chemotherapy vs. placebo/chemotherapy Median PFS, 7.5 vs. 5.6 months; HR, 0.82 (95% CI 0.69–0.97) 6-month PFS, 55.4% vs. 47.8% 12-month PFS 29.8% vs. 20.9% OS (NR)	ORR (NR) DoR (NR) DCR (NR)	29 countries	Pembrolizumab 200 mg Q3W plus chemotherapy (nab-paclitaxel, paclitaxel, gemcitabine plus carboplatin)	Placebo plus chemotherapy	847	Pembrolizumab/chemotherapy, median (IQR), 53 (44–63) Placebo/chemotherapy, median (IQR), 53 (43–63)	Premenopausal and postmenopausal	ITT population White 68.4% ($n = 579$) Asian 20.7% ($n = 175$) Black 4.4% ($n = 37$) Other 3.7% ($n = 31$) Unknown 3.0% ($n = 25$)	Locally recurrent inoperable or metastatic triple-negative	Triple negative, 100%	Negative
Yusof et al. 2020 [119] KEYNOTE-355 Asian subgroup analysis	Pembrolizumab/chemotherapy vs. placebo/chemotherapy Median PFS, 8.8 vs. 6.7 months; HR, 0.61 (95% CI 0.41–0.90)	–	Hong Kong, Japan, Korea, Malaysia, and Taiwan	–	–	160	–	–	Asian	–	–	–

Table 5 (continued)

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, *n*	Age (years)	Menopausal status	Race	Stage	HR status	HER2 status
Schmid et al. 2020 [134] KEYNOTE-522	Pembrolizumab-chemotherapy vs. placebo-chemotherapy Pathological CR (pathological stage ypT0/Tis ypN0), 64.8% vs. 51.2%; treatment difference (95% CI), 13.6% (5.4–21.8%); $p < 0.001$ Event-free survival at 18 months, 91.3% vs. 85.3%; HR, 0.63 (95% CI 0.43–0.93)	Pembrolizumab-chemotherapy vs. placebo-chemotherapy Pathological CR (pathological stage ypT0 ypN0), 59.9% vs. 45.3%; treatment difference (95% CI), 14.5% (6.2–22.7%) Pathological CR (pathological stage ypT0/Tis), 68.6% vs. 53.7%; treatment difference (95% CI), 14.8% (6.8–23.0%) Pathological CR (pathological stage ypT0/Tis ypN0), PD-L1-positive patients, 68.9% vs. 54.9%; treatment difference (95% CI), 14.2% (5.3–23.1%) Pathological CR (pathological stage ypT0/Tis ypN0), PD-L1-negative patients, 45.3% vs. 30.3%; treatment difference (95% CI), 18.3% (− 3.3 to 36.8%)	21 countries	Pembrolizumab 200 mg Q3W plus chemotherapy	Placebo plus chemotherapy	1174	Pembrolizumab-chemotherapy, median (range), 49 (22–80) Placebo-chemotherapy, median (range), 48 (24–79)	Premenopausal and postmenopausal	–	Early stage triple negative	Triple negative, 100%	Negative

Table 5 (continued)

Study or subgroup	Primary endpoint	Secondary endpoints	Countries	Intervention	Comparator	Patients, *n*	Age (years)	Menopausal status	Race	Stage	HR status	HER2 status
Dent et al. 2020 [117] KEYNOTE-522 Asian subgroup analysis	Pembrolizumab/chemotherapy vs. placebo/chemotherapy Pathological CR (pathological stage ypT0/Tis ypN0), 59% vs. 40%; treatment difference (95% CI), 19% (1–35%)	Pembrolizumab/chemotherapy vs. placebo/chemotherapy Pathological CR (pathological stage ypT0 ypN0), 51% vs. 30% Pathological CR (pathological stage ypT0/Tis), 61% vs. 42%	Korea, Japan, Taiwan, and Singapore	–	–	215	Pembrolizumab/chemotherapy, median, 46 years Placebo/chemotherapy, median, 51 years	–	Asian	–	–	–

AE adverse event, *BID* twice daily, *BSA* body surface area, *CI* confidence interval, *CR* complete response, *DCR* disease control rate, *DoR* duration of response, *HRQoL* health-related quality of life, *HR* hazard ratio, *HR status* hormone receptor status, *HR+* hormone receptor positive, *IQR* interquartile range, *IM* intramuscular, *ITT* intention to treat, *IV* intravenously, *NE* not evaluable, *NR* not reported, *ORR* objective response rate, *OS* overall survival, *PARP* poly-ADP ribose polymerase, *PD-L1* programmed death-ligand 1, *PFS* progression-free survival, *PI3K* phosphoinositide 3-kinase, *PO* orally, *Q3W* every 3 weeks

managed by dose adjustment, suggesting a pharmacokinetic mechanism.

Ethnic disparity has been ignored or meagerly addressed in the past, especially during the era of chemotherapies. With the emergence of evolving targeted agents, some evidence has shed light on ethnic differences in treatment response. This highlights the importance of considering ethnic differences in pharmacokinetics and pharmacodynamics when designing clinical trials of new therapies and it is expected that the greater insights into tumor and patient characteristics from future studies will help guide treatment selection for Asians. Combined with increased recruitment of Asians into clinical trials to facilitate robust subgroup analysis and ongoing pharmacovigilance reporting, incremental improvements in clinical outcomes for Asians with BC can be expected in the future.

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Declarations

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