



The impact of ethnicity on efficacy and toxicity of cyclin D kinase 4/6 inhibitors in advanced breast cancer: a meta-analysis

Kirsty Wai Chung Lee¹ · Sally Lord² · Richard S. Finn³ · Elgene Lim⁴ · Andrew Martin² · Sherene Loi⁵ · Jodi Lynch¹ · Michael Friedlander⁶ · Chee Khoon Lee^{1,2}

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Abstract

Purpose Adding cyclin-dependent kinase (CDK) 4/6 inhibitor to endocrine therapy improves progression-free survival (PFS) in advanced breast cancer but the impact of ethnicity on efficacy and toxicity is unclear. We aimed to estimate the relative treatment efficacy and toxicity of endocrine therapy with and without CDK4/6 inhibitors, and compare between Asian/non-Asian subgroups.

Method This meta-analysis included published first-line randomized trials comparing CDK4/6 inhibitor-endocrine therapy versus endocrine monotherapy. Hazard ratios (HR) and 95% confidence intervals (CI) for the overall population and Asian/non-Asian subgroups were extracted. The inverse-variance-weighted method was used to pool treatment estimates of PFS.

Results Four trials ($N=2499$) were included. Patients received combination CDK4/6 inhibitor-endocrine therapy ($N=1441$; ribociclib, [46.4%]; palbociclib, [30.8%]; or abemaciclib, [22.8%]) versus endocrine monotherapy ($N=1058$). CDK4/6 inhibitor-endocrine therapy was associated with prolonged PFS compared with endocrine monotherapy (HR 0.56; 95% CI 0.50–0.62). In Asians ($N=492$), PFS HR was 0.39 (95% CI 0.29–0.51, $P < 0.0001$). In non-Asians ($N=2007$), PFS HR was 0.62 (95% CI 0.54–0.71, $P < 0.0001$). There was a significant treatment-by-ethnicity interaction ($P=0.002$). Toxicity data by ethnic subgroup were only available from two trials ($n=1334$) with no convincing evidence that the risk of toxicity between CDK4/6 inhibitor-endocrine therapy and endocrine monotherapy varied by ethnicity.

Conclusion Adding CDK4/6 inhibitor to endocrine therapy prolongs PFS compared to endocrine therapy alone as first-line treatment in advanced breast cancer. The magnitude of PFS benefit is ethnicity-dependent but there is no interethnic differences in relative treatment-related toxicities. These findings may assist in the design and interpretation of trials, inform economic analyses, and stimulate pharmacogenomic research.

Keywords Cyclin-dependent kinase 4/6 inhibitor · Breast cancer · Meta-analysis · Ethnicity

✉ Chee Khoon Lee
chee.lee@ctc.usyd.edu.au

¹ Cancer Care Centre, St George Hospital, Sydney, NSW, Australia

² National Health and Medical Research Council (NHMRC) Clinical Trials Centre, University of Sydney, Locked Bag 77, Camperdown, NSW 1450, Australia

³ Division of Hematology and Oncology, Department of Medicine, David Geffen School of Medicine at the University of California, Los Angeles, CA, USA

⁴ Garvan Institute of Medical Research and St Vincent's Clinical School, University of New South Wales, Sydney, NSW, Australia

⁵ Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

⁶ Prince of Wales Hospital, Sydney and Prince of Wales Clinical School, University of New South Wales, Sydney, NSW, Australia

Introduction

Breast cancer is the most common malignancy and a leading cause of cancer-related death in Asia-Pacific women [1]. Over half of all advanced breast cancers diagnosed in Asia are hormone receptor positive in post-menopausal women [2]. Endocrine blockade has been the cornerstone first-line therapy for these patients. However, clinical practice is changing, based on recent evidence that combination cyclin-dependent kinase 4/6 (CDK4/6) inhibitors and endocrine therapy further prolonged progression-free survival (PFS) over endocrine monotherapy [3–6].

In randomized trials of CDK4/6 inhibitors [3–6], Asians are under-represented, constituting only 8–30% of total study subjects. Interethnic pharmacogenomic variations can influence drug metabolism and impact on treatment efficacy as illustrated by differences in clinical outcomes with tamoxifen therapy for different ethnicities [7]. The impact of interethnic differences on the efficacy and toxicity of CDK4/6 inhibitors remains poorly understood.

Investigation of ethnicity–treatment interactions is important to inform the interpretation of trial results and can provide valuable biological insights. Individual trials are neither designed nor powered to assess ethnic subgroup differences. We address this clinical need by performing a systematic review and literature-based meta-analysis of trials of CDK4/6 inhibitors.

Methods

We searched PubMed, MEDLINE, and EMBASE up to January 2018 to identify randomized trials of combination CDK4/6 inhibitor-endocrine therapy versus endocrine monotherapy as first-line treatment of advanced breast cancer. We searched conference proceedings of American Society of Clinical Oncology, European Society for Medical Oncology, American Association of Cancer Research, and San Antonio Breast Cancer Symposium to identify unpublished studies and obtain updated data.

For each trial, we extracted PFS hazard ratio (HR) and 95% confidence interval (CI) of the overall population and Asian/non-Asian subgroups. For treatment-related toxicities, we extracted the number of adverse events (AEs), dose reduction due to AEs, and treatment interruptions.

We used the fixed-effects inverse-variance-weighted method for pooling results to estimate the PFS benefit and the Mantel–Haenszel method to estimate the risk of treatment-related toxicities. For the ethnic subgroup analysis, we tested for treatment–ethnic interactions to assess differences in relative treatment benefits/toxicity between Asian/

non-Asian subgroups. We used the χ^2 Cochran Q test to detect heterogeneity across trials. Two authors (KL, CL) extracted the data independently and discrepancies were resolved by consensus.

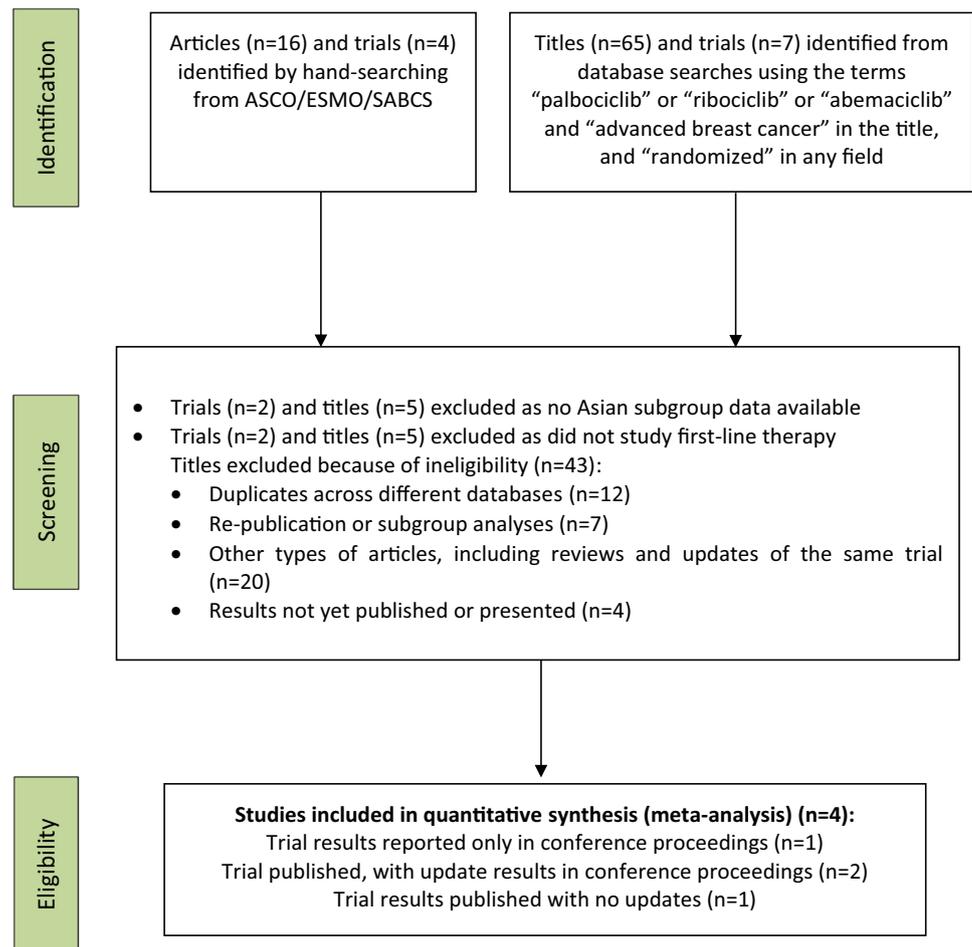
Results

We identified four eligible trials (Fig. 1). All were blinded placebo-controlled trials (Table 1). The risk of bias was low for three trials [3–5] and unclear for an unpublished study [6]. Patients were randomized to receive combination CDK4/6 inhibitor-endocrine therapy ($N=1441$; ribociclib, [46.4%]; palbociclib, [30.8%]; or abemaciclib, [22.8%]) versus endocrine monotherapy ($N=1058$). The pooled overall PFS HR was 0.56 (95% CI 0.50–0.62, $P<0.0001$, heterogeneity $P=0.99$). In Asians ($N=492$), PFS HR was 0.39 (95% CI 0.29–0.51, $P<0.0001$). In non-Asians ($N=2007$), PFS HR was 0.62 (95% CI 0.54–0.71, $P<0.0001$). There was a statistically significant interaction between treatment effect on PFS and ethnicity ($P=0.002$, Fig. 2).

The most common AEs of combination therapy were neutropenia, infections, diarrhea, and nausea (Table 2; Fig. 3). Only two trials [3, 8] reported AEs rates, dose reduction, and treatment interruptions for Asian/non-Asian subgroups. Asians had higher rates of all grade neutropenia than non-Asians with combination (90.9% vs. 75.1%, $P=0.00001$) and endocrine monotherapy (11.5% vs. 4.9%, $P=0.04$) but there was no significant interethnic difference in relative risk (interaction $P=0.07$). Asians had similar rates of all grade nausea as non-Asians on combination therapy (39.4% vs. 42.4%, $P=0.76$) but lower rates than non-Asians on endocrine monotherapy (8.2% vs. 29.7%, $P=0.003$), hence the relative risk of nausea varied by ethnicity (interaction $P=0.007$). Asians had lower rates of all grade diarrhea than non-Asians on combination (15.2% vs. 32.1%, $P=0.003$) and endocrine monotherapy (6.6% vs. 22.8%, $P=0.01$, interaction $P=0.35$). There were no significant interethnic differences in other examined toxicities. Asians had high rates of dose reduction (58.0%) and treatment interruptions (75.0%) due to AEs in the combination therapy group but there was no significant interethnic difference in the relative risks of these events (Table 3).

Discussion

In this meta-analysis, CDK4/6 inhibitor-endocrine therapy reduced the risk of disease progression or death by 44% compared to endocrine monotherapy. The pooled PFS HR for Asian and non-Asian were significantly different (0.39 vs. 0.62, interaction $P=0.002$). There was, however,

Fig. 1 Flow diagram showing inclusion and exclusion of studies

no convincing evidence that the risk of toxicity between CDK4/6 inhibitor-endocrine therapy and endocrine monotherapy varied by ethnicity.

This meta-analysis demonstrates consistency in PFS benefit across first-line trials overall and within ethnic subgroups with no significant heterogeneity. However, interethnic differences in PFS result were not observed in the second-line setting. PALOMA-3, [9] a second-line trial, compared fulvestrant with or without palbociclib reported no significant difference between Asians and non-Asians (PFS HR 0.49 vs. 0.45, interaction $P=0.83$). Similar finding was reported for MONARCH-2, [10] another second-line study. The conflicting findings could be explained by different partnering endocrine agents where aromatase inhibitors were used instead of fulvestrant. The patient populations were also different; none had chemotherapy for their advanced disease in the first-line trials, whereas 78% of patients in PALOMA-3 received chemotherapy.

The high rates of neutropenia observed in first-line trials are also consistently reported in later line trials of CDK4/6 inhibitor [9, 11, 12]. PALOMA-3 trial reported

pre-treatment absolute neutrophil count was 19% lower for Asians compared to non-Asians [9] and it remains unclear whether this would result in greater risk of neutropenia during CDK4/6 inhibitor therapy. In our meta-analysis, the relative risk of neutropenia on combination versus endocrine monotherapy was not significantly different between Asians/non-Asians (interaction $P=0.07$). Our analysis, however, could not quantify clinically significant toxicities, such as grade 4 neutropenia, as these results are not published in all trials by Asian/non-Asian subgroups. Importantly, our analysis showed no interethnic differences in relative treatment interruptions and dose reduction due to this and other AEs.

Interethnic differences in drug exposure could potentially explain the finding of this meta-analysis. However, pharmacokinetic (PK) studies are conflicting and do not yet provide strong support for this hypothesis. In a phase 1 study (A5481032) of palbociclib, Japanese healthy subjects ($N=14$) had mean drug concentration area under curve (AUC) and maximum drug concentration (C_{max}) values of 30% and 35% higher, respectively, when compared with demographic-matched non-Asian subjects ($N=13$) after

Table 1 Characteristics of first-line randomized clinical trials of endocrine therapy plus CDK4/6 inhibitors in hormone receptor positive advanced breast cancer included in the meta-analysis

Study	Regimen	ITT N	Asians N (%)	Menopausal status	PR positive N (%)	ECOG 0 N (%) ^a	Visceral metastases N (%)	Bone-only metastases (%)	Prior endocrine therapy N (%)	Median PFS (months) ^b
MONALEESA-2	Letrozole with or without ribociclib	668	51 (8)	Post-menopausal	546 (82)	407 (61)	373 (56)	147 (22)	346 (52)	25.3 versus 16.0
MONALEESA-7	NSAI/Tamoxifen with or without ribociclib	672	198 (29)	Pre- or peri-menopausal	572 (85)	500 (74)	343 (51)	159 (24)	NA	23.8 versus 13.0
PALOMA-2	Letrozole with or without palbociclib	666	95 (14)	Post-menopausal	NA	359 (54)	324 (49)	151 (23)	375 (56)	24.8 versus 14.5
MONARCH-3	NSAI with or without abemaciclib	493	148 (30)	Post-menopausal	382 (77)	296 (60)	261 (53)	109 (22)	230 (47)	NR versus 14.7

ITT intention-to-treat, PR progesterone receptor, ECOG Eastern Cooperative Oncology Group score for performance status, CDK4/6 cyclin-dependent kinase 4/6, PR progesterone receptor, PFS progression-free survival, NSAI non-steroidal aromatase inhibitor, NA not available, NR not reached

^aData were missing in 1% of patients in the MONALEESA-7 trial and 2% of patients on the PALOMA-2 trial were ECOG 2. All other patients had performance status of ECOG 0 or 1

^bThe median progression-free survival (PFS) was for the comparison of endocrine therapy and cyclin-dependent kinase 4/6 inhibitor versus endocrine monotherapy

single 125-mg dose. However, this finding was not consistently reproduced in subsequent studies. PALOMA-3 trial reported no significant difference in drug exposure for Asians from predominantly Taiwan and Japan ($N=105$) versus non-Asians ($N=416$) [9]. Another phase I Chinese trial ($N=26$) reported drug exposure similar to those obtained in Caucasian patients following the same dosing regimen [13]. In a phase I study ($N=17$) of Japanese patients treated with ribociclib, mean AUC was 1.5–2 times greater than reported in studies of non-Asian populations [14]. However, the investigators noted the wide inter-individual variability limited conclusions about differences in drug metabolism for Asian versus non-Asian populations. These cumulative pharmacokinetic data from multiple trials across the three CDK 4/6 inhibitors do not provide sufficient evidence for dose adjustment based on Asian race.

Very little is known of the impact of cytochrome P450 polymorphism on CDK4/6 inhibitor metabolism. Palbociclib undergoes hepatic metabolism primarily metabolized by CYP3A and sulfotransferase enzyme SULT2A1. Ribociclib also undergoes extensive hepatic metabolism, the majority of which is mediated by CYP3A4. CYP3A is also the enzyme responsible for the majority of the CYP-mediated metabolism of abemaciclib and its metabolite. Differences in the frequencies of different CYP3A alleles have been reported between Asians and Caucasians [15]. A single polymorphism of CYP3A4 could result in more than a three-fold difference in CYP3A4 enzyme expression between Caucasians and Asians [16]. We hypothesize that interethnic difference in CYP3A4 polymorphism may account for the differences in treatment efficacy.

This meta-analysis has limitations. Ethnicity was self-reported with no standardized definitions across trials. Some trials defined Asian ethnicity based on country of residence or whereas other studies based on patient self-reporting. There is no clear definition of mixed race in all of the included studies. AEs, dose reduction, and treatment interruption data stratified by ethnicity subgroup were only available in two trials which limited our power to identify true ethnic differences. Finally, we regarded ribociclib, palbociclib, and abemaciclib as a single class of drug with equivalent therapeutic efficacy. All three agents, however, have some differences in mechanisms of actions and are also metabolized slightly differently as well.

Despite these limitations, the findings of this meta-analysis have important implications. Future CDK4/6 inhibitor trials should stratify patients based on ethnicity to improve estimation and interpretation of treatment benefits. Standardized definition of ethnicity is recommended. Differences in treatment efficacy impact cost-effectiveness and these findings also have important implications for economic evaluations for reimbursement decisions for CDK4/6 inhibitors in different regions. Further

Fig. 2 Forest plot of hazard ratios comparing progression-free survival in Asian and non-Asian subgroups of patients who received cyclin D kinase 4/6 (CDK4/6) inhibitor-endocrine therapy versus endocrine monotherapy. Hazard ratios for each trial are represented by the squares and the horizontal line crossing the square represents the 95% confidence interval (CI). The diamonds represent the estimated overall effect based on the meta-analysis fixed effect of the trials. All statistical tests were two-sided

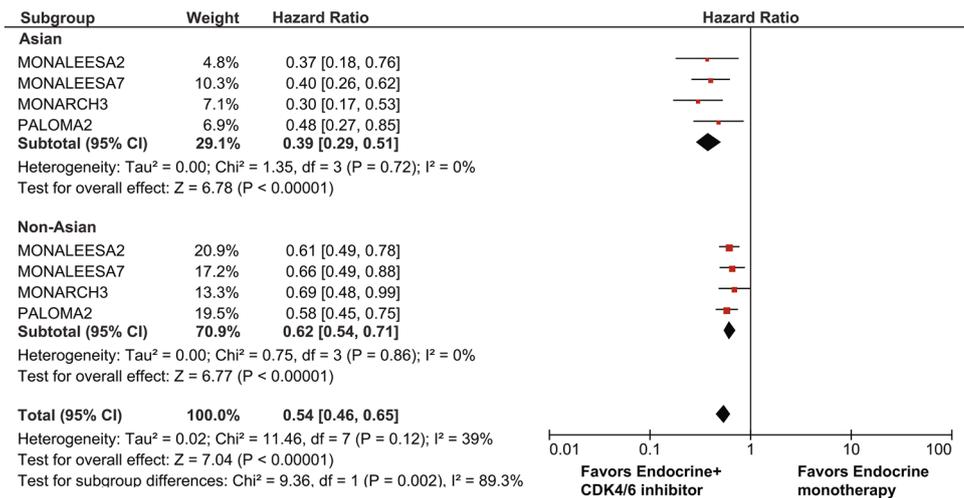


Table 2 Common toxicities of cyclin D kinase 4/6 (CDK4/6) inhibitor-endocrine therapy versus endocrine monotherapy in the intention-to-treat population and Asian/non-Asian subgroups

Toxicity (all grades)	Intention-to-population [†]		Asian population [‡]		Non-asian population [‡]		P*	P [†]	P ^x
	CDK4/6 inhibitor-endocrine therapy n/N (%)	Endocrine monotherapy n/N (%)	CDK4/6 inhibitor-endocrine therapy n/N (%)	Endocrine monotherapy n/N (%)	CDK4/6 inhibitor-endocrine therapy n/N (%)	Endocrine monotherapy n/N (%)			
Neutropenia	996/1440 (69.2)	59/1050 (5.6)	90/99 (90.9)	7/61 (11.5)	510/679 (75.1)	24/491 (4.9)	0.07	<0.001	0.04
Anemia	349/1440 (24.2)	82/1050 (7.8)	21/99 (21.2)	3/61 (4.9)	148/679 (21.8)	32/491 (6.5)	0.86	0.81	0.72
Nausea	566/1440 (39.3)	257/1050 (24.5)	39/99 (39.4)	5/61 (8.2)	288/679 (42.4)	146/491 (29.7)	0.007	0.76	0.003
Rash	145/778 (18.6)	54/552 (9.8)	20/99 (20.2)	3/61 (4.9)	125/679 (18.4)	50/491 (10.2)	0.24	0.63	0.25
Diarrhea	578/1440 (40.1)	235/1050 (22.4)	15/99 (15.2)	4/61 (6.6)	218/679 (32.1)	112/491 (22.8)	0.37	0.003	0.01
Infection [#]	574/1105 (51.9)	286/713 (40.1)	51/99 (51.5)	19/61 (31.1)	249/679 (36.7)	111/491 (22.6)	0.71	0.01	0.22
Cough	188/778 (24.2)	112/552 (20.3)	20/99 (20.2)	10/61 (16.4)	155/679 (22.8)	92/491 (18.7)	0.64	0.50	0.65

*P value for the test of interaction between relative treatment toxicity on combination CDK4/6 inhibitor-endocrine therapy versus endocrine monotherapy and ethnicity

[†]P value for the test of difference between Asian versus non-Asian subgroup treated with combination CDK4/6 inhibitor-endocrine therapy

^xP value for the test of difference between Asian versus non-Asian subgroup treated with endocrine monotherapy therapy

[#]PALOMA-2 and MONARCH-3 trials report data for any type of infection; MONALEESA-2 Asian/non-Asian subgroup reports only upper respiratory tract infections. Data were unavailable for MONALEESA-7 trial

[†]Includes data from MONALEESA-2, MONALEESA-7, PALOMA-2, and MONARCH-3 trials

[‡]Includes data from MONALEESA-2 and PALOMA-2 trials only

pharmacogenomic studies are required to investigate the interethnic differences in genetic polymorphisms of CYP3A4, CDK4/6 inhibitor PK, and clinical outcomes to potentially guide future clinical practice. This future work

should also include development of objective genomic classifiers to define ethnicity given the potential impact of pharmacogenomics differences on treatment efficacy and toxicity.

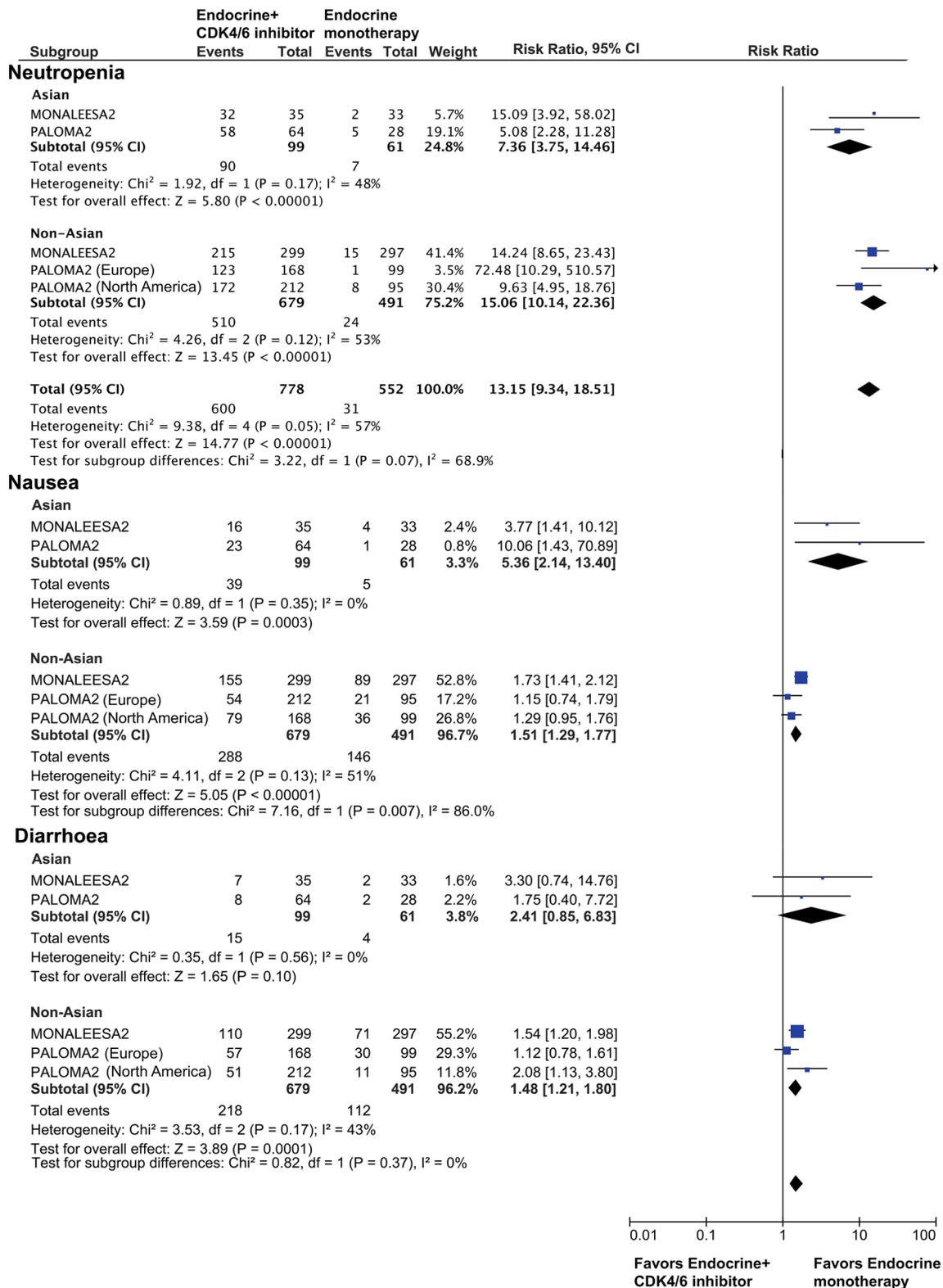


Fig. 3 Forest plot of risk ratios comparing neutropenia, nausea, and diarrhea as treatment-related adverse events (all grades) for Asian and non-Asian subgroups in patients who received cyclin D kinase 4/6 (CDK4/6) inhibitor-endocrine therapy versus endocrine monotherapy. Risk ratios for each trial are represented by the squares, and the hori-

zontal line crossing the square represents the 95% confidence interval (CI). The diamonds represent the estimated overall effect based on the meta-analysis fixed effect of the trials. All statistical tests were two-sided

Table 3 Study drug dose reduction and treatment interruptions due to adverse events in the intention-to-treat population and Asian/non-Asian subgroups

	Intention-to-population [†]		Asian population [‡]		Non-Asian population [‡]		<i>P</i> *	<i>P</i> [†]	<i>P</i> [×]
	CDK4/6 inhibitor therapy <i>n/N</i> (%)	Placebo <i>n/N</i> (%)	CDK4/6 inhibitor therapy <i>n/N</i> (%)	Placebo <i>n/N</i> (%)	CDK4/6 inhibitor therapy <i>n/N</i> (%)	Placebo <i>n/N</i> (%)			
Study drug dose reduction due to adverse events	575/1440 (39.9)	44/1054 (4.2)	58/100 (58.0)	2/63 (3.2)	271/678 (40.0)	15/489 (3.0)	0.88	< 0.001	0.67
Study drug treatment interruptions [#]	993/1440 (69.0)	381/1054 (36.1)	75/100 (75.0)	14/63 (22.2)	449/678 (66.2)	122/489 (24.9)	0.39	0.05	0.37

**P* value for the test of interaction between relative treatment toxicity on combination CDK4/6 inhibitor-endocrine therapy versus endocrine monotherapy (study drug dose reduction / drug treatment interruptions) and ethnicity

[‡]Placebo agent used in combination with aromatase inhibitor in the endocrine monotherapy arm

[†]*P* value for the test of difference between Asian versus non-Asian subgroup treated with combination CDK4/6 inhibitor-endocrine therapy

[×]*P* value for the test of difference between Asian versus non-Asian subgroup treated with placebo

[#]PALOMA-2 and MONALEESA-7 reported study drug treatment interruptions from any cause, whereas MONALEESA-2 and MONARCH-3 only reported study drug interruptions from adverse events

[†]Includes data from MONALEESA-2, MONALEESA-7, PALOMA-2, and MONARCH-3 trials

[‡]Includes data from MONALEESA-2 and PALOMA-2 trials only

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Compliance with ethical standards

Conflict of interest RSF acted as a consultant for AstraZeneca, Bayer, Bristol Myers Squibb, Eisai, Eli Lilly, Novartis, Merck, Pfizer. EL received research funding from Novartis Australia and Bayer (to the institution); acted as a consultant for Novartis Australia, Pfizer Australia, Roche Australia. SL received research funding from Novartis, Bristol Meyers Squibb, Merck, Roche-Genentech, Puma Biotechnology, and Pfizer (to the institution); acted as a consultant for Seattle Genetics, Pfizer, Novartis, BMS, Merck, and Roche-Genentech. MF received remuneration and acted as a consultant for AstraZeneca and MSD. CKL received remuneration and acted as a consultant for AstraZeneca, Roche, Takeda, Boehringer Ingelheim, Novartis. All remaining authors have declared no conflict of interest.

Ethical approval This research work is a meta-analysis of published data and does not contain any direct involvement of human participants.

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