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The Combination of CDK 4/6 Inhibitors plus Endocrine Treatment versus Endocrine Treatment Alone in Hormone-receptor (HR)-Positive breast Cancer: a Systematic Review and Meta-analysis

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ABSTRACT

Background: The identification of the novel targeted therapy i.e., cyclin-dependent kinases (CDKs) 4/6 inhibitor as combined with the endocrine regimen revealed a considerable capability to increase the managements' effectivity of hormone-receptor-positive (HR+) and HER2- breast cancer (BC). **Objective:** This study aims to compare the latter combination strategies versus hormonal therapy alone to determine its applicability in the treatment of HR+/HER2- BC. **Methods:** We established the review based on the clinical trials as collected from several scientific databases from January 2011 to April 2021. RevMan 5.4 was utilized in statistical analysis and risk of bias (RoB) measurement. 5110 participants from 9 different trials were included in this review with similar baseline characteristics. **Results:** According to our analysis of the intention-to-treat (ITT) group, CDK 4/6 inhibitor arms exhibited better overall response rate (ORR) as indicated by the relative risk (RR) (randomized-effect model (REM), 1.59 [1.37, 1.86]; 95% confidence interval (CI); P <0.00001) and higher clinical benefit rate (CBR) (RR, 1.22 [1.13, 1.32]; 95% CI; REM; P <0.00001). The combination regiment also proved to be effective in reducing the rate of progressive disease (PD) in the ITT group (RR 0.46 [0.39, 0.54]; CI 95%; FEM; P <0.00001. Although the rate of adverse effects especially the hematological reactions was significantly lower in the endocrine alone arm, other system reactions were fairly comparable. **Conclusion:** The introduction of CDK 4/6 inhibitor to the endocrine-based regiment is proved beneficial to patients with HR+/HER2- BC even though the most recommended anti-hormonal to be combined remains questionable.

Keywords: Breast cancer, CDK 4/6 inhibitor, Endocrine treatment.

1. BACKGROUND

Breast cancer (BC) is the most common malignancy diagnosed worldwide with the incidence rate of 24.5% and a considerable 15.5% mortality rate, both ranked highest compared to the other cancer generally (GLOBOCAN 2020); with noteworthy urgency regarding the overall increase globally (1, 2). The role of steroid hormone receptors (HR) e.g., estrogen receptor (ER) or progesterone receptor (PR) have been postulated as an integral factor when it comes to determining BCs treatment intention (3). The expression status of specific regulating genes i.e., human epidermal growth factor receptor 2 (HER2) also correlate with overall disease aggressivity, higher recurrence rate, and unfavorable prognosis (4, 5). Approximately 70% of BC worldwide are categorized as HR+/HER2- subtype with comparable rate in every region worldwide according to American Cancer Society (ACS) (6). Although the HR+HER2- category generally showed better prognosis relative to the other subtypes; extensive understanding regarding its management is highly necessary (2, 3, 7, 8).

BCs treatment options are vast with numerous approaches available. Continuous importance regarding BC's occurrence worldwide and the identification of novel targeted therapy generate an opportunity to improve the cu-

rrent approaches. Several agents of the specific essential pathway in BC's pathology namely cyclic-dependent kinases (CDKs) 4/6 inhibitors e.g., abemaciclib, palbociclib, and ribociclib exhibit considerable BC's therapeutic capability (9-11). CDKs activity is paralleled with certain oncogene i.e., cyclin D in cell cycle regulation; as its activation leads to hyperphosphorylation of retinoblastoma protein (pRb). Moreover, the relationship between cyclin D1-CDK 4/6-RB1 complex and estrogen signaling exhibits greater value of the combined approach in hormone-related malignancy. Therefore, inhibition of these interactions are expected to be efficacious especially toward HR+ BC considering its degrading natures among those groups; hence the treatment approach in HR+ BC always includes endocrine therapy e.g., letrozole or fulvestrant generally due to their essence in the BC pathology (12, 13). The combination of CDK 4/6 inhibitors and endocrine therapy has not been evaluated in an extensive and systematic fashion considering its distinctly separate treatment mechanism may offer better collaboration in future oncologic management.

2. OBJECTIVE

In this study, we aim to compare CDK 4/6 inhibitors and endocrine treatment combination efficacy versus endocrine treatment alone as the treatment of HR+/HER2- BC to determine its applicability in future treatment for BC. Therefore, a systematic approach and quantitative analysis of several trials conducted e.g., MONALEESA, PALOMA, and MONARCH were evaluated thoroughly to attain this goal.

3. MATERIAL AND METHODS

Study protocol

The Preferred Reporting Items for Systematic review and Meta analyses (PRISMA) protocol was followed for this study. The ethics committee of Universitas Sumatera Utara had approved the study following the study protocol advocation. This review was registered on PROSPERO (CRD42021281006) on 23rd October 2021 (14).

Eligibility criteria

We design the eligibility criteria according to the applied PICO format from January 2012 to December 2021; Participants-female with HR+/HER2- breast cancer (BC); Intervention-CDK 4/6 inhibitor plus subsequent endocrine therapy as the either first-line or second-line treatment since we aimed to define the agent's efficacy in luminal A BC regardless prior treatment administered; Comparison-as compared to the endocrine therapy alone; Outcomes- treatment response and adverse reactions. We also limit the studies to the randomized controlled trial (RCT) only preferentially with explicit study protocol, and restricted to English-based literatures. The literature identification was restricted from January 2011 to September 2021 for its publication dates.

Systematic screening and study selection

This study utilized the following databases: PubMed, Cochrane Library, and Google Scholar according to the Boolean term search protocol. Two authors (M.N.A. and N.N.F.) carried out the literature identification using strategic keywords e.g., "CDK 4/6 inhibitors" or "abemaciclib" or "palbociclib" or "ribociclib" AND "breast cancer" restricted to the titles and abstracts identification. The disagreement in this stage was resolved through internal discussion and re-elaboration of each other findings. Even though screening method was applied the most in MEDLINE-based screening, we adapt the protocol to the other databases consequently. We also manually screened the references list from recent systematic-reviews to secure all relevant literature. Any disagreement regarding the literatures screening was resolved through internal discussion to integrate the results according to PRISMA flow diagram in following section.

Quality control and risk of bias assessment

The risk of bias assessment was accomplished by one author (N.N.F.) by utilizing the revised Cochrane risk-of-bias (RoB) tool for RCTs as provided by RevMan 5.4.1 software; the tool consists of 6 parameters e.g., selection bias (random sequence generation and allocation concealment), performance bias, detection bias, attrition bias, reporting bias, and the other potential bias.

Data extraction

We collected the baseline characteristics of each trial to function as the foundation to compare the studies either systematically or quantitatively. Several details of the studies e.g., the number of regions or countries, trial conduction period, specific trials' treatment design, and participants demographics were extracted thoroughly. The event-to-total ratio of treatment response (according to and limited to the evaluation criteria in solid tumors by RECIST guideline version 1.1 as applied to both arms) which categorize the assessment to overall response rate (ORR), clinical benefit rate (CBR), and progressive disease (PD; toward the unfavorable stage of disease) will be classified further into either intention-to-treat (ITT) or measurable disease group; as well as the adverse reactions data (15). The data extraction was collectively done by two authors (D.H. and N.N.F.) with thorough internal reporting and subsequent validation from the other authors.

Statistical analysis

The meta-analysis of this study was performed using RevMan 5.4.1 software and the discrepancy of each trial extraction was resolved by internal re-evaluation. We applied a dichotomous analysis i.e., relative risk (RR) outcomes with the Mantel-Haenszel test (95% CI) to both RECIST 1.1-based treatment evaluation or adverse reactions; following the application of a fixed-effect model (FEM) or randomized-effect model (REM), in accordance with its heterogeneity results. To exemplify the statement, we implemented the most appropriate analysis in all-trials-included or total analysis. The determination of the applied analysis model was based on the I^2 value, in which >40% represents moderate heterogeneity hence REM was used. Conversely, in trial-specific analysis e.g., MONALEESA-restricted, we utilized FEM analysis thoroughly; considering the number of included studies in each trial and the intention to homogenize the trial itself. In response to the assessment outcomes, RR

Trial	MONALEESA-2	MONALEESA-3	MONALEESA-7	MONARCH-2	MONARCH-3	MONARCH Plus	PALOMA-1	PALOMA-2	PALOMA-3
Detail of the studies									
Regions	223 centers in 29 countries	174 centers in 20 countries	188 centers in 30 countries	142 centers in 19 countries	158 centers in 22 countries	45 centers in 4 countries	50 centers in 12 countries	186 centers in 17 countries	144 centers in 17 countries
Phases	III	III	III	III	III	III	II	III	III
Trial Period	January 2014 to March 2015	June 2015 to June 2016	December 2014 to August 2016	August 2014 to December 2015	November 2014 to November 2015	December 2016 to March 2019	December 2009 to May 2012	February 2013 to July 2014	October 2013 to Augustus 2014
Inclusion Criteria	Postmenopausal women; HR+; HER2-; ABC; first-line	Postmenopausal women; HR+; HER2-; ABC; second-line	Premenopausal or perimenopausal women, HR+; HER2-; ABC; first-line	Any menopausal status women; HR+; HER2-; ABC; second-line	Postmenopausal women; HR+; HER2-; ABC with loco-regionally recurrent BC; first-line	Postmenopausal women; HR+, HER2-, loco-regionally recurrent BC; first line	Post-menopausal women; HR+; HER2-; ABC; first-line	Any menopausal status women; HR+; HER2-; ABC; first line	Any menopausal status women; HR+; HER2-; ABC; second-line
Study Design (in 28-day treatment cycles)									
Intervention	Ribociclib (600 mg daily; 3-weeks-on, 1-week-off) plus letrozole (2.5 mg daily continuously)	Ribociclib (600 mg daily; 3-weeks-on, 1-week-off) plus fulvestrant (500 mg intramuscularly on day 1)	Ribociclib (600 mg daily; 3-weeks-on, 1-week-off) plus tamoxifen (20 mg) or an NSAI (letrozole 2.5 mg or anastrozole 1 mg daily)	Abemaciclib (200 mg twice daily) plus fulvestrant (500 mg intra-muscularly on day 1 and 15 of cycle 1; and on day 1 of subsequent cycles)	Abemaciclib (150 mg twice daily continuously) plus NSAI (1 mg anastrozole or 2.5 letrozole; daily)	Abemaciclib (150 mg twice daily) plus anastrozole (1 mg) or letrozole (2.5 mg) once daily for cohort A OR fulvestrant (500 mg intra-muscularly on days 1 and 15 of cycle 1; and on day 1 of subsequent cycles) for cohort B	Palbociclib (125 mg daily; 3-weeks-on, 1-week-off) plus letrozole (2.5 mg daily)	Palbociclib (125 mg daily; 3-weeks-on, 1-week-off) plus letrozole (2.5 mg daily)	Palbociclib (125 mg daily; 3-weeks-on, 1-week-off) plus fulvestrant (500 mg intra-muscularly on day 1 and 15 on the first cycles; and on day 1 of subsequent cycles)
Control	Placebo plus letrozole with same protocol as intervention	Placebo plus fulvestrant with same protocol as intervention	Placebo plus matching endocrine therapy as intervention	Placebo plus fulvestrant with same protocol as intervention	Placebo plus matching endocrine therapy as intervention	Placebo plus NSAI with same protocol as intervention	Placebo plus letrozole with same protocol as intervention	Placebo plus letrozole with same protocol as intervention	Placebo plus fulvestrant with same protocol as intervention
Participants Demographic and Characteristic									
Age	I: 62 (23-91) C: 63 (29-88)	I: 63 (31-89) C: (63 (34-86)	I: 43 (25-58) C: 45 (29-58)	I: 59 (32-91) C: 62 (32-87)	I: 63 (38-87) C: 63 (32-88)	I: 54 (32-83) C: 54 (27-77)	I: 63 (54-71) C: 64 (56-70)	I: 62 (30-89) C: 61 (28-88)	I: 57 (30-88) C: 56 (29-80)
No. of Participants	I: 334 C: 334	I: 484 C: 242	I: 335 C: 337	I: 446 C: 223	I: 328 C: 165	I: 311 (207;104) C: 152 (99;53)	I: 84 C: 81	I: 444 C: 222	I: 347 C: 174

Table 1. Base characteristic of each trial evaluated in this systematic review and meta-analysis. Abbreviation: ABC, Advanced Breast Cancer; C, Control; HER2, Human Epidermal Growth-factor Receptor-2; HR, Hormone Receptor; I, Intervention; NSAI, Non-Steroidal Aromatase Inhibitor

value > 1.0 implies the parameter was favoring combination treatment; conversely for PD outcomes which the value of > 1.0 was explaining the superiority of the control arm. Overall heterogeneity of the outcomes was concluded by the I^2 value and the P-value of <. 05 was considered to be statistically significant.

4. RESULTS

According to our literature screening strategy, 3 different trials were identified from the several databases which consisted of three sub-trials each e.g., MONALEESA-2, -3, and -7; hence 9 studies were included in the final analysis. Our systematic screening process is depicted in Figure 1. In total, 9 different trials enrolling 5110 participants were analyzed along with the risk of bias (RoB) analysis in Figure 2, in which most of the included trials were exhibiting low risk of bias in the majority of the assessed variables, with only the PALOMA-1 trial disclosed a high risk of bias in participants blinding and outcomes assessment. The baseline characteristics of each trial are shown in Table 1.

Overall response rate analysis

The addition of CDK 4/6 inhibitors exhibited better outcomes in overall response rate (ORR) encompassing two different sub-outcomes i.e., complete response (CR) and partial response (PR) (Figure 3A; details of CR and PR are available in eFigure 1 and 2 respectively in the supplemental data). Cumulative sub-total relative risk (RR) in ITT and measurable disease were also similar (REM, 1.59 [1.37, 1.86] and 1.51 [1.29, 1.77] respectively; 95% CI) with both favoring the combination arm significantly (P<.05). In trial specific analysis particularly in ITT groups, it was revealed that MONARCH trials prevailed more favorably ORR as proved by better RR (2.03 [1.70, 2.42]) than either MONALEESA (1.45 [1.27, 1.65]) and PALOMA (1.34 [1.13, 1.59]) with a P-value of < 0.5 and 95% CI (Table 2).

Only the MONARCH trials found a significant result (P<.05) for CR outcomes with an OR value of 4.16 [1.26, 13.70] for ITT group and 10.65 [1.44, 78.76] for measurable disease group in FEM analysis, which is significantly higher than the other trials. The abemaciclib arms superiority was also markedly demonstrated in PR outcomes in which the trials revealed higher RR values along with the significant P value in ITT sub-analysis, even though the identical outcomes were not identified in measurable disease groups. Despite the pattern similarity, the integrated approach of anti-CDK 4/6 plus endocrine treatment trials is substantially significant as indicated by P<.05 in both sub-groups regardless of the influence of CR and PR in the evaluated arm, indicating that the addition of CDK 4/6 inhibitors may prove accountable for the ORR increase. Moreover, other approach of subgroup pooled analysis by grouping the trials i.e., MONARCH studies versus both of MONALEESA and PALOMA studies revealed a significant difference with P value of <.002 in ITT group, although similar outcomes were not observed in the measurable disease group (Supplemental data).

A. Intention-to-treat groups						
RECIST Parameter (ITT)	All Trials RR (Total) α	Analysis models	P value (Total analysis)	Trials-specific RR* in FEM		
				MONALEESA	MONARCH	PALOMA
Overall Response Rate (ORR)	1.59 [1.37, 1.86]	REM	<.05	1.45 [1.27, 1.65]	2.03 [1.70, 2.42]	1.34 [1.13, 1.59]
Clinical Benefit Rate (CBR)	1.22 [1.13, 1.32]	REM	<.05	1.12 [1.06, 1.18]	1.26 [1.16, 1.35]	1.35 [1.24, 1.47]
Complete Response (CR)	1.46 [0.93, 2.31]	FEM	>.05	1.55 [0.80, 3.01]	4.16 [1.26, 13.70]	0.58 [0.25, 1.33]
Partial Response (PR)	1.55 [1.32, 1.81]	REM	<.05	1.44 [1.25, 1.65]	1.75 [1.49, 2.07]	1.40 [1.17, 1.68]
Stable Disease (SD)	0.90 [0.79, 1.02]	REM	>.05	0.93 [0.80, 1.08]	0.78 [0.70, 0.86]	1.14 [0.98, 1.32]
Stable Disease (SD) >24 Weeks	1.04 [0.90, 1.20]	REM	>.05	-	0.89 [0.77, 1.02]	1.20 [1.05, 1.36]
Progressive Disease (PD)β	0.46 [0.39, 0.54]	FEM	<.05	0.52 [0.40, 0.67]	0.40 [0.30, 0.54]	0.44 [0.32, 0.60]

*Grey area of the table in the trial specific section indicates the significant analysis result (P <.05)
αPositive value of the RR are favoring the outcomes in the treatment arm
βOnly in the PD outcomes, the RR value as inversely applied therefore negative value are favoring the results in the treatment arm

B. Measurable disease groups						
RECIST Parameter (Measurable disease)	All Trials RR (Total)α	Analysis models	P value (Total analysis)	Trials-specific RR* in FEM		
				MONALEESA	MONARCH	PALOMA
Overall Response Rate (ORR)	1.51 [1.29, 1.77]	REM	<.05	1.41 [1.21, 1.66]	1.75 [1.44, 2.14]	1.39 [1.19, 1.63]
Clinical Benefit Rate (CBR)	1.23 [1.13, 1.34]	REM	<.05	1.15 [1.08, 1.23]	1.27 [1.14, 1.41]	1.35 [1.22, 1.50]
Complete Response (CR)	1.57 [0.96, 2.58]	FEM	>.05	1.47 [0.73, 2.92]	10.65 [1.44, 78.76]	0.65 [0.09, 4.83]
Partial Response (PR)	1.46 [1.27, 1.68]	REM	<.05	1.41 [1.24, 1.60]	1.57 [1.31, 1.88]	1.45 [1.23, 1.70]
Stable Disease (SD)	0.85 [0.73, 0.99]	REM	<.05	0.88 [0.79, 0.99]	0.68 [0.57, 0.81]	1.13 [0.92, 1.40]
Stable Disease (SD) >24 Weeks	0.97 [0.84, 1.11]	FEM	>.05	-	0.79 [0.62, 1.01]	1.09 [0.92, 1.29]
Progressive Disease (PD) β	0.45 [0.38, 0.55]	FEM	<.05	0.48 [0.36, 0.64]	0.43 [0.29, 0.63]	0.44 [0.32, 0.61]

*Grey area of the table in the trial specific section indicates the significant analysis result (P <.05)
αPositive value of the RR are favoring the outcomes in the treatment arm
βOnly in the PD outcomes, the RR value as inversely applied therefore negative value are favoring the results in the treatment arm

Table 2. Summarize of RECIST criteria as reported by several trials in both treatment groups. All trials (cumulative) analysis had been adjusted according to the most appropriate model based on the heterogeneities. The fixed-effect model (FEM) analysis in trials-specific outcomes were implemented thoroughly considering the number of studies of each trial.

Clinical benefit rate analysis

Basically, CBR is ORR plus stable disease (SD >24 weeks) hence proportionately representative of the treatment utility, particularly on its beneficial effect. The combination arm provides higher and significant RR (REM) in ITT (1.22 [1.13, 1.32]) and measurable disease group (1.23 [1.13, 1.34]) (Figure 3B; details of SD> 24 weeks is available in eFigure 3). In this analysis, higher CBR in the ITT group was observed in PALOMA trials therefore better clinical stability (>24 weeks) after palbociclib administration can be predicted eventually. MONALEESA trials exhibited least favorable outcomes in the CBR parameter with RR (FEM, 1.12 [1.06, 1.18] and 1.15 [1.08, 1.23] with 95% CI) for ITT and measurable disease, respectively. The data were also implied to the measurable disease group as those trials-specific evaluation is statistically significant in all trials analyzed (Table 2A and 2B).

The MONALEESA trials do not provide the rate of SD >24 weeks although the details of CBR are available. Nevertheless, a considerable result was not observed in this analysis (P>.05) with higher rate of SD either in cumulative or only >24 weeks outcomes were marked in endocrine therapy alone group. This data suggest that the combination approach possibly alters the disease stability; therefore, several clinical implications should be considered even if higher probability of better response can be anticipated. Accordingly, PALOMA trials exhibited a considerable SD rate particularly in >24 weeks follow-up as indicated by specific analysis of palbociclib in ITT group which revealed a significant impact (P<.05) with RR (FEM, 1.20 [1.05, 1.36]). Our approach by reviewing the pooled-specific-trials also confirmed that PALOMA trials may had an advantage in CBR analysis in either ITT or measureable disease group, followed by MONARCH and MONALEESA trials respectively.

Progressive disease rate analysis

Exposure to CDK 4/6 inhibitors is statistically advantageous to reduce progressive disease (PD) rate. Our meta-analysis demonstrated a significantly determining result (P<.05) with RR in ITT and measurable disease sub-group of 0.46 [0.39, 0.54] and 0.45 [0.38, 0.55] in FEM analysis, respectively. A practically equivalent comparison between each trial is also observed with every agent

Adverse effects	CDK 4/6 inhibitor plus endocrine therapy	Endocrine therapy alone	RR (CI 95%)	Analysis models	P value (Pooled analysis)	Trial specific RR (sub-group analysis) in FEM			
	All grades % (n/total)					MONALEESA	MONARCH	PALOMA	No. of included studies respectively
	Hematological								
Neutropenia	70.2 (2178/3103)	6.2 (119/1915)	13.13 [7.90, 21.83]	REM	<.05	14.77 [11.17, 19.55]	6.67 [5.03, 8.85]	15.48 [10.53, 22.75]	3/3/3
Leukopenia	37.9 (1176/3103)	5.2 (99/1915)	8.88 [5.33, 14.77]	REM	<.05	7.77 [5.56, 10.85]	4.79 [3.63, 6.30]	13.42 [8.20, 21.96]	3/3/3
Thrombocytopenia	19.6 (383/1959)	2.5 (29/1183)	7.44 [5.11, 10.82]	FEM	<.05	4.78 [1.64, 13.90]	5.58 [3.52, 8.84]	14.56 [6.51, 32.58]	1/2/3
Anemia	28.8 (893/3103)	8.3 (159/1915)	3.36 [2.63, 4.30]	REM	<.05	2.79 [2.14, 3.63]	4.34 [3.31, 5.70]	2.95 [2.19, 3.98]	3/3/3
	Non-hematological								
Alopecia	23.4 (653/2792)	9.9 (174/1763)	2.64 [1.97, 3.52]	REM	<.05	2.22 [1.79, 2.75]	3.59 [2.35, 5.49]	2.44 [1.84, 3.23]	3/2/3
Pruritus	14.6 (184/1259)	5.2 (42/801)	2.58 [1.86, 3.58]	FEM	<.05	2.77 [1.86, 4.11]	2.22 [1.24, 3.96]	-	2/1/-
Rash	16.1 (437/2709)	7.4 (125/1686)	2.24 [1.85, 2.71]	FEM	<.05	2.30 [1.78, 2.99]	2.75 [1.69, 4.47]	1.87 [1.31, 2.66]	3/2/2
Increased ALT	14.1 (281/1987)	6.4 (85/1322)	2.02 [1.41, 2.89]	REM	<.05	2.34 [1.56, 3.49]	1.96 [1.46, 2.63]	1.58 [0.64, 3.88]	2/3/1
Abdominal pain	16.4 (272/1656)	8.1 (80/991)	1.94 [1.53, 2.46]	FEM	<.05	1.47 [0.89, 2.41]	2.24 [1.60, 3.15]	1.84 [1.17, 2.90]	1/2/2
Stomatitis	17.8 (279/1565)	8.7 (83/954)	1.93 [1.25, 2.96]	REM	<.05	1.32 [0.81, 2.14]	1.47 [0.94, 2.30]	2.62 [1.86, 3.68]	1/1/2
Diarrhea	46.5 (1444/3103)	21.3 (408/1915)	1.90 [1.35, 2.69]	REM	<.05	1.38 [1.18, 1.61]	3.48 [2.99, 4.06]	1.31 [1.05, 1.64]	3/3/3
Increased AST	14.3 (284/1987)	7.2 (95/1322)	1.86 [1.31, 2.63]	REM	<.05	2.05 [1.41, 2.96]	1.85 [1.38, 2.48]	1.50 [0.69, 3.26]	2/3/1
Decreased appetite	19.0 (590/3103)	11.1 (212/1915)	1.86 [1.57, 2.21]	FEM	<.05	1.30 [1.00, 1.68]	2.65 [1.97, 3.58]	2.05 [1.42, 2.96]	3/3/3
Pyrexia	12.3 (192/1565)	7.1 (68/954)	1.78 [1.37, 2.33]	FEM	<.05	1.90 [1.22, 2.95]	1.87 [1.03, 3.37]	1.66 [1.11, 2.49]	1/1/2
Vomiting	23.0 (715/3103)	14.1 (270/1915)	1.67 [1.28, 2.18]	REM	<.05	1.71 [1.43, 2.06]	2.12 [1.64, 2.74]	1.17 [0.90, 1.53]	3/3/3
Nausea	39.0 (1209/3103)	24.3 (466/1915)	1.61 [1.47, 1.77]	FEM	<.05	1.66 [1.46, 1.89]	1.81 [1.51, 2.17]	1.34 [1.12, 1.61]	3/3/3
Dizziness	12.0 (146/1220)	8.3 (65/782)	1.35 [0.82, 2.21]	REM	>.05	1.22 [0.68, 2.19]	2.26 [1.26, 4.03]	0.98 [0.67, 1.45]	1/1/1
Constipation	19.8 (553/2792)	15.0 (264/1763)	1.35 [1.18, 1.55]	FEM	<.05	1.51 [1.25, 1.82]	1.10 [0.82, 1.49]	1.29 [1.00, 1.66]	3/2/3
Cough	19.4 (437/2252)	15.3 (223/1454)	1.27 [1.10, 1.48]	FEM	<.05	1.24 [1.02, 1.50]	1.62 [0.90, 2.91]	1.26 [0.97, 1.64]	3/1/2
Fatigue	34.9 (930/2662)	29.0 (490/1692)	1.20 [1.10, 1.32]	FEM	<.05	1.07 [0.94, 1.22]	1.24 [1.01, 1.52]	1.41 [1.19, 1.66]	3/2/3
Dyspnea	10.5 (127/1204)	8.2 (66/809)	1.23 [0.93, 1.63]	FEM	>.05	1.11 [0.61, 2.03]	0.97 [0.62, 1.53]	1.63 [1.03, 2.59]	1/1/1
Headache	22.1 (600/2709)	20.8 (351/1686)	1.09 [0.97, 1.23]	FEM	>.05	1.09 [0.93, 1.28]	1.28 [0.98, 1.68]	0.96 [0.77, 1.20]	3/2/2
Back pain	17.5 (488/2792)	18.2 (321/1763)	1.00 [0.88, 1.13]	FEM	>.05	1.05 [0.88, 1.25]	0.87 [0.64, 1.18]	0.99 [0.79, 1.24]	3/2/3
Arthralgia	23.6 (659/2794)	25.4 (449/1765)	0.98 [0.88, 1.09]	FEM	>.05	1.01 [0.88, 1.16]	0.83 [0.63, 1.10]	1.02 [0.84, 1.23]	3/2/3
Pain in extremity	13.2 (212/1607)	13.0 (126/972)	0.97 [0.79, 1.20]	FEM	>.05	0.91 [0.68, 1.21]	-	1.06 [0.78, 1.43]	2/-/2
Hot flush	19.3 (475/2465)	23.2 (371/1602)	0.91 [0.81, 1.03]	FEM	>.05	0.95 [0.81, 1.10]	1.06 [0.65, 1.71]	0.83 [0.67, 1.02]	3/1/3
				Specific Adverse Effects					
Increased creatinine	17.5 (170/973)	2.7 (13/483)	5.91 [2.68, 13.05]	REM	<.05	-	5.91 [2.68, 13.05]	-	-/3/-
QTcF> 480 ms	5.4 (62/152)	12.2 (12/908)	4.53 [1.19, 17.23]	FEM	<.05	4.53 [1.19, 17.23]	-	-	3/-/-
QTcF> 500 ms	1.3 (15/1152)	0.2 (2/908)	3.78 [2.08, 6.87]	FEM	<.05	3.78 [2.08, 6.87]	-	-	3/-/-

Table 3. Summary of reported adverse events plus the result of trial specific RR analysis from every grade of BC in both treatment arms.*Grey area of the table in the trial specific section indicates the significant analysis result (P <.05)

introduced to the population conveying comparable RR value (Figure 3C). However, MONARCH trials provided the most remarkable result (RR 0.40 [0.30, 0.54] in ITT and 0.43 [0.29, 0.63] in measurable disease group; 95% CI, P<.05) with slightly better outcomes compared to either MONALEESA trials; or even PALOMA trials which somehow provided insignificant outcomes (P >.05) as demonstrated by both of RECIST-based table, in which notably influenced by its heterogeneity value (I^2 of 74%).

Adverse effect rate analysis

Hematological adverse effects rate was found to be dramatically affected in the combination arms; especially for neutropenia, leukopenia, and thrombocytopenia with RR values greater than 5 according to our analysis (FEM, 13.13 [7.90, 21.83]; 8.88 [5.33, 14.77]; and 7.44 [5.11, 10.82], respectively; 95% CI; P<.05). Those hematological reactions were observed in 70.2%; 19.6%; and 37.9% respectively of the combination arm compared to endocrine therapy alone with under 10% involvement from cumulative population. Inversely, certain adverse effects associated with endocrine-related management e.g., higher risk of arthralgia and hot flush, were found in the CDK 4/6 inhibitors arm as indicated by <1.0 RR even though the analysis was statistically insignificant (Table 3).

The trial specific analysis revealed each agent manifests relatively different adverse effects systemically even though the hematological reactions were similarly reported (Table 3). Accordingly, PALOMA trials reported the highest rate of hematological events as indicated by its prominent RR value except for anemia; followed

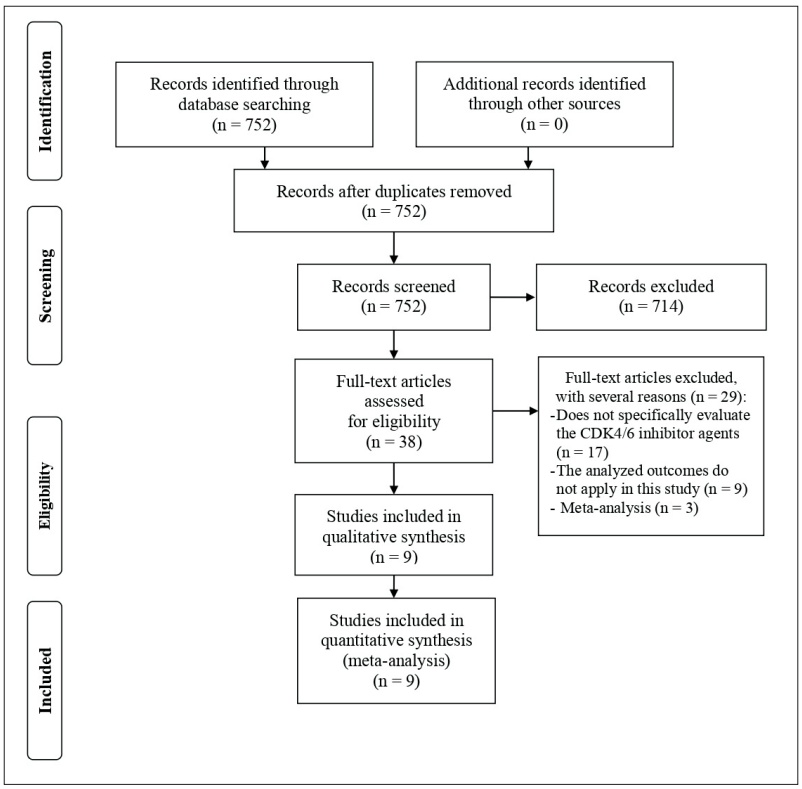

Figure 1. Flowchart of literature searching strategy of this systematic review and meta-analysis in PRISMA 2009 diagram

by MONALEESA with marginally lower results. In MONARCH studies, diarrhea presents with an alarmingly higher RR value (FEM, 3.48 [2.99, 4.06]) compared to the other trials with significantly lower value (RR< 1.5). A predominantly higher rate of integument reactions e.g., rash and alopecia along with several gastrointestinal (GI) involvement issues such as decrease of appetite and vomiting, were also markedly observed in the MONARCH trials; possibly correlated with its higher treatment response as elaborated earlier. Furthermore, the palbociclib-arm also provided better tolerance towards the adverse reactions rate as indicated by the lower RR in almost all parameters except for the hematological reactions, even though the risk of stomatitis and alopecia were fairly noticeable; henceforth the anticipation of the latter effects should always be made in the pre-treatment phase.

Further prediction and clinical accordance of the side effects can be adjusted to the anti-CDK 4/6 agents as the endocrine treatment related-reactions were fairly reduced or assimilated with the combination approach. The consideration toward medication-specific reactions as seen among MONALEESA trials e.g., QT wave prolongation or increased blood creatinine level in MONARCH trials should always be perceived as well.

5. DISCUSSION

In cellular oncologic sciences, the 'restriction point' during the G_1 phase possesses a significant role in cell cycle as the determination of cell division continuation (S phase) or the sequence renouncement toward inactive G_0 phase occurs at that particular point.(12, 16-18) The progression of the cycles is highly mediated by antiproliferative signals, which are communicated by the Rb protein and its relatives. The latter proteins are specifically influenced by phosphorylation and perform as a negative regulator in a hypophosphorylated state, leading to alteration of E2F family protein function and reducing the genes expression. Conversely, hyperphosphorylated Rb (as a result of cyclin D activation) will diminish the capacity of E2F transcription factors hence the cell cycle progress further. Therefore, the administration of CDK 4/6 inhibitors will act as a cellular progression control by interrupting the Cyclin D-CDK 4/6-Rb pathway (12, 13, 16, 18, 19).

Estrogen receptor (ER) signaling pathways in HR+ BC also directly upregulate cyclin D mRNA expression. Cross-talk between ER and the CDK 4/6 pathway reveals a strong interaction toward multiple neoplastic regulators as the culmination of its expression is possibly mediated by the

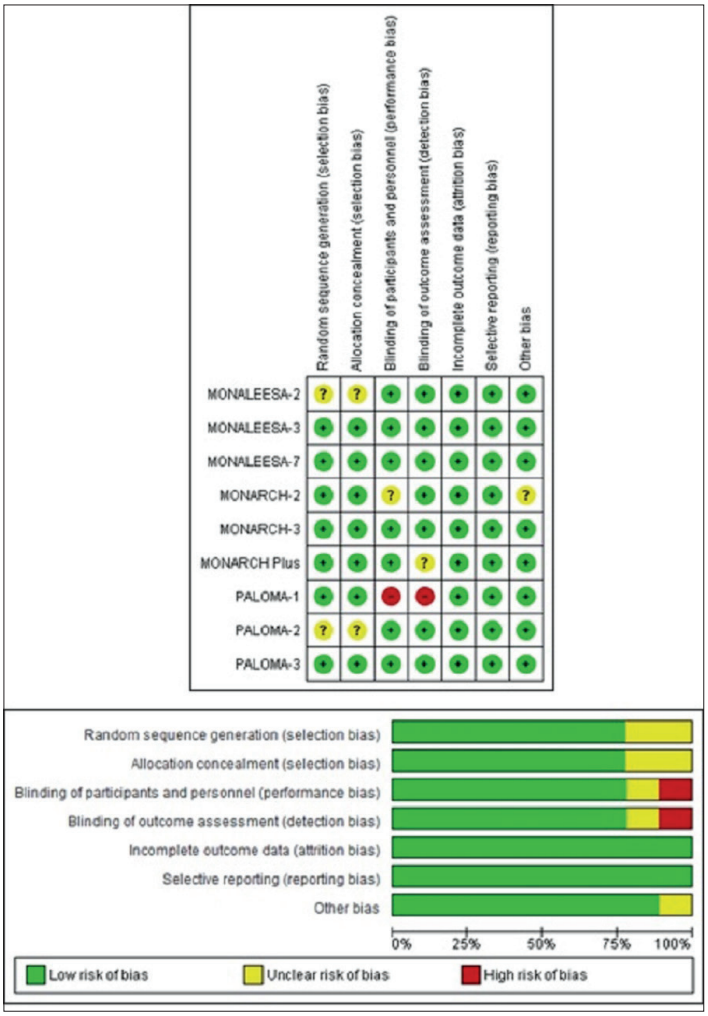

Figure 2. A. Risk of potential bias of individual studies analysis; B. Summation of every bias assessment focus from all included studies

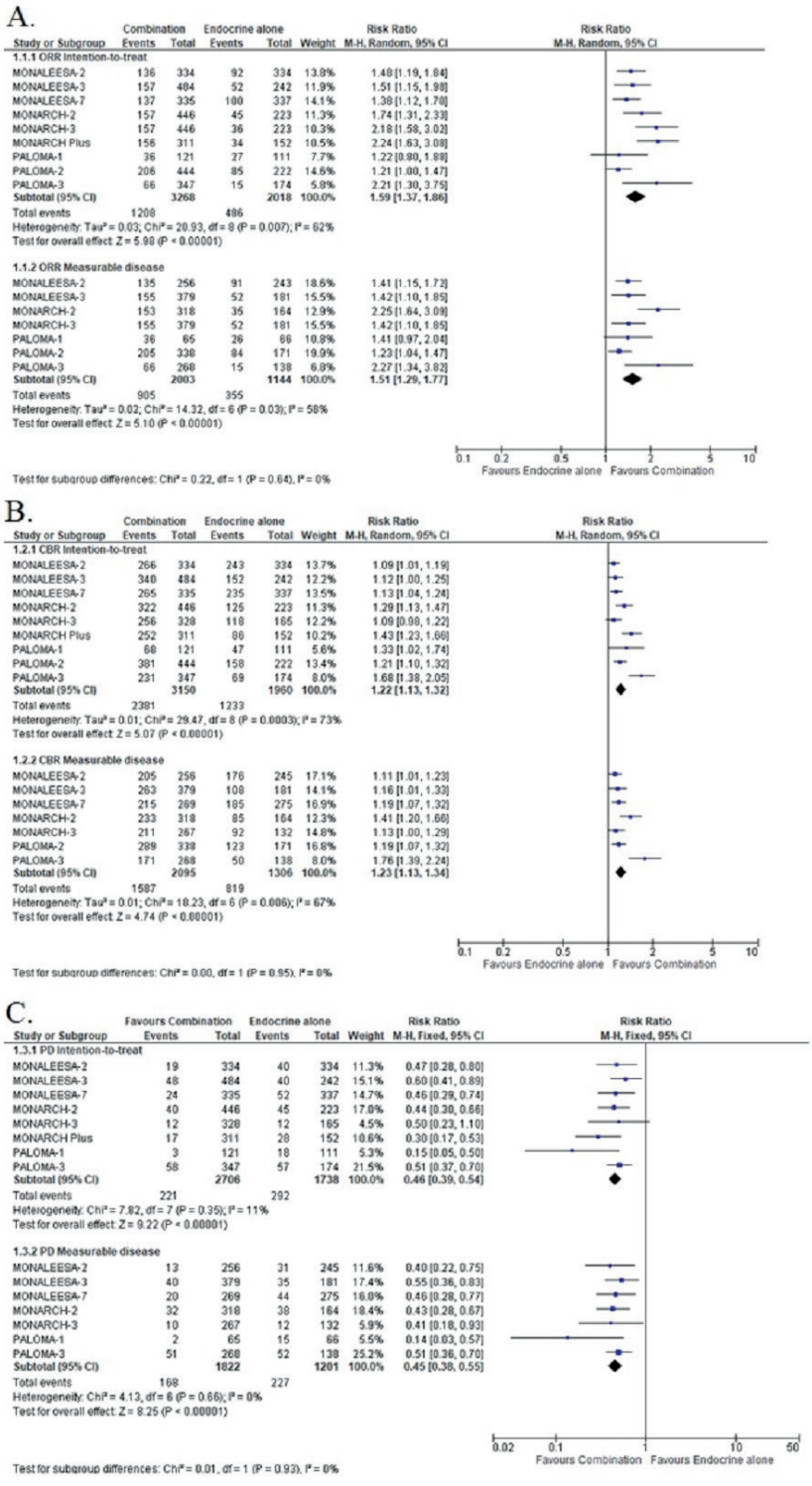

Figure 3. A. Forest plot of overall response rate (ORR; complete response (CR) + partial response (PR)) in combination regiment versus endocrine treatment alone; B. Clinical benefit rate (CBR; complete response (CR) + partial response (PR) + stable disease for >24 weeks (SD >24)) in combination regiment versus endocrine treatment alone; C. Progressive disease rate of the analyzed trials in combination regiment versus endocrine treatment alone.

following interchange deregulation. For instance, Cyclin D upregulates ER-mediated transcription by binding to the ERα domain; initiating its activation in the absence of estrogen, thus the regulations are not inhibited by the feedback mechanism as seen in physiologic states. Therefore, it is plausible to approach the treatment plan of HR+ BC with a combination strategy especially in advanced breast cancer (ABC; and also HER2-) which include both small-molecule CDK 4/6 inhibitors and endocrine modulators considering both mechanism are influencing each pathway (17, 19-22).

Although all of the agents revealed similar inhibitory ability as indicated by lower IC_{50} against CDK4, palbociclib is currently the most advanced CDK 4/6 inhibitor with a higher rate of evaluation and trials worldwide. Accordingly, all of the CDK 4/6 inhibitors are markedly pharmacologically hence reasonable to expect different response. The combination with several endocrine treatments will also yield positive outcomes either in treatment response or tolerability of the adverse effects especially considering the risk of locoregional and/or distant relapses with single endocrine intervention (20-26) Generally, the combination group exhibited a better overall response rate (ORR) in both the ITT and measurable disease subgroups. Therefore, the introduction of CDK 4/6 inhibitors on the treatment regimen will develop a better proportion of either CR or PR rate. The trials-specific analysis revealed that MONARCH trials had the most potential response toward the treatment group (9, 27-29). The addition of the later agent also proved beneficial to the sub-parameter of ORR as MONARCH trials revealed superior outcomes of both CR and PR with the RR in ITT group 4.16 [1.26, 13.70] and 1.75 [1.49, 2.07], respectively, which was statistically favorable compared to the other trials (30-40).

The analysis of clinical benefit rate (CBR) revealed the clinical efficacy of palbociclib was superior as indicated by higher rate of the OR in PALOMA compared to the other evaluated trials. However, the overall CBR in all CDK 4/6 inhibitor groups were also markedly substantial and statistically significant therefore indicating superior beneficial effect of the combination regimen. As a pyridopyrimidine compound, the addition of palbociclib in the treatment strategy provides superior CBR or disease stabilization (both cumulative or restrictive to stable disease (SD)) for longer than 24 weeks. The data were indicative as PALOMA trials exhibited higher RR in ITT CBR analysis within 1.35 [1.24, 1.47]; significantly higher than MONALEESA (1.12 [1.06, 1.18]) and

MONARCH (1.26 [1.16, 1.35]). Therefore, disease stabilization in both groups demonstrated the superiority of palbociclib to impact such advantageous outcomes; as the SD response implies the patient does not meet the criteria for CR, PR, or progressive disease (PD) with no symptomatic deterioration attributed to tumor progression observed hence the malignancy was postulated as clinically 'stable'. The analysis of PD also manifested such favorable outcomes for the combination arm as the RR of each analysis, either all trials or the specific trial evaluation will more likely exhibit the superior outcomes.

However, the attainability of the hematological reactions following palbociclib's regiments were also remarkably high. Higher rates of neutropenia, leukopenia, and thrombocytopenia exemplify its problematic reactions in the hematological system, contrasted to abemaciclib which revealed significantly lower RR in the same parameter except in the incidence of anemia, where the MONARCH trials reported the highest risk of anemia in its investigations (Table 3). Still, the reversibility of hematological reactions especially by the CDK 4/6 inhibitor is perceivably tentative, as the induction of DNA damage and bone marrow apoptosis by the chemotherapy agents were nearly irreversible-posed such direful effects in the overall treatment rationale (41, 42). The rate of the other undesirable reactions in PALOMA trials were slightly favorable as well; indicated by lower RR in roughly all evaluated reactions albeit conditions involving GI tract particularly nausea and stomatitis or systemic symptoms e.g., fatigue, should be anticipated. Even though the reports from MONALEESA trials practically manifest superior outcomes, it is notable that our analysis of those studies revealed some consistencies as the comparison was constructed. Interestingly, the administration of ribociclib will almost ranked in the middle of other agents, equidistantly placed the outcomes between the other anti-CDK 4/6 albeit the overall responses toward the agent was comparatively inferior; hence place the agent in the fairly 'safe' state to be administered yet the foremost clinical judgement may relatively burdensome to be expected (32, 37-40, 43, 44).

The pharmacological characteristic of each CDK 4/6 inhibitor as elaborated in the previous section differed; as represented by the IC_{50} or inhibition potential specifically toward either CDK4-Cyclin D1 or CDK6-Cyclin D1-2-3. To date, abemaciclib is currently the most potent agent as the IC_{50} to affect both CDK-cyclin complex mentioned earlier with the dose of only 2 nm and 10 nm, respectively, overwhelming both palbociclib (11 nm and 15 nm) and ribociclib (10 nm and 39 nm). Moreover, abemaciclib also disclosed potential inhibitory activity against CDK9 which involved several transcriptional events and genomic integrity regulation hence induce further cellular stress or molecular-level damage (26, 45, 46). Therefore, an exceptionally higher response rate in MONARCH trials is fairly reasonable considering the extensive mechanism of action of abemaciclib may also participate in the cellular responses. The administration strategy of the abemaciclib was also continuously prescribed, contrasted to the other CDK 4/6 inhibitors

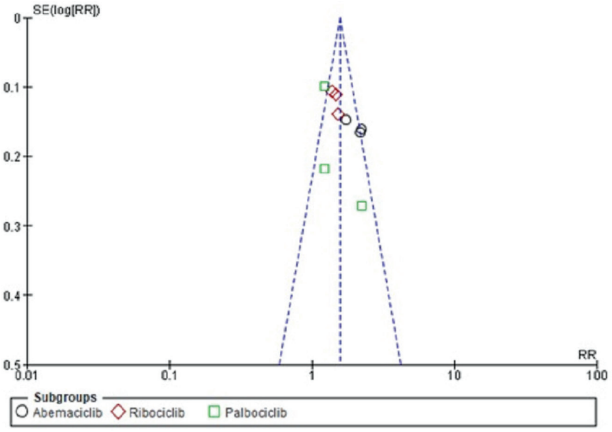

Figure 4. Funnel plot of overall response rate (ORR; complete response (CR) + partial response (PR)) in intention-to-treat (ITT) sub-analysis with OR value of >1 is favoring combination arm.

which were applied using a 3 weeks-on and 1 week-off method therefore the intermittent approach possibly influences the outcomes. Higher lipophilicity of abemaciclib in which will enhances thepenetrating ability toward breast tissue is also suggested to amplify the general treatment response. The estimation was made according to the value of cLog P, with abemaciclib lipophilicity markedly higher (5.5) than both palbociclib (2.7) and ribociclib (2.3) (26, 43, 47).

Even though all of the CDK 4/6 inhibitors are metabolized at the liver through the oxidation by CYP3A4, palbociclib is also known to undergoes an additional process in the same organ involving sulfotransferase enzyme (SULT2A1). Hence, its circulating level will be effectively reduced correlated with its lower response rate, but offers better stability of the disease, even comparatively better than the endocrine treatment alone at some points. The concomitant administration of those agents with several potent CYP3A4 inhibitors will possibly lead to the further augmentation of the agent's toxicity as the higher circulating level can be expected. Therefore, collective recommendation of the HR+/HER2- BC involving those CDK 4/6 inhibitor should raise some awareness as the pharmacological interactions were likely (25, 26, 44, 46, 48, 49). The advantageous response in accordance of CDK 4/6 inhibitor administration will certainly provide molecular level suppressions of cancer cell proliferation without alteration of cells' DNA as seen in current chemotherapy. Theoretically, these beneficial effects will be expected to occur in the larger spectrum starting from the early to even the ABC populations e.g., with brain metastases involvement as the lipophilicity features of the agents will ensure the penetration of blood-brain barrier more effectively (47-49).

The justification of a combination approach for HR+/HER2- BC treatment is practically acceptable according to the outcomes of this meta-analysis. Nevertheless, it is reasonable to note several noteworthy limitations in this review e.g., a) specific CDK 4/6 inhibitors analyses were not carried out to determine the most recommended endocrine treatment counterpart (or even its ideal

dosage arrangement) as our objective itself was to compare the combination treatment versus exclusively anti-endocrine therapy; b) analysis of specific participant's group i.e., restricted to pre- or postmenopausal population was not conducted as our approach was apparently focused on the treatment response and risk ratio of adverse reactions in both study arms; c) the projection of overall patients survivability and progression-free survival (PFS) analysis was not performed as the meta-analysis by Ding et al., and Li et al., had already evaluated the outcomes, although we included more trials hence more participants (50, 51). However, the results of this study showing superior disease response after the addition of anti-CDK 4/6 agents in the treatment strategy should suffice to improve the credibility and encourage either further trials or more profound analysis toward each CDK 4/6 inhibitor agent in the future..

6. CONCLUSION

The addition of CDK 4/6 inhibitors into the current anti-hormonal treatment strategy of HR+/HER2- BC was shown to be beneficial for most patients as the treatment responses favored the combination arm; even though a considerable rate of adverse effects were observable especially in hematological-related reactions. Nevertheless, the preeminent endocrine treatment counterpart in this combined strategy remains questionable; henceforth it is reasonable to suggest further endocrine-selection specific analysis of respective anti-CDK 4/6 agents to determine the most recommended regiment for e treatment of HR+/HER2- advanced breast cancer.

- **Author's contribution**: We used the CRediT taxonomy to elaborate the contributions of each author mentioned in the first page to facilitate the recognition of our works involvement Dedy Hermansyah: Conceptualization, data curation, formal analysis, investigation, project administration, software, supervision, validation, writing-original draft preparation, writing-review & editing. Naufal Nandita Firsty: Conceptualization, formal analysis, investigation, methodology, project administration, software, visualization, writing-original draft preparation, writing-review & editing. Muhammad Nuh Alhudawy: Conceptualization, data curation, investigation, methodology, project administration, writing-original draft preparation. Raja Alwan Nasution: Conceptualization, data curation, formal analysis, methodology, writing-original draft preparation
- **Conflicts of interest**: There are no conflicts of interest.
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