# SYSTEMATIC REVIEW

**BMC** Cancer



# CDK4/6 inhibitors plus endocrine therapy vs. placebo plus endocrine therapy for HR+/ HER2- advanced breast cancer: a phase III RCTs based meta-analysis



Cailu Luo<sup>1</sup>, Kunlin Yu<sup>1</sup>, Xiaodan Luo<sup>1</sup>, Tao Lian<sup>1</sup>, Xuejuan Liu<sup>1</sup>, Wang Xu<sup>1</sup> and Zhongkui Jin<sup>1\*</sup>

# Abstract

**Background** Does incorporating Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors into endocrine therapy (ET) effectively enhance survival outcomes, notably overall survival (OS), among individuals with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer? This remains a clinical controversy. We compared the antitumor efficacy and adverse effects (AEs) between CDK4/6 inhibitors + ET (CET) and placebo + ET (PET) by conducting a phase III randomized controlled trials (RCTs) based meta-analysis.

**Methods** Seven databases were searched to identify eligible studies, comprising Phase III RCTs comparing CET to PET. The primary endpoints were OS and progression-free survival (PFS), with secondary endpoints including responses and adverse events (AEs).

**Results** Seven RCTs (DAWNA-2, MONALEESA-2, MONALEESA-3, MONALEESA-7, MONARCH-3, PALOMA-2, and PALOMA-4) were included. The CET group exhibited significantly improved OS (HR: 0.81 [0.74, 0.88]), PFS (HR: 0.57 [0.52, 0.63]), objective response rate (RR: 1.31 [1.20, 1.43]), and clinical benefit rate (RR: 1.11 [1.07, 1.15]). These benefits were consistent across almost all subgroups. Additionally, the CET group showed better overall survival rates (OSR) from 24 to 60 months (OSR 24–60 m) and progression-free survival rates (PFSR) from 6 to 60 months (PFSR 6–60 m). However, more total AEs, grade 3–5 AEs, and serious AEs were found in CET group. The top 5 grade 3–5 AEs in the CET group were neutropenia (59.39%), leukopenia (24.11%), decreased white blood cell count (12.99%), hypertension (7.03%), and increased alanine aminotransferase (5.91%).

**Conclusions** The superiority of CET over PET in HR+/HER2- advanced breast cancer is evident, showing improved survival and responses. Nonetheless, the higher incidence of AEs, specifically hematologic AEs, requires cautious attention.

Keywords CDK4/6 inhibitors, Endocrine therapy, Breast Cancer, Meta-analysis, Randomized controlled trials

\*Correspondence: Zhongkui Jin jinzk1975@163.com <sup>1</sup>Department of General Surgery, Yichun People's Hospital, No. 1061 Jinxiu Avenue, Yiyang New District, Yichun, jiangxi 336000, China



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http:// creativecommons.org/licenses/by-nc-nd/4.0/.

#### Introduction

For decades, breast cancer has been the most prevalent cancer worldwide, with approximately 2.26 million new cases diagnosed annually [1]. However, the fiveyear survival rate for hormone receptor-positive (HR+)/ human epidermal growth factor receptor 2-negative (HER2-) breast cancer patients still remains below 30% [2, 3]. These tumors predominantly rely on hormonal signaling for cell survival and proliferation, representing over 70% of breast cancer cases in clinical settings. This underscores the importance of endocrine therapy (ET) for these patients [4]. However, research indicates that approximately one-third of HR+patients experience a relapse within 15 years following ET. Additionally, initial ET fails to benefit 50% of HR+breast cancer patients [5]. Consequently, the exploration of new therapeutic strategies in conjunction with ET is imperative.

Recently, Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors have become a focal point for breast cancer [6]. CDKs are essential regulators of the tumor cell cycle, controlling cell proliferation through a series of enzymatic reactions [7]. One key mechanism underlying resistance to ET in HR+patients is the cyclin D-CDK4/6 signaling pathway activated by the estrogen pathway [8]. Consequently, the combination of CDK4/6 inhibitors with ET has emerged as a new treatment method for patients with HR+/HER2- breast cancer. Commonly used CDK4/6 inhibitors in clinical practice (Dalpiciclib, Palbociclib, Ribociclib, and Abemaciclib) have been proven effective, although results (survival, and adverse events [AEs]) vary across different studies [9–15].

Therefore, this study (a phase III randomized controlled trial [RCT]-based meta-analysis) aimed to assess and compare the efficacy of CDK4/6 inhibitors+ET versus placebo+ET for HR+/HER2- breast cancer patients.

# Materials and methods

# Search strategy

We searched PubMed, Scopus, EMBASE, ScienceDirect, Ovid MEDLINE, the Cochrane Library, and Web of Science from their inception until April 1, 2024, as detailed in Table S1. The search utilized keywords such as 'CDK4/6 Inhibitors' (including Palbociclib, Ribociclib, Abemaciclib, and Dalpiciclib), 'Randomized' (Randomized OR Randomly OR Randomised), and 'Breast Cancer'. Furthermore, we reviewed the references of the selected RCTs to identify additional pertinent research.

### Selection criteria

The studies selected for inclusion were published in English and adhered to the PICOS criteria:

(1) Participants: patients diagnosed with HR+/HER2advanced breast cancer.

- (2) Intervention: CDK4/6 inhibitors+ET, defined as the CET group.
  - (3) Control: placebo+ET, defined as the PET group.
  - (4) Outcomes: survival, responses, and AEs.
  - (5) Study design: phase III RCTs.

Studies lacking original data, such as meta-analyses, conference presentations, and case studies, were omitted. Various articles stemming from a single RCT that reported different results were evaluated. For outcomes that were the same, only the latest findings were incorporated.

#### **Data extraction**

The extracted data include: study characteristics (including registration number and study duration), patient particulars (menopausal status, ECOG PS, etc.), treatment details (CDK4/6 inhibitor utilized, ET utilized, etc.), cancer attributes (hormone receptor status, etc.), antitumor efficacy (overall survival [OS], objective response rate [ORR], etc.), and adverse event frequencies (total AEs, etc.). Two researchers independently gathered the data, and any inconsistencies were settled by deliberation.

#### **Outcome assessments**

The main endpoints examined in this investigation were OS and PFS. Additionally, we assessed the overall survival rate (OSR) and progression-free survival rate (PFSR) at intervals of 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months. We also examined OS and PFS within specific subgroups. These subgroups included variables such as age, race category, menopausal status, hormone receptor status, ECOG PS, disease-free interval, number of meta-static sites, presence of liver or lung metastases, presence of bone-only disease, choice of CDK4/6 inhibitor therapy partner, choice of endocrine therapy partner, history of previous adjuvant or neoadjuvant ET, type of previous ET, and history of previous neoadjuvant or adjuvant chemotherapy.

#### **Quality assessment**

The quality of RCTs was evaluated using the Jadad scale, assessing randomization, blinding, and inclusion of patients based on a scale of five points. Trials achieving a score of three or higher were deemed of high quality [16]. Additionally, the Cochrane Risk of Bias Assessment Tool was employed to evaluate biases related to selection, performance, detection, attrition, and reporting. Risks were classified as low, unclear, or high, and depicted in a bias graph [17].

Moreover, the GRADE approach was applied to analyze result quality, examining bias, indirectness, imprecision, and publication bias. This method ranks certainty across four levels: very low, low, moderate, and high [18].

#### Statistical analysis

This meta-analysis was performed according to PRISMA guidelines (Table S2). Data was analyzed via Review Manager 5.3. Data on survival employed hazard ratios (HRs), which indicated an advantage for the CET group when HR was less than 1. Risk ratios (RRs) were used for dichotomous variables, RR>1 favored the PET group in the analysis of AEs. Conversely, in analyzing OSR and PFSR, RR>1 favored the CET group. To assess heterogeneity, the  $I^2$  statistic and  $\chi^2$  test were utilized. Low heterogeneity, indicated by  $I^2$  being less than 50% or p-value greater than 0.1, led to the employment of a fixed-effects model. In contrast, a random-effects model was implemented. The determination of statistical significance was based on p-values less than 0.05. Publication bias was assessed visually using funnel plots. (Registered in PROS-PERO: CRD42024539851)

#### Page 3 of 14

## Results

## Search results

The analysis included twenty-six studies from seven RCTs (DAWNA-2, MONALEESA-2, MONALEESA-3, MONALEESA-7, MONARCH-3, PALOMA-2, and PALOMA-4) (Fig. 1) [9–15, 19–37]. Table 1 presents baseline information of the seven RCTs. The CET group comprised 2,103 patients, while the PET group comprised 1,463 patients. Of the RCTs, five (MONA-LEESA-2, MONALEESA-3, MONALEESA-7, MON-ARCH-3, and PALOMA-2) were global multicenter, one (PALOMA-4) was Asia multicenter, and one (DAWNA-2) was China multicenter. All seven phase III RCTs were deemed of high quality (Figure S1 and Table S3). According to the GRADE approach, the outcomes were assessed as medium to high quality (Table S4).



	Ω Ω
	slud
2070	בע
: + +	
0 00 10 10 10 10 0	
, c C C	
Ì	υ
4	

Study	Register	Phase	Period	Groups	Patients	Age	CDK4/6	Endocrine	Menopau	isal status	ECOG	PS	Р	rmone	Fol-
	number					(Mean, year)	inhibitor	therapy					sta	eptor tus	low up (months)
									Post-M	Pre-M	0	-	2 ER-	+ PR+	1
DAWNA-2 [9]	NCT03966898	=	2019.07-2020.12	CET group	303	55	Dalpiciclib	Letrozole or	183	120	141	161	0 302	258	21.6
				PET group	153	55		Anastrozole	66	54	69	84	0 153	134	
MONALEESA-2	NCT01958021	≡	2014.01-2015.03	CET group	334	62	Ribociclib	Letrozole	334	0	205	129	0 332	271	80.0
[10,19–23]				PET group	334	63			334	0	202	132	0 333	278	
MONALEESA-3	NCT02422615	≡	2015.06-2016.06	CET group	237	63	Ribociclib	Fulvestrant	237	0	152	92	0 236	173	70.8
[11,24–26]				PET group	128	63			128	0	77	44	0 127	88	
MONALEESA-7	NCT02278120	≡	2014.12-2016.08	CET group	288	43	Ribociclib	Tamoxifen or	0	288	211	75	0 285	249	53.5
[12,27,28]				PET group	290	45		Letrozole or Anastrozole	0	290	219	67	1 288	248	
MONARCH-3	NCT02246621	≡	2014.11-2015.11	CET group	328	63	Abemaciclib	Letrozole or	328	0	192	136	0 328	3 255	70.2
[13,29–32]				PET group	165	63		Anastrozole	165	0	104	61	0 165	127	
PALOMA-2	NCT02246621	≡	2013.02-2014.07	CET group	444	62	Palbociclib	Letrozole	444	0	257	178	9 444	1	90.1
[14,33–37]				PET group	222	61			222	0	102	117	3 222	'	
PALOMA-4 [15]	NCT02297438	≡	2015.03-2020.08	CET group	169	54	Palbociclib	Letrozole	169	0	88	85	0 165	-	52.8
				PET group	171	54			171	0	81	6	0 171	ı	

#### Survival (OS and PFS)

The CET group achieved better OS (HR: 0.81 [0.74, 0.88], p < 0.00001) and PFS (HR: 0.57 [0.52, 0.63], p < 0.00001) (Fig. 2). OSR 24–60 m significantly favored the CET group (Figure S2). Meanwhile, PFSR 6–60 m significantly favored the CET group (Figure S3). As survival prolonged, CET also exhibited a growing OS and PFS advantage over PET (Fig. 3).

#### Subgroup analysis of survival (OS and PFS)

We subgroup analyzed survival (OS and PFS) according to Age, Race category, Menopausal status, Hormone receptor status, ECOG PS, Disease-free interval, Metastatic status, CDK4/6 inhibitor therapy partner, ET partner, Previous adjuvant or neoadjuvant ET, Previous ET type, and Previous neoadjuvant or adjuvant chemotherapy. OS and PFS generally favored the CET group in all subgroups (Table 2).

## Responses

In all patients, the ORR (RR: 1.31 [1.20, 1.43]) and clinical benefit rate (CBR, RR: 1.11 [1.07, 1.15]), along with partial response (PR, RR: 1.30 [1.19, 1.43]), were better in the CET group. Although the complete response (CR, RR: 1.53 [0.90, 2.59]) tended to favor the CET group, it lacked statistical significance. Conversely, the rate of stable disease (SD, RR: 0.90 [0.82, 0.98]) was higher in the PET group (Fig. 4).

Among patients with measurable disease, the ORR (RR: 1.31 [1.21, 1.42]), CBR (RR: 1.13 [1.08, 1.18]), and PR (RR: 1.29 [1.19, 1.41]) were better in the CET group. The CR

(RR: 1.64 [0.93, 2.87]) tended to favor the CET group without statistical significance. The rate of SD (RR: 0.85 [0.77, 0.94]) was lower in the CET group (Figure S4).

#### Toxicity

In summary, the CET group resulted in more total AEs (RR: 1.05 [1.03, 1.06]), grade 3–5 AEs (RR: 2.96 [2.30, 3.81]), serious AEs (RR: 1.67 [1.37, 2.03]), AEs leading to treatment discontinuation (RR: 2.61 [1.88, 3.62]), AEs leading to dose reduction (RR: 11.70 [3.76, 36.36]), and AEs leading to dose interruption (RR: 5.67 [2.59, 12.43]). However, AEs leading to death (RR: 1.31 [1.21, 1.42]) were similar between the two groups (Fig. 5).

In the assessment of any grade AEs, more cases of neutropenia, decreased white blood cell count, leukopenia, nausea, fatigue, diarrhea, anemia, hyponatremia, thrombocytopenia, alopecia, vomiting, hypokalemia, cough, constipation, decreased appetite, abdominal pain, increased blood creatinine, rash, pruritus, urinary tract infection, hypokalaemia, stomatitis, pyrexia, prolonged electrocardiogram QT, dry skin, hypophosphataemia, dysgeusia, and oropharyngeal pain were observed in the CET group (Table S5). The top 5 any grade AEs were neutropenia (74.66%), decreased white blood cell count (49.55%), leukopenia (42.80%), nausea (37.54%), and fatigue (33.56%) (Table 3). Incidence rate of any grade interstitial lung diseases (ILDs) tended to be higher in the CET group without statistical significance (Figure S5).

In the assessment of grade 3–5 AEs, more cases of neutropenia, leukopenia, decreased white blood cell count, increased alanine aminotransferase, anemia,

				Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% CI
4.1.1 Overall survival					
DAWNA-2	-0.26136	0.190869	2.9%	0.77 [0.53, 1.12]	
MONALEESA-2	-0.27444	0.099353	10.6%	0.76 [0.63, 0.92]	
MONALEESA-3	-0.31471	0.107723	9.1%	0.73 [0.59, 0.90]	
MONALEESA-7	-0.24846	0.126096	6.6%	0.78 [0.61, 1.00]	
MONARCH 3	-0.22314	0.120405	7.2%	0.80 [0.63, 1.01]	
PALOMA-2	-0.08338	0.09892	10.7%	0.92 [0.76, 1.12]	
PALOMA-4	-0.06188	0.157634	4.2%	0.94 [0.69, 1.28]	
Subtotal (95% CI)			51.4%	0.81 [0.74, 0.88]	•
Heterogeneity: Chi <sup>2</sup> = 4	.06, df = 6 (P = 0.67)	; I² = 0%			
Test for overall effect: Z	Z = 4.71 (P < 0.00001	)			
4.1.2 Progression-free	e survival				
DAWNA-2	-0.67334	0.152174	4.5%	0.51 [0.38, 0.69]	
MONALEESA-2	-0.57982	0.131496	6.1%	0.56 [0.43, 0.72]	
MONALEESA-3	-0.52763	0.106954	9.2%	0.59 [0.48, 0.73]	-
MONALEESA-7	-0.56212	0.125632	6.7%	0.57 [0.45, 0.73]	-
MONARCH 3	-0.61619	0.132789	6.0%	0.54 [0.42, 0.70]	
PALOMA-2	-0.57982	0.103435	9.8%	0.56 [0.46, 0.69]	-
PALOMA-4	-0.40048	0.128343	6.4%	0.67 [0.52, 0.86]	· · ·
Subtotal (95% CI)			48.6%	0.57 [0.52, 0.63]	•
Heterogeneity: Chi <sup>2</sup> = 2	.43, df = 6 (P = 0.88)	; l² = 0%			
Test for overall effect: Z	Z = 11.99 (P < 0.0000	01)			
Total (95% CI)			100.0%	0.68 [0.64, 0.73]	♦
Heterogeneity: Chi <sup>2</sup> = 3	4.69. df = 13 (P = 0.0	)009): l <sup>2</sup> = 6	63%		
Test for overall effect: 7	7 = 11.73 (P < 0.000)	)1)	/ •		0.05 0.2 1 5 20
Test for subgroup differ	2 - 2 - 2 - 2 - 2 - 2 - 2 - 2 - 2 - 2 -	df = 1 (P <	0 00001)	12 = 96 5%	Favours CET group Favours PET group

Fig. 2 Forest plots of overall survival and progression-free survival associated with CET group versus PET group



Fig. 3 Comparisons of overall survival rate (6–60 months, A: trend of overall survival rate; C: trend of risk ratios) and progression-free survival rate (6–42 months, B: trend of progression-free survival rate; D: trend of risk ratios) associated with CET group versus PET group

hyponatremia, increased aspartate aminotransferase, thrombocytopenia, diarrhea, fatigue, and decreased appetite were found in the CET group (Table S6). The top 5 grade 3–5 AEs were neutropenia (59.39%), leukopenia (24.11%), decreased white blood cell count (12.99%), hypertension (7.03%), and increased alanine aminotransferase (5.91%) (Table 4). Incidence rate of grade 3–5 ILDs also tended to be higher in the CET group without statistical significance (Figure S5).

#### Sensitivity analysis

Analysis of OSR-6 m, PFS (Asian race category), and Grade 3–5 AEs revealed notable heterogeneity. The stability and reliability of the results remained unaffected by the exclusion of any study, as demonstrated by sensitivity analysis (Figure S6).

# **Publication bias**

Funnel plots were observed for survival (OS and PFS), OSR, responses, and AEs summary, suggesting acceptable publication bias (Fig. 6).

### Discussion

Although ET has established itself as the standard treatment for HR+breast cancer patients, its widespread application has gradually unveiled issues of drug resistance, diminishing its benefits and prompting clinicians to explore more effective and rational treatment strategies. Recent studies have highlighted the link between HR+/HER2- breast cancer and abnormal activation of the cyclin D1-CDK4/6 pathway [38]. Notably, CDK4/6 inhibitors such as Palbociclib have garnered FDA approval for breast cancer treatment [39, 40]. The use of CDK4/6 inhibitors in combination with other agents has emerged as a significant focus of recent research. The Phase III trial PALOMA-2 demonstrated Palbociclib's ability to extend the median PFS of patients with advanced HR+breast cancer by over two years, underscoring its substantial efficacy in improving PFS outcomes [14]. Similarly, a study by Slamon et al. provided compelling evidence that Palbociclib in combination with letrozole significantly enhances PFS [37]. Furthermore, investigations have indicated that compared to the fulvestrant

# Table 2 Subgroup analysis of overall survival and progression-free survival

Hit (95% C)         P         Hit (95% C)         P           Total         /         0.81 (0.74, 0.88]         <0.00001         /         0.57 (0.52, 0.6.)         <0.00001           > 65 years         4         0.79 (0.66, 0.91)         0.001         6         0.55 (0.46, 0.62)         <0.00001           Adan         /         0.79 (0.66, 0.91)         0.005         6         0.55 (0.46, 0.62)         <0.00001           Others         5         0.81 (0.73, 0.91)         0.0064         4         0.61 (0.53, 0.70)         <0.00001           CCG PS         0         0.50 (0.67, 0.80)         0.002         7         0.56 (0.50, 0.64)         <0.0001           Hermenopausal status         Portmenopausal or performenopausal         1         0.78 (0.70, 0.88)         <0.00001         4         0.58 (0.50, 0.67)         <0.00001           Hormore receptor status         1         0.78 (0.70, 0.88)         <0.00001         4         0.58 (0.50, 0.67)         <0.00001           Hormore receptor status         1         0.78 (0.70, 0.88)         <0.0001         4         0.58 (0.64, 0.07)         <0.00001           Denove metastatic disease         3         0.59 (0.70, 1.73)         0.12         4         0.58 (0.64, 0.07)         <0.00001	Subgroups	No. of studies	Overall Survival		No. of studies	Progression-free survival		
Total         7         0.81 (0.74, 0.88)         < 0.00001         7         0.57 (0.52, 0.63)         < 0.00001           Age          0.80 (0.69, 0.91)         0.001         6         0.55 (0.49, 0.62)         < 0.00001           > 65 years         4         0.80 (0.69, 0.91)         0.007         6         0.55 (0.49, 0.62)         < 0.00001           Alian         7         0.75 (0.66, 0.93)         0.000         4         0.51 (0.38, 0.02)         < 0.00001           ECOG PS         0         5         0.80 (0.67, 0.96)         0.000         7         0.55 (0.50, 0.64)         < 0.00001           Postmenopausal staus         Postmenopausal         1         0.78 (0.67, 0.88)         < 0.00001         6         0.58 (0.50, 0.67)         < 0.00001           Postmenopausal or perimenopausal         1         0.78 (0.67, 0.80)         0.0000         2         0.56 (0.45, 0.70)         < 0.00001           Denotom metastatic         Bostmenopausal         4         0.89 (0.76, 1.03)         0.12         4         0.38 (0.20, 0.0001           Denotom metastatic disease         3         0.89 (0.76, 1.03)         0.12         4         0.89 (0.42, 0.07]         < 0.00001           Dessest fee interval         Denotom metastatic disease         <			HR (95% CI)	Р	_	HR (95% CI)	Р	
Age         Set Syars         4         0.79 (69,0.91)         0.01         6         0.55 (0.49, 0.62)         <0.0001           > 6.5 yars         4         0.80 (0.64, 0.04)         0.00         6         0.55 (0.49, 0.62)         <0.00001           Race category <td>Total</td> <td>7</td> <td>0.81 [0.74, 0.88]</td> <td>&lt; 0.00001</td> <td>7</td> <td>0.57 [0.52, 0.63]</td> <td>&lt; 0.00001</td>	Total	7	0.81 [0.74, 0.88]	< 0.00001	7	0.57 [0.52, 0.63]	< 0.00001	
<ul></ul>	Age							
> 65 years         4         0.80 (068, 0.94)         0.007         6         0.55 (0.49, 0.62)         < 0.0000	< 65 years	4	0.79 [0.69, 0.91]	0.001	6	0.55 [0.49, 0.62]	< 0.00001	
Reserved by the set of the	> 65 years	4	0.80 [0.69, 0.94]	0.007	6	0.55 [0.49, 0.62]	< 0.00001	
Asia         7         0.78 (066,039)         0.005         6         0.51 (0.38,0.70)         < 0.0001           CHers         5         0.81 (0.73,0.91)         0.0004         4         0.81 (0.53,0.70)         < 0.00001	Race category							
Others         S         0.81 [0.73, 0.71]         0.0004         4         0.61 [0.53, 0.70]         < 0.0001           ECO         S         0.80 [0.67, 0.96]         0.020         7         0.56 [0.50, 0.64]         < 0.0001           Menopausal status         S         0.20 [0.67, 0.96]         0.0001         6         0.58 [0.52, 0.64]         < 0.0001           Permenopausal or permenopausal or permenopausal or 1         0.78 [0.70, 0.86]         < 0.0001         6         0.58 [0.52, 0.64]         < 0.0001           Demone receptor status         I         0.28 [0.57, 0.07]         0.0001         4         0.58 [0.50, 0.67]         < 0.0001           Denove metastatic disease         4         0.89 [0.70, 0.09]         0.001         4         0.58 [0.40, 0.08]         < 0.0001           Denove metastatic disease         4         0.89 [0.70, 0.09]         0.001         3         0.59 [0.40, 0.01]         < 0.0001         0.55 [0.47, 0.46]         < 0.00001           Denove metastatic disease         4         0.89 [0.70, 0.90]         0.014         3         0.59 [0.40, 0.61]         < 0.00001           Stating disease         3         0.77 [0.66, 0.90]         0.014         3         0.59 [0.40, 0.61]         < 0.00001           Ves         3	Asian	7	0.78 [0.66, 0.93]	0.005	6	0.51 [0.38, 0.70]	< 0.0001	
ECGC PS         U </td <td>Others</td> <td>5</td> <td>0.81 [0.73, 0.91]</td> <td>0.0004</td> <td>4</td> <td>0.61 [0.53, 0.70]</td> <td>&lt; 0.00001</td>	Others	5	0.81 [0.73, 0.91]	0.0004	4	0.61 [0.53, 0.70]	< 0.00001	
0         5         0.80 [0.67, 0.96]         0.029         7         0.56 [0.50, 0.64]         <0.00001	ECOG PS							
1         5         0.78 [0.67, 0.90]         0.0009         7         0.57 [0.50, 0.66]         < 0.0001	0	5	0.80 [0.67, 0.96]	0.02	7	0.56 [0.50, 0.64]	< 0.00001	
Memopausal or perimenopausal40.78 [0.70,0.8]0.000060.58 [0.57,0.64]0.0000Permenopausal or perimenopausal0.78 [0.70,0.00]0.000440.58 [0.50,0.67]<0.00001	1	5	0.78 [0.67, 0.90]	0.0009	7	0.57 [0.50, 0.66]	< 0.00001	
Postmenopausal         4         0.78 (0.70, 0.88)         <0.00001	Menopausal status							
Premenopausal or perimenopausal         1         0.78 (0.61, 1.00)         0.05         2         0.56 (0.45, 0.70)         < 0.00001           Hormore receptor status	Postmenopausal	4	0.78 [0.70, 0.88]	< 0.00001	6	0.58 [0.52, 0.64]	< 0.00001	
Hormone receptor status         Hormone receptor status         Hormone receptor status         Hormone receptor status           ER positive +PR positive         4         0.80 [0.70, 0.90]         0.0004         4         0.58 [0.50, 0.67]         < 0.00001	Premenopausal or perimenopausal	1	0.78 [0.61, 1.00]	0.05	2	0.56 [0.45, 0.70]	< 0.00001	
Ep positive + PR positive         4         0.80 [07.0, 090]         0.0004         4         0.58 [0.50, 0.67]         < 0.0001           Drivers         4         0.65 [0.51, 0.79]         < 0.0001         4         0.39 [0.29, 0.52]         < 0.00001           Disease-free interval              < 0.0001            De-novo metastatic disease         4         0.65 [0.48, 1.01]         0.66         6         0.50 [0.42, 0.60]         < 0.0001           Exiting disease         3         0.89 [0.76, 1.03]         0.12         4         0.58 [0.49, 0.68]         < 0.0001           Number of metastatic disease         4         0.77 [0.66, 0.90]         0.01         3         0.59 [0.49, 0.71]         < 0.00001           Viscari metastase at study entry         V         2         0.81 [0.66, 0.99]         0.44         4         0.61 [0.52, 0.72]         0.0001           No         1         0.98 [0.74, 1.30]         0.89         3         0.53 [0.43, 0.65]         0.0001           No         3         0.72 [0.56, 0.88]         0.003         3         0.55 [0.48, 0.67]         0.0001           No         4         0.81 [0.72, 0.91]         0.0004         4         0.55 [0.63,	Hormone receptor status							
Others         4         0.63 (0.51, 0.79)         < 0.0001         4         0.39 (0.29, 0.52)         < 0.0001           Disease         3         0.69 (0.48, 1.01)         0.06         6         0.50 (0.42, 0.00)         0.0001           Denovo metastatic disease         3         0.89 (0.76, 1.03)         0.12         4         0.58 (0.49, 0.68)         < 0.00001	ER positive + PR positive	4	0.80 [0.70, 0.90]	0.0004	4	0.58 [0.50, 0.67]	< 0.00001	
Disease-free interval         Number of metastatic disease         4         0.69 [0.48, 1.01]         0.06         6         0.50 [0.42, 0.60]         <0.00001           Existing disease         3         0.69 [0.76, 1.03]         0.12         4         0.59 [0.49, 0.68]         <0.00001	Others	4	0.63 [0.51, 0.79]	< 0.0001	4	0.39 [0.29, 0.52]	< 0.00001	
De-novo metastatic disease         4         0.69 [0.48, 101]         0.06         6         0.50 [0.42, 0.60]         <000001           Fixing disease         3         0.89 [0.76, 1.03]         0.12         4         0.58 [0.49, 0.68]         <000001	Disease-free interval		- , -			- , -		
Existing disease         3         0.89 [0.76, 1.03]         0.12         4         0.58 [0.49, 0.68]         < 0.0001           Numer of metastatic sites         -         -         -         -         -         -         0.001         3         0.59 [0.49, 0.71]         < 0.00001	De-novo metastatic disease	4	0.69 [0.48, 1.01]	0.06	6	0.50 [0.42, 0.60]	< 0.00001	
Number of metastatic sites         Number of metastatic sites         Number of metastatic sites           < 3	Existing disease	3	0.89 [0.76, 1.03]	0.12	4	0.58 [0.49, 0.68]	< 0.00001	
<3	Number of metastatic sites							
>3         5         0.81 [0.70, 0.94]         0.004         5         0.85 [0.47, 0.64]         <0.0001           Visceral metastases at study entry	< 3	3	0.77 [0.66, 0.90]	0.001	3	0.59 [0.49, 0.71]	< 0.00001	
Visceral metastases at study entry         Visceral metastases at study entry         Visceral metastases         Visceral metastases         Visceral metastase           Yes         2         0.81 [0.66, 0.99]         0.04         4         0.61 [0.52, 0.72]         <0.00001	> 3	5	0.81 [0.70, 0.94]	0.004	5	0.55 [0.47, 0.64]	< 0.00001	
Yes         2         0.81 [0.66, 0.99]         0.04         4         0.61 [0.52, 0.72]         < 0.00011           No         1         0.98 [0.74, 1.30]         0.89         3         0.53 [0.43, 0.65]         < 0.00001	Visceral metastases at study entry							
No         1         0.98 [0.74, 1.30]         0.89         3         0.53 [0.43, 0.65]         < 0.00001           Presence of liver or lung metastases         .	Yes	2	0.81 [0.66, 0.99]	0.04	4	0.61 [0.52, 0.72]	< 0.00001	
Presence of liver or lung metastases           Yes         3         0.39 [0.10, 1.58]         0.19         3         0.57 [0.48, 0.67]         <0.0001           No         3         0.72 [0.60, 0.86]         0.0003         3         0.58 [0.48, 0.71]         <0.0001           Bone-only disease               <0.002         5         0.50 [0.40, 0.64]         <0.0001           No         4         0.81 [0.72, 0.91]         0.0004         4         0.59 [0.52, 0.67]         <0.0001           CDK4/6 inhibitor therapy partner           Dalpiciclib         1         0.77 [0.53, 1.12]         0.17         1         0.51 [0.38, 0.69]         <0.0001           Abemaciclib         2         0.93 [0.79, 1.09]         0.36         2         0.60 [0.51, 0.7]         <0.0001           Abemaciclib         1         0.80 [0.63, 1.01]         0.06         1         0.54 [0.42, 0.70]         <0.00001           Abemaciclib         2         0.93 [0.79, 1.09]         0.36         2         0.60 [0.51, 0.71]         <0.0001           Protocile         3         0.75 [0.57, 0.97]         0.01         5         0.58 [0.51, 0.65]         <0.0001	No	1	0.98 [0.74, 1.30]	0.89	3	0.53 [0.43, 0.65]	< 0.00001	
Yes         3         0.39 [0.10, 1.58]         0.19         3         0.57 [0.48, 0.67]         <0.0001           No         3         0.72 [0.60, 0.86]         0.0003         3         0.58 [0.48, 0.71]         <0.0001           Bone-only disease               <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001	Presence of liver or lung metastases							
No         3         0.72 [0.60, 0.86]         0.0003         3         0.58 [0.48, 0.71]         <0.0001           Bone-only disease	Yes	3	0.39 [0.10, 1.58]	0.19	3	0.57 [0.48, 0.67]	< 0.00001	
Bone-only disease         Bone-only disease         Bone-only disease         Bone-only disease           Yes         5         0.72 [0.58, 0.88]         0.002         5         0.50 [0.40, 0.64]         <0.0001	No	3	0.72 [0.60, 0.86]	0.0003	3	0.58 [0.48, 0.71]	< 0.00001	
Yes         5         0.72         0.58         0.802         5         0.50         0.40         0.6001           No         4         0.81         0.72,01         0.0004         4         0.59         0.50         0.40,0.64]         <0.0001	Bone-only disease							
No         4         0.81 [0.72, 0.91]         0.0004         4         0.52 [0.52, 0.67]         <0.00001           CDK4/6 inhibitor therapy partner	Yes	5	0.72 [0.58, 0.88]	0.002	5	0.50 [0.40, 0.64]	< 0.00001	
CDK4/6 inhibitor therapy partner         International partner         International partner           Dalpiciclib         1         0.77 [0.53, 1.12]         0.17         1         0.51 [0.38, 0.69]         <0.00001	No	4	0.81 [0.72, 0.91]	0.0004	4	0.59 [0.52, 0.67]	< 0.00001	
Dalpiciclib         1         0.77 [0.53, 1.12]         0.17         1         0.51 [0.38, 0.69]         <0.0001	CDK4/6 inhibitor therapy partner							
Ribociclib       3       0.75 [0.67, 0.85]       <0.00001	Dalpiciclib	1	0.77 [0.53, 1.12]	0.17	1	0.51 [0.38, 0.69]	< 0.00001	
Abemaciclib         1         0.80 [0.63, 1.01]         0.06         1         0.54 [0.42, 0.70]         <0.0001           Palbociclib         2         0.93 [0.79, 1.09]         0.36         2         0.60 [0.51, 0.70]         <0.0001           Endocrine therapy partner         U         U         U         0.054 [0.42, 0.70]         <0.0001           Endocrine therapy partner         U         U         U         0.058 [0.51, 0.65]         <0.00001           Anastrozole         -         -         2         0.51 [0.37, 0.71]         <0.0001           Fulvestrant         1         0.73 [0.59, 0.90]         0.003         1         0.59 [0.48, 0.73]         <0.0001           Tamoxifen         1         0.70 [0.47, 1.04]         0.08         1         0.59 [0.49, 0.66]         <0.0001           No         5         0.57 [0.49, 0.66]         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.0001         <0.00001         <0.0001         <0.00001 <td>Ribociclib</td> <td>3</td> <td>0.75 [0.67, 0.85]</td> <td>&lt; 0.00001</td> <td>3</td> <td>0.58 [0.50, 0.66]</td> <td>&lt; 0.00001</td>	Ribociclib	3	0.75 [0.67, 0.85]	< 0.00001	3	0.58 [0.50, 0.66]	< 0.00001	
Palbociclib         2         0.93 [0.79, 1.09]         0.36         2         0.60 [0.51, 0.70]         <0.00001           Endocrine therapy partner	Abemaciclib	1	0.80 [0.63, 1.01]	0.06	1	0.54 [0.42, 0.70]	< 0.00001	
Endocrine therapy partner         Image: Part Part Part Part Part Part Part Part	Palbociclib	2	0.93 [0.79, 1.09]	0.36	2	0.60 [0.51, 0.70]	< 0.00001	
Letrozole         3         0.85 [0.75, 0.97]         0.01         5         0.58 [0.51, 0.65]         <0.0001           Anastrozole         -         -         2         0.51 [0.37, 0.71]         <0.001	Endocrine therapy partner	-			-			
Anastrozole       -       -       2       0.51 [0.37, 0.71]       <0.0001	l etrozole	3	0.85 [0.75, 0.97]	0.01	5	0.58 [0.51, 0.65]	< 0.00001	
Fulvestrant       1       0.73 [0.59, 0.90]       0.003       1       0.59 [0.48, 0.73]       <0.00001	Anastrozole	-	-	-	2	0.51 [0.37, 0.71]	< 0.0001	
Tamoxifen       1       0.70 [0.47, 1.04]       0.08       1       0.59 [0.39, 0.89]       0.01         Previous adjuvant or neoadjuvant endocrine therapy       V       V       V       V       V       V       V       V         Yes       4       0.81 [0.70, 0.94]       0.005       5       0.57 [0.49, 0.66]       <0.0001         No       5       0.79 [0.65, 0.96]       0.02       6       0.56 [0.49, 0.65]       <0.0001         Previous endocrine therapy type       V       V       V       V       V       V       V       V       V         Selective oestrogenreceptor modulator       2       0.88 [0.68, 1.14]       0.32       5       0.61 [0.51, 0.74]       <0.0001         Aromatase inhibitors       2       0.58 [0.40, 0.83]       0.003       5       0.56 [0.47, 0.68]       <0.0001         Previous neoadjuvant or adjuvant chemotherapy       V       V       V       V       V       V       V       V         Yes       3       0.83 [0.70, 0.98]       0.03       3       0.58 [0.43, 0.64]       V       V         No       3       0.79 [0.59, 1.06]       0.11       3       0.53 [0.43, 0.64]       V       V       V <td>Fulvestrant</td> <td>1</td> <td>0.73 [0.59, 0.90]</td> <td>0.003</td> <td>1</td> <td>0.59 [0.48, 0.73]</td> <td>&lt; 0.00001</td>	Fulvestrant	1	0.73 [0.59, 0.90]	0.003	1	0.59 [0.48, 0.73]	< 0.00001	
Previous adjuvant or neoadjuvant endocrine therapy       Yes       4       0.81 [0.70, 0.94]       0.005       5       0.57 [0.49, 0.66]       <0.0001	Tamoxifen	1	0.70 [0.47, 1.04]	0.08	1	0.59 [0.39, 0.89]	0.01	
Yes       4       0.81 [0.70, 0.94]       0.005       5       0.57 [0.49, 0.66]       <0.0001	Previous adjuvant or neoadjuvant endoc	rine therapy						
No       5       0.79 [0.65, 0.96]       0.02       6       0.56 [0.49, 0.65]       <0.0001         Previous endocrine therapy type	Yes	4	0.81 [0.70, 0.94]	0.005	5	0 57 [0 49 0 66]	< 0.00001	
Previous endocrine therapy type         0.09 [0.05, 0.05]         0.02         0         0.05 [0.17, 0.05]         0.0001           Aromatase inhibitors         2         0.88 [0.68, 1.14]         0.32         5         0.61 [0.51, 0.74]         <0.0001	No	5	0.79 [0.65 0.96]	0.02	6	0.56 [0.49 0.65]	< 0.00001	
Selective oestrogenreceptor modulator         2         0.88 [0.68, 1.14]         0.32         5         0.61 [0.51, 0.74]         <0.0001           Aromatase inhibitors         2         0.58 [0.40, 0.83]         0.003         5         0.56 [0.47, 0.68]         <0.0001	Previous endocrine therapy type	-	5 5 [0.005, 0.50]	0.02	~	5.56 [0.15, 0.65]	. 0.00001	
Aromatase inhibitors       2       0.58 [0.40, 0.83]       0.003       5       0.56 [0.47, 0.68]       <0.0001	Selective oestrogenreceptor modulator	2	0.88 [0.68 1 14]	0.32	5	0.61 [0.51 0.74]	< 0.00001	
Previous neoadjuvant or adjuvant chemotherapy         2         0.03         3         0.58 [0.48, 0.70]         < 0.0001           No         3         0.79 [0.59, 1.06]         0.11         3         0.53 [0.43, 0.64]         < 0.0001	Aromatase inhibitors	2	0.58 [0.40, 0.83]	0.003	5	0.56 [0.47. 0.68]	< 0.00001	
Yes         3         0.83 [0.70, 0.98]         0.03         3         0.58 [0.48, 0.70]         < 0.0001           No         3         0.79 [0.59, 1.06]         0.11         3         0.53 [0.43, 0.64]         < 0.0001	Previous neoadiuvant or adiuvant chemo	otherapy	,		-	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		
No         3         0.79 [0.59, 1.06]         0.11         3         0.53 [0.43, 0.64]         < 0.0001	Yes	3	0.83 [0,70. 0.98]	0.03	3	0.58 [0.48. 0.70]	< 0.00001	
	No	3	0.79 [0.59, 1.06]	0.11	3	0.53 [0.43, 0.64]	< 0.00001	

Abbreviations CET: CDK4/6 inhibitors plus endocrine therapy; CDK4/6: Cyclin-dependent kinase 4/6; CI: Confidence interval; ECOG PS: Participants, Intervention, Control, Outcome and Study design Performance Status; HR: Hazard ratio; PET: Placebo plus endocrine therapy

	CET gi	roup	PET gr	oup		Risk Ratio	Risk	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fix	ed, 95% Cl
5.3.1 Objective respo	onse rate							
DAWNA-2	174	303	73	153	3.3%	1.20 [0.99, 1.46]		-
MONALEESA-2	136	334	92	334	3.1%	1.48 [1.19, 1.84]		
MONALEESA-3	77	237	28	128	1.2%	1.49 [1.02, 2.16]		
MONALEESA-7	118	288	86	290	2.9%	1.38 [1.10, 1.73]		
MONARCH 3	163	328	61	165	2.7%	1.34 [1.07, 1.69]		
PALOMA-2	206	444	85	222	3.8%	1.21 [1.00, 1.47]		-
PALOMA-4	63	169	54	1/1	1.8%	1.18 [0.88, 1.59]		<b>A</b>
Subtotal (95% CI)	007	2103	470	1403	10.0%	1.31 [1.20, 1.43]		•
Hotorogonoity Chi2 =	937 275 df - 1	e (D = 0	4/9	20/				
Test for overall effect:	Z = 6.13 (	P < 0.00	001)	J 76				
5.3.2 Clinical benefit	rate							
DAWNA-2	263	303	122	153	5.4%	1.09 [0.99, 1.19]		*
MONALEESA-2	266	334	243	334	8.2%	1.09 [1.01, 1.19]		-
MONALEESA-3	166	237	80	128	3.5%	1.12 [0.96, 1.31]		+
MONALEESA-7	228	288	202	290	6.8%	1.14 [1.03, 1.25]		*
MONARCH 3	256	328	118	165	5.3%	1.09 [0.98, 1.22]		<b>†</b>
PALOMA-2	381	444	158	222	7.1%	1.21 [1.10, 1.32]		*
PALOMA-4	134	169	137	171	4.6%	0.99 [0.89, 1.10]		t
Subtotal (95% CI)		2103		1463	40.8%	1.11 [1.07, 1.15]		1
Total events	1694		1060					
Heterogeneity: Chi <sup>2</sup> = Test for overall effect:	8.12, df = Z = 5.30 (l	6 (P = 0 P < 0.00	.23); l² = : 001)	26%				
5.3.5 Complete resp	onse							
DAWNA-2	2	303	0	153	0.0%	2.53 [0.12, 52.43]		
MONALEESA-2	9	334	7	334	0.2%	1.29 [0.48, 3.41]		
MONALEESA-3	4	237	0	128	0.0%	4.88 [0.26, 89.89]		
MONALEESA-7	7	288	6	290	0.2%	1.17 [0.40, 3.45]		
MONARCH 3	9	328	1	165	0.0%	4.53 [0.58, 35.43]		
PALOMA-2	10	444	5	222	0.2%	1.00 [0.35, 2.89]		
PALOMA-4	2	169	1	171	0.0%	2.02 [0.19, 22.11]		
Subtotal (95% CI)		2103		1463	0.8%	1.53 [0.90, 2.59]		
Total events	43		20					
Heterogeneity: Chi <sup>2</sup> = Test for overall effect:	2.80, df = Z = 1.57 (	6 (P = 0. P = 0.12	.83); l² = ( :)	0%				
5.3.6 Partial respons	e							
DAWNA-2	172	303	73	153	3.3%	1.19 [0.98 1.44]		-
MONALEESA-2	127	334	85	334	2.9%	1.49 [1.19, 1.88]		-
MONALEESA-3	73	237	28	128	1.2%	1 41 [0.96, 2.06]		
MONALEESA-7	111	288	80	290	2.7%	1.40 [1.10, 1.77]		
MONARCH 3	154	328	60	165	2.7%	1.29 [1.02, 1.63]		<b>-</b>
PALOMA-2	196	444	80	222	3.6%	1.23 [1.00, 1.50]		-
PALOMA-4	61	169	53	171	1.8%	1.16 [0.86, 1.57]		<b>+-</b>
Subtotal (95% CI)		2103		1463	18.0%	1.30 [1.19, 1.43]		♦
Total events	894		459					
Heterogeneity: Chi <sup>2</sup> = Test for overall effect:	3.62, df = Z = 5.75 (	6 (P = 0 P < 0.00	.73); l² = ( 001)	0%				
5.3.7 Stable disease								
DAWNA-2	87	303	59	153	2.6%	0.74 [0.57, 0.97]	-	-
MONALEESA-2	95	334	111	334	3.7%	0.86 [0.68, 1.08]	-	†
MONALEESA-3	79	237	44	128	1.9%	0.97 [0.72, 1.31]	-	t
MONALEESA-7	91	288	103	290	3.4%	0.89 [0.71, 1.12]	-	f
MONARCH 3	128	328	82	165	3.7%	0.79 [0.64, 0.96]	-	-
PALOMA-2	175	444	73	222	3.3%	1.20 [0.96, 1.49]		-
PALOMA-4	78	169	90	171	3.0%	0.88 [0.71, 1.09]	7	t
Subtotal (95% CI)		2103		1463	21.7%	0.90 [0.82, 0.98]		
Total events	733		562					
Heterogeneity: Chi <sup>2</sup> = Test for overall effect:	10.62, df = Z = 2.32 (	= 6 (P = ) P = 0.02	0.10); l² = :)	44%				
Total (95% CI)		10515		734F	100 0%	1 14 [1 40 4 40]		
Total (35% CI)	4204	10313	2500	1313	100.0%	1.14 [1.10, 1.18]		ľ
Heterogeneity: Chi2 -	4001 78 20 df -	= 34 (D -	2000	l <sup>2</sup> = 57	%		+	<b>↓ ↓</b>
Test for overall effect:	7 = 7.58 //	- J+ (F < P < 0.00	0.0001);	57	/0		0.01 0.1	1 10 100
Test for subaroup diffe	erences: C	hi² = 48.	43. df = 4	(P < 0	.00001). I²	= 91.7%	Favours PET group	Favours CET group

Fig. 4 Forest plots of responses associated with CET group versus PET group in all patients

monotherapy group, the Ribociclib+fulvestrant combination therapy group exhibits significantly prolonged PFS [12].

This study further confirms the potential benefits of CET for HR+/HER2- breast cancer patients in terms of OS and PFS. However, previous clinical trials have yielded inconsistent OS data, leading to controversy

regarding whether OS benefits are achieved. Notably, OS outcomes in combined drug treatment groups in the PALOMA-1 and PALOMA-3 studies did not demonstrate statistically significant differences. Nevertheless, recent updates from the MONALEESA-7 and MONA-LEESA-3 studies suggest significantly better OS for HR+/HER2- breast cancer in the CET group [11, 12, 41, 42].

Study or Subaroup		oub	PET are	DUD		Risk Ratio	
	Events	Total	Events	Total	Weight	M-H. Fixed, 95% Cl	M-H. Fixed. 95% Cl
1.1.1 Total adverse eve	ents						
DAWNA-2	302	303	143	153	7.0%	1.07 [1.02, 1.11]	
MONALEESA-2	331	334	323	334	11.9%	1.02 [1.00, 1.05]	Ī
MONALEESA-3	235	237	124	128	6.0%	1.02 [0.99, 1.06]	[
MONALEESA-7	283	288	273	290	10.1%	1.04 [1.01, 1.08]	
MONARCH 3	323	328	152	165	7.5%	1.07 [1.02, 1.12]	[
PALOMA-2	439	444	212	222	10.5%	1.04 [1.00, 1.07]	
PALOMA-4	168	169	155	171	5.7%	1.10 [1.04, 1.15]	
Fotol events	2094	2103	1202	1403	30.0%	1.05 [1.03, 1.00]	
lotar events	2001	6 (P = 0	1302	45%			
Telefogeneity. Chir - To	= 6 81 (P	0 (F = 0. C < 0.000	09), I= - 01)	4070			
	- 0.01 (1	< 0.000	01)				
1.1.2 Grade 3-5 advers	e events					Modified by Random-effects model	
DAWNA-2	274	303	20	153	2.9%	6.92 [4.59, 10.43]	-
MONALEESA-2	297	334	140	334	3.1%	2.12 [1.86, 2.42]	-
MONALEESA-3	211	237	54	128	3.1%	2.11 [1.71, 2.60]	-
MONALEESA-7	221	288	86	290	3.1%	2.59 [2.14, 3.12]	-
MONARCH 3	191	328	40	165	3.0%	2.40 [1.81, 3.19]	-
PALOMA-2	336	444	54	222	3.1%	3.11 [2.45, 3.95]	-
PALOMA-4	149	169	36	171	3.0%	4.19 [3.12, 5.63]	
Subtotal (95% CI)		2103		1463	21.3%	2.96 [2.30, 3.81]	•
otal events	1679		430				
leterogeneity: Tau <sup>2</sup> = 0.	10; Chi <sup>2</sup>	= 52.40,	df = 6 (F	< 0.00	0001); l² =	89%	
est for overall effect: Z	= 8.44 (F	o < 0.000	01)				
.1.3 Serious adverse e	events	0.5-5	-	4		0.50.50.40.55.155	
AWNA-2	2	303	0	153	0.0%	2.53 [0.12, 52.43]	
IONALEESA-2	71	334	39	334	1.4%	1.82 [1.27, 2.61]	
IUNALEESA-3	68	237	21	128	1.0%	1.75 [1.13, 2.71]	
IUNALEESA-7	52	288	34	290	1.3%	1.54 [1.03, 2.30]	<u> </u>
ALUMA-2 Subtotal (95% CI)	87	444	28	222	1.4%	1.55 [1.05, 2.30]	•
otol ovorto	200	1000	100	1121	5.1%	1.07 [1.37, 2.03]	•
otal events	280	(D - 0 0	122	.o/			
leterogeneity: Chi* = 0.0	= 5.00 (5)	P = 0.9	6); I* = ( 01)	1%			
est for overall effect. Z	= 5.09 (P	< 0.000	01)				
1 4 Adverse event lea	nding to	treatmer	nt disco	ntinuat	tion		
AWNA-2	1	303	0	153	0.0%	1 52 [0 06 37 09]	
IONAL FESA-2	25	334	7	334	0.0%	3 57 [1 57 8 14]	
IONAL EESA-3	21	237	5	128	0.2%	2 27 [0 88 5 87]	
IONAL FESA-7	10	288	9	290	0.3%	1 12 [0.46 2 71]	
IONARCH 3	54	328	5	165	0.2%	5.43 [2.22, 13.32]	
		020	•		0.270	0.10 [2.22, 10.02]	
	54	444	13	222	0.6%	2.08 [1.16, 3.72]	
PALOMA-2	54 13	444 169	13 5	222 171	0.6%	2.08 [1.16, 3.72] 2.63 [0.96, 7.22]	
PALOMA-2 PALOMA-4 Subtotal (95% CI)	54 13	444 169 2103	13 5	222 171 1463	0.6% 0.2% 1.9%	2.08 [1.16, 3.72] 2.63 [0.96, 7.22] 2.61 [1.88, 3.62]	 ►
PALOMA-4 Subtotal (95% CI) Fotal events	54 13 178	444 169 2103	13 5 44	222 171 1463	0.6% 0.2% 1.9%	2.08 [1.16, 3.72] 2.63 [0.96, 7.22] 2.61 [1.88, 3.62]	•
PALOMA-4 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 7.4 Fest for overall effect <sup>+</sup> 7	54 13 178 42, df = 6 = 5,76 /F	444 169 2103 6 (P = 0.2 P < 0.000	13 5 44 8); I <sup>2</sup> = 1 01)	222 171 1463 9%	0.6% 0.2% 1.9%	2.08 [1.16, 3.72] 2.63 [0.96, 7.22] 2.61 [1.88, 3.62]	•
PALOMA-2 PALOMA-4 Subtotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = 7.4 Fest for overall effect: Z	54 13 178 42, df = 6 = 5.76 (F	444 169 2103 6 (P = 0.2 P < 0.000	13 5 44 8); I <sup>2</sup> = 1 01)	222 171 1463 9%	0.6% 0.2% 1.9%	2.08 [1.16, 3.72] 2.63 [0.96, 7.22] 2.61 [1.88, 3.62]	•
ALOMA-4 Subtotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = 7.4 Fest for overall effect: Z I.1.5 Adverse event lea	54 13 178 42, df = 6 = 5.76 (F ading to	444 169 2103 6 (P = 0.2 P < 0.000 dose rec	13 5 44 8); I <sup>2</sup> = 1 01) Iuction	222 171 1463 9%	0.6% 0.2% 1.9%	2.08 [1.16, 3.72] 2.63 [0.96, 7.22] 2.61 [1.88, 3.62] Modified by Random-effects model	•
ALOMA-4 Subtotal (95% CI) Fotal events Heterogeneity: Chi <sup>2</sup> = 7.4 Fest for overall effect: Z I.1.5 Adverse event lea DAWNA-2	54 13 178 42, df = 6 = 5.76 (F ading to 85	444 169 2103 6 (P = 0.2 P < 0.000 dose rec 303	13 5 44 8); I <sup>2</sup> = 1 01) Iuction 0	222 171 1463 9% 153	0.6% 0.2% 1.9% 0.5%	2.08 [1.16, 3.72] 2.63 [0.96, 7.22] 2.61 [1.88, 3.62] Modified by Random-effects model 86.63 [5.41, 1386.75]	• •
ALOMA-4 Subtotal (95% CI) Total events leterogeneity: Chi <sup>2</sup> = 7. est for overall effect: Z .1.5 Adverse event les DAWNA-2 MONALEESA-2	54 13 178 42, df = 6 = 5.76 (F ading to 85 180	444 169 2103 6 (P = 0.2 9 < 0.000 dose rec 303 334	13 5 44 8); I <sup>2</sup> = 1 01) Iuction 0 23	222 171 1463 9% 153 334	0.6% 0.2% 1.9% 0.5% 2.9%	2.08 [1.16, 3.72] 2.63 [0.66, 7.22] 2.61 [1.88, 3.62] Modified by Random-effects model 86.63 [5.41, 1386.75] 7.83 [5.21, 11.75]	• •
ALOMA-4 subtotal (95% CI) iotal events leterogeneity: Chi <sup>2</sup> = 7.4 est for overall effect: Z .1.5 Adverse event let MWNA-2 MONALEESA-2 MONALEESA-3	54 13 42, df = 6 = 5.76 (F ading to 85 180 90	444 169 2103 6 (P = 0.2 < 0.000 dose rec 303 334 237	13 5 44 8); I <sup>2</sup> = 1 01) Iuction 0 23 5	222 171 1463 9% 153 334 128	0.6% 0.2% 1.9% 0.5% 2.9% 2.1%	2.08 [1.16, 3.72] 2.63 [0.66, 7.22] 2.61 [1.88, 3.62] Modified by Random-effects model 86.63 [5.41, 1386.75] 7.83 [5.21, 11.75] 9.72 [4.06, 23.31]	• •
ALOMA-2 ALOMA-4 Jubtotal (95% CI) iotal events leterogeneity: Chi <sup>2</sup> = 7. est for overall effect: Z .1.5 Adverse event lea DAWNA-2 IONALEESA-2 IONALEESA-7	54 13 178 42, df = 6 5.76 (F ading to 85 180 90 219	444 169 2103 6 (P = 0.2 P < 0.000 dose rec 303 334 237 288	13 5 44 8); I <sup>2</sup> = 1 01) Iuction 0 23 5 108	222 171 1463 9% 153 334 128 290	0.6% 0.2% 1.9% 0.5% 2.9% 2.1% 3.1%	2.08 [1.16, 3.72] 2.63 [0.66, 7.22] 2.61 [1.88, 3.62] Modified by Random-effects model 86.63 [5.41, 1366.75] 7.83 [5.21, 11.75] 9.72 [4.05, 23.31] 2.04 [1.73, 2.40]	• •
ALOMA-2 ALOMA-2 ALOMA-4 viabtotal (95% CI) viale events leterogeneity: Chi <sup>a</sup> = 7.4 est for overall effect: Z .1.5 Adverse event lea JAWNA-2 IONALEESA-2 IONALEESA-3 IONALEESA-3 IONACH 3	54 13 178 42, df = 6 = 5.76 (F ading to 85 180 90 219 152	444 169 2103 6 (P = 0.2 P < 0.000 dose rec 303 334 237 288 328	13 5 44 8); I <sup>2</sup> = 1 01) Iuction 0 23 5 108 10	222 171 1463 9% 153 334 128 290 165	0.6% 0.2% 1.9% 0.5% 2.9% 2.1% 3.1% 2.6%	2.08 [1.16, 3.72] 2.83 [0.66, 7.22] 2.61 [1.86, 3.62] Modified by Random-effects model 86.63 [5.41, 1386.75] 7.83 [5.21, 11.75] 9.72 [4.05, 23.31] 2.04 [1.73, 2.40] 7.65 [4.14, 10]	• •
ALOMA-2 ALOMA-2 ALOMA-4 ValOMA-2 (stal events leterogeneity: Chi <sup>2</sup> = 7. 'est for overall effect: Z .1.5 Adverse event les JAWNA-2 HONALEESA-2 HONALEESA-3 HONALEESA-7 HONALEESA-7 HONALECH 3 'ALOMA-2	54 13 178 42, df = 6 = 5.76 (F ading to 85 180 90 219 152 160	444 169 2103 6 (P = 0.2 6 < 0.000 dose rec 303 334 237 288 328 444	13 5 44 8); I <sup>2</sup> = 1 01) Iuction 0 23 5 108 10 3	222 171 1463 9% 153 334 128 290 165 222	0.6% 0.2% 1.9% 0.5% 2.9% 2.1% 3.1% 2.6% 1.7%	2.08 [1.16, 3.72] 2.63 [0.66, 7.22] 2.61 [1.88, 3.62] Modified by Random-effects model 86, 63 [6, 41, 1386, 75] 7.83 [5, 21, 41, 75] 9.72 [4.05, 23, 31] 2.04 [1, 73, 2.40] 7.65 [4, 15, 14, 10] 2.65 [7 [6, 16, 26, 11]	• •
ALOMA-2 ALOMA-2 ALOMA-4 otal events leterogeneity: Chi <sup>p</sup> = 7.4 est for overall effect: Z .1.5 Adverse event lez MWNA-2 IONALEESA-2 IONALEESA-7 IONARCH 3 ALOMA-4	54 13 178 42, df = 6 = 5.76 (F ading to 85 180 90 219 152 160 48	444 169 2103 6 (P = 0.2 6 < 0.000 dose rec 303 334 237 288 328 444 169	13 5 44 8); I <sup>2</sup> = 1 01) <b>luction</b> 0 23 5 108 10 3 0	222 171 1463 9% 153 334 128 290 165 222 171	0.6% 0.2% 1.9% 0.5% 2.9% 2.1% 3.1% 2.6% 1.7%	2.08 [1.16, 3.72] 2.63 [0.66, 7.22] 2.61 [1.86, 3.62] Modified by Random-effects model 86.63 [5.41, 1366.75] 7.83 [52, 11.75] 9.72 [4.05, 23.31] 2.04 [1.73, 2.40] 7.65 [4.15, 14, 10] 2.66.7 [8.61, 82.61] 86.14 [6.10, 1757.75]	• •
ALOMA-2 ALOMA-2 ALOMA-4 (Jalovents leterogeneity: Chi <sup>2</sup> = 7. 'est for overall effect: Z .1.5 Adverse event lez JAWNA-2 JAWNA-2 ALOMA-2 JALOMA-2 JALOMA-4 Libtotati (95% CI)	54 13 178 42, df = 6 = 5.76 (F ading to 85 180 90 219 152 160 48	444 169 2103 6 (P = 0.2 C < 0.000 dose rec 303 334 237 288 328 444 169 2103	13 5 44 8); I <sup>2</sup> = 1 01) Iuction 0 23 5 108 10 3 0	222 171 1463 9% 153 334 128 290 165 222 171 1463	0.6% 0.2% 1.9% 0.5% 2.9% 2.1% 3.1% 2.6% 1.7% 0.5% 13.5%	2.08 [1.16, 3.72] 2.63 [0.66, 7.22] 2.64 [1.88, 3.62] Modified by Random-effects model 86.63 [5.41, 1386,75] 7.83 [5.21, 11.76] 9.72 [4.05, 72.33] 2.04 [1.73, 2.40] 7.85 [4.15, 14.10] 2.66,7 [2.61, 82.61] 88.14 [6.10, 1578,75] 11.70 [3.76, 83.63]	
ALOWA-2 ALOMA-4 ALOMA-4 valotati (95% CI) otal events leterogeneity: Ch <sup>2</sup> = 7. est for overall effect: Z .1.5 Adverse event let AWNA-2 TONALEESA-2 IONALEESA-3 IONALEESA-7 IONACCH 3 ALOMA-2 ALOMA-4 vabotal (95% CI) otal events	54 13 178 42, df = 6 = 5.76 (F ading to 85 180 90 219 152 160 48 934	444 169 2103 6 (P = 0.2 C < 0.000 dose rec 303 334 237 288 328 444 169 2103	13 5 44 8); I <sup>2</sup> = 1 01) Iuction 0 23 5 108 10 3 0 149	222 171 1463 9% 153 334 128 290 165 222 171 1463	0.6% 0.2% 1.9% 0.5% 2.9% 2.1% 3.1% 2.6% 1.7% 0.5% 13.5%	2.08 [1.16, 3.72] 2.63 [0.66, 7.22] 2.61 [1.86, 3.62] Modified by Random-effects model 86 63 [5.41, 1386.75] 7.83 [5.21, 11.75] 9.72 [4.05, 23.31] 2.04 [1.73, 2.40] 7.65 [4.15, 14.10] 26.67 [6.10, 1578.75] 11.70 [3.76, 36.36]	· · · · · · · · · · · · · · · · · · ·
ALOMA-2 ALOMA-2 ALOMA-4 calevents eterogeneity: Chi <sup>2</sup> = 7. est for overall effect: Z avwna-2 lonALEESA-3 lonALEESA-3 lonALEESA-3 lonALEESA-3 lonALEESA-3 lonACH 3 ALOMA-2 ALOMA-2 ALOMA-2 atoms eterogeneity: Tau <sup>2</sup> = 1.	54 13 178 42, df = 6 = 5.76 (F adding to 85 180 90 219 152 160 48 934 89; Chi <sup>2</sup>	444 169 2103 6 (P = 0.2 P < 0.000 dose rec 303 334 237 288 328 444 169 2103 = 141.69	13 5 44 8); l <sup>2</sup> = 1 01) luction 0 23 5 108 10 3 0 149 , df = 6 (	222 171 1463 9% 153 334 128 290 165 222 171 1463 P < 0.0	0.6% 0.2% 1.9% 0.5% 2.9% 2.1% 3.1% 2.6% 1.7% 0.5% 13.5%	2.08 [1.16, 3.72] 2.63 [0.66, 7.22] 2.64 [1.88, 3.62] Modified by Random-effects model 86.63 [5.41, 1386.75] 7.83 [5.21, 11.75] 9.72 [4.05, 23.31] 2.04 [1.73, 2.40] 7.65 [4.51, 41.01] 2.66 7 [8.61, 82.61] 98.14 [6.10, 1757.75] 11.70 [3.76, 36.36] = 96%	• • • • •
ALOWA-2 ALOMA-4 ALOMA-4 ALOMA-4 otal events leterogeneity: Chi <sup>2</sup> = 7. est for overall effect: Z .1.5 Adverse event lea AWNA-2 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONACH 3 ALOMA-2 ALOMA-2 ALOMA-4 ubtotal (95% CI) otal events leterogeneity: Tau <sup>2</sup> = 1. est for overall effect: Z	54 13 178 42, df = 6 = 5.76 (F ading to 85 180 90 219 152 160 48 934 89; Chi <sup>2</sup> = 4.25 (F	444 169 2103 6 (P = 0.2 C < 0.000 dose rec 303 334 237 288 328 444 169 2103 = 141.69 C < 0.000	13 5 44 8); I <sup>2</sup> = 1 01) <b>luction</b> 0 23 5 108 10 3 0 149 , df = 6 ( 1)	222 171 1463 9% 153 334 128 290 165 222 171 1463 P < 0.0	0.6% 0.2% 1.9% 0.5% 2.9% 2.1% 3.1% 2.6% 1.7% 0.5% 13.5%	2.08 [1.16, 3.72] 2.63 [0.66, 7.22] 2.61 [1.88, 3.62] Modified by Random-effects model 86, 63 [6, 41, 1386, 75] 7.83 [5, 21, 41, 75] 9.72 [4.05, 23, 31] 2.04 [1, 73, 2.40] 7.65 [4, 16, 12, 61] 98, 14 [6, 10, 1578, 75] 11,70 [3.76, 36, 36] = 96%	· ·
ALOMA-2 ALOMA-4 ALOMA-4 ALOMA-4 Iderogeneity: Chi <sup>2</sup> = 7. est for overall effect: Z .1.5 Adverse event lez XWNA-2 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONACEESA-3 IONACESA-3 I	54 13 178 42, df = 6 = 5.76 (F ading to 85 180 90 219 152 160 48 934 89; Chi <sup>2</sup> = 4.25 (F	444 169 2103 6 (P = 0.2 C < 0.000 dose rec 303 334 237 288 444 169 2103 = 141.69 C < 0.000 dose rec 303 334 237 288 444 169 2103	13 5 44 8); I <sup>2</sup> = 1 01) luction 0 23 5 108 10 3 0 149 , df = 6 ( 1)	222 171 1463 9% 153 334 128 290 165 222 171 1463 P < 0.0	0.6% 0.2% 1.9% 0.5% 2.9% 2.1% 3.1% 2.6% 1.7% 0.5% 13.5%	2.08 [1.16, 3.72] 2.63 [0.66, 7.22] 2.61 [1.88, 3.62] Modified by Random-effects model 86.63 [5.41, 1366.75] 7.83 [5.21, 11.75] 9.72 [4.05, 23.31] 2.04 [1.73, 2.40] 7.65 [4.15, 14.10] 26.67 [8.61, 82.61] 98.14 [5.10, 1578.75] 11.70 [3.76, 38.36] = 96%	
ALOMA-2 ALOMA-2 ALOMA-4 ALOMA-4 otal events leterogeneity: Chi <sup>2</sup> = 7. est for overall effect: Z .1.5 Adverse event lea AVWA-2 ONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONACA ALOMA-4 ALOMA-4 ALOMA-4 ALOMA-4 Jubtotal (95% CI) otal events leterogeneity: Tau <sup>2</sup> = 1. est for overall effect: Z .1.6 Adverse event lea	54 13 178 42, df = 6 = 5.76 (F ading to 85 180 90 219 152 160 48 934 89; Chi <sup>2</sup> = 4.25 (F ading to	444 169 2103 6 (P = 0.2 6 < 0.000 dose rec 303 334 237 288 328 444 169 2103 = 141.69 > < 0.000 dose into dose into 200 dose into 200 200 dose into 200 200 200 200 200 200 200 20	13 5 44 8); I <sup>2</sup> = 1 01) 1uction 0 23 5 108 100 3 0 149 , df = 6 ( 1) erruptio	222 171 1463 9% 153 334 128 290 165 222 171 1463 P < 0.0	0.6% 0.2% 1.9% 2.9% 2.1% 3.1% 2.6% 13.5% 00001); l <sup>2</sup>	2.08 [1.16, 3.72] 2.63 [0.66, 7.22] 2.64 [1.88, 3.62] Modified by Random-effects model 86.63 [5.41, 1386,75] 7.83 [5.21, 11.75] 9.72 [405, 23.31] 2.04 [1.73, 2.40] 7.65 [4.15, 14.10] 2.66,7 [2.61, 82.21] 88.14 [6.10, 1578,75] 11.70 [3.76, 36.36] = 96%	· · · · · · · · · · · · · · · · · · ·
ALOMA-2 ALOMA-4 ALOMA-4 ALOMA-4 Cotal events leterogeneity: Chi <sup>2</sup> = 7. est for overall effect: Z 1.5 Adverse event lea WAWA-2 10NALEESA-3 10NALEESA-3 10NALEESA-3 10NALEESA-3 10NACH 3 ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 1.6 Adverse event lea WWAA-2 10NALEESA-2	54 13 178 42, df = 6 = 5.76 (F ading to 85 180 90 219 152 160 48 934 89; Chi <sup>2</sup> = 4.25 (F ading to 194 257	444 169 2103 6 (P = 0.2 6 < 0.000 dose rec 303 334 237 288 328 444 169 2103 = 141.69 P < 0.000 dose int 303 324	13 5 44 8); I <sup>2</sup> = 1 01) luction 0 23 5 108 10 3 0 149 , df = 6 ( 1) erruptio	222 171 1463 9% 153 334 128 290 165 222 171 1463 P < 0.0	0.6% 0.2% 1.9% 0.5% 2.9% 2.1% 3.1% 2.6% 1.7% 0.5% 13.5% 00001); I <sup>2</sup> 0.5% 3.1%	2.08 [1.16, 3.72] 2.63 [0.66, 7.22] 2.61 [1.86, 3.62] Modified by Random-effects model 86 63 [6.41, 1386.75] 7.83 [5.21, 11.75] 9.72 [4.05, 23.31] 2.04 [1.73, 2.40] 7.65 [4.15, 14.10] 26.67 [6.6, 18.261] 98.14 [6.10, 1578.75] 11.70 [3.76, 36.36] = 96%	
ALOMA-2 ALOMA-2 ALOMA-4 ALOMA-4 otal events eterogeneity: Chi <sup>2</sup> = 7. est for overall effect: Z AWNA-2 ALOMA-ESA-3 IONALEESA-3 IONALEESA-3 IONACH 3 ALOMA-2 AL	54 13 178 42, df = 6 = 5.76 (F ading to 85 180 90 219 152 160 48 934 89; Chi <sup>2</sup> = 4.25 (F ading to 194 257 70	444 169 2103 6 (P = 0.2 9 < 0.000 dose rec 303 334 237 288 328 444 169 2103 = 141.69 9 < 0.000 dose int 303 334 227	13 5 44 8); I <sup>2</sup> = 1 01) Iuction 0 23 5 108 10 3 0 149 , df = 6 ( 1) erruptio	222 171 1463 9% 153 334 128 29% 165 222 171 1463 P < 0.0 153 334	0.6% 0.2% 1.9% 0.5% 2.9% 2.1% 3.1% 2.6% 1.7% 0.5% 13.5% 00001); I <sup>2</sup> 0.5% 3.1%	2.08 [1.16, 3.72] 2.63 [0.66, 7.22] 2.64 [1.88, 3.62] Modified by Random-effects model 66.63 [5.41, 1386,75] 7.83 [5.21, 11.75] 9.72 [4.05, 23.31] 2.04 [1.73, 2.40] 7.65 [4.10] 26.67 [8.61, 82.61] 80.14 [0.10, 1578,75] 11.70 [3.76, 36.36] = 96%	
ALOWA-2 ALOMA-2 ALOMA-4 ALOMA-4 valtotat (95% CI) otal events leterogeneity: Chi <sup>2</sup> = 7. est for overall effect: Z .1.5 Adverse event let AWWA-2 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONARCH 3 ALOMA-2 ALOMA-4 ubtotat (95% CI) otal events leterogeneity: Tau <sup>2</sup> = 1. est for overall effect: Z .1.6 Adverse event let AWWA-2 IONALEESA-3 IONALEESA-3 IONALEESA-3	54 13 178 42, df = 6 = 5.76 (F ading to 85 180 90 219 152 160 48 934 89; Chi <sup>2</sup> = 4.25 (F ading to 194 257 78 80 80	444 169 2103 6 (P = 0.2 9 < 0.000 dose rec 303 324 237 288 328 444 169 2103 = 141.69 9 < 0.000 dose int 303 334 237 288	13 5 44 8); I <sup>2</sup> = 1 01) luction 0 23 5 108 10 3 0 149 9 , df = 6 ( 1) erruptic	222 171 1463 99% 153 334 128 290 165 222 171 1463 0 165 222 171 1463 171 1463 200	0.6% 0.2% 1.9% 0.5% 2.9% 2.1% 3.1% 2.6% 1.7% 0.5% 13.5% 3.1% 2.0% 2.0% 2.7%	2.08 [1.16, 3.72] 2.63 [0.66, 7.22] 2.61 [1.86, 3.62] Modified by Random-effects model 86, 63 [6, 41, 1386, 75] 7.83 [5, 21, 41, 75] 9.72 [4.05, 23, 31] 2.04 [1, 73, 2.40] 7.65 [4, 15, 14, 10] 2.65 7 [6, 6, 22, 61] 98, 14 [6, 10, 1578, 75] 11, 70 [3.76, 36, 36] = 96% Modified by Random-effects model 197.06 [1, 237, 3140, 36] 1.55 [168, 2.26] 1.55 [168, 2.26] 1.55 [168, 2.26]	
ALOMA-2 ALOMA-2 ALOMA-4 ALOMA-4 Cotal events leterogeneity: Chi <sup>2</sup> = 7. est for overall effect: Z .1.5 Adverse event lez WWNA-2 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONARCH 3 ALOMA-2 ALOMA-4 ALOMA-4 ALOMA-4 ALOMA-4 ALOMA-4 SALOMA-2 ALOMA-4 SALOMA-2 ALOMA-4 SALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 SALOMA-2 ALOMA-2 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-7 ALOMA-2 ALOMA-2	54 13 178 42, df = 6 5.76 (F 85 180 90 219 152 160 48 934 89; Chi <sup>2</sup> = 4.25 (F 194 257 78 89 292	444 444 169 2103 3 (P = 0.2 C = 0.000 dose rec 303 334 237 288 328 444 169 2103 = 141.69 C = 0.000 dose rec 303 334 237 288 328 444 169 2103 34 240 334 240 240 334 240 240 334 240 240 334 240 240 334 240 240 334 240 240 240 334 240 240 334 240 240 334 240 240 334 240 240 334 240 240 334 240 240 240 240 240 240 240 24	$\begin{array}{c} 13\\ 5\\ 44\\ 8); \ l^{2}=1\\ 001) \\ \begin{array}{c} 1\\ 0\\ 23\\ 5\\ 108\\ 10\\ 3\\ 0\\ 149\\ 9\\ , \ df=6\\ (1) \\ 132\\ 4\\ 15\\ 22\\ 2\\ 2\\ 2\\ 2\\ 2\\ 2\\ 2\\ 2\\ 2\\ 2\\ 2\\ 2$	222 171 1463 9% 153 334 128 290 165 222 171 1463 P < 0.0 n 153 334 128 290 0 222 271 153 334 290 0 222 222 222 222 222 222 222 222 2	0.6% 0.2% 1.9% 0.5% 2.9% 2.1% 3.1% 2.6% 1.7% 0.5% 3.1% 3.1% 3.1% 3.1% 3.1% 3.1% 3.1% 3.1	2.08 [1.16, 3.72] 2.63 [0.06, 7.22] 2.64 [1.88, 3.62] Modified by Random-effects model 86.63 [5.41, 1386.75] 7.83 [5.21, 11.75] 9.72 [4.05, 23.31] 2.04 [1.73, 2.40] 7.65 [4.51, 41.01] 26.67 [8.61, 82.61] 98.14 [6.10, 1578.75] 11.70 [3.76, 36.36] = 96% Modified by Random-effects model 197.06 [12.37, 3140.36] 197.06 [2.37, 3140.36] 10.53 [3.95, 28.10] 5.97 [3.54, 10.07] 1 at [1.96, 12.91]	
ALOMA-2 ALOMA-2 ALOMA-4 ALOMA-4 otal events leterogeneity: Chi <sup>2</sup> = 7. est for overall effect: Z .1.5 Adverse event lez AWNA-2 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONACA JUSTORI (S% CI) otal events leterogeneity: Tau <sup>2</sup> = 1. est for overall effect: Z .1.6 Adverse event lez AWNA-2 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-7 ALOMA-2 AI OMA-4 AI OMA-4	54 13 178 e 6 42, df = 6 42, df = 6 842, df = 6 843, d	444 449 2103 6 (P = 0.2 9 < 0.000 dose rec 303 334 237 288 328 444 169 2103 = 141.69 9 < 0.000 dose int 303 334 237 288 444 169	13 5 44 8); I <sup>2</sup> = 1 001) 1 <b>luction</b> 0 23 5 108 100 23 5 108 100 3 0 149 9 , df = 6 ( 1) 1 122 4 15 92 0	222 171 1463 9% 153 334 128 290 165 222 171 1463 P < 0.0 n 153 334 128 290 222 290 222	0.6% 0.2% 1.9% 0.5% 2.9% 2.1% 3.1% 2.6% 1.7% 0.5% 3.1% 0.5% 3.1% 2.7% 3.1% 0.5%	2.08 [1.16, 3.72] 2.63 [0.06, 7.22] 2.61 [1.86, 3.62] Modified by Random-effects model 86.63 [5.41, 1386,75] 7.83 [5.21, 11.75] 9.72 [4.05, 23.31] 2.04 [1.73, 2.40] 7.65 [4.15, 14, 10] 2.66 7 [8.6], 82.61] 98.14 [6.10, 1578.75] 11.70 [3.76, 36.36] = 96% Modified by Random-effects model 197.06 [1.237, 3140.36] 1.95 [1.237, 3140.36] 1.95 [1.237, 3140.36] 2.91 [1.51, 52, 51] 1.55 [1.53, 1.91] 2.41 [1.15, 1.93, 1.91]	
ALOMA-2 ALOMA-2 ALOMA-4 ALOMA-4 leterogeneity: Chi <sup>2</sup> = 7. est for overall effect: Z st for overall effect: Z in ChalEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONACET 3 ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 int for overall effect: Z i.1.6 Adverse event lea AWWA-2 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-7 ALOMA-4 JUbta1 (05% CI)	54 13 17, df = (- 42, df = (- 85, 76 (F 85, 76 (F 85, 76 (F) 84 180 90 90 48 90 48 93 44 89; Chi <sup>2</sup> + 152 160 48 89; Chi <sup>2</sup> + 257 78 8 84 30; Chi 2 42, ff = (- 152 160 48 152 160 48 152 160 152 160 152 160 160 160 160 160 160 160 160 160 160	444 169 2103 8 (P = 0.2 203 8 (P = 0.2 303 303 303 303 203 303 203 303 203 2	$\begin{array}{c} 13\\ 5\\ 44\\ 8); \  i^{2}=1\\ 001) \end{array}$	222 1711 1463 99% 153 334 128 290 165 222 1711 1463 0 8 290 165 222 1711 1463 0 222 1711 1298	0.6% 0.2% 1.9% 0.5% 2.9% 2.1% 0.5% 13.5% 0.5% 13.5% 0.0001); I <sup>2</sup> 0.5% 3.1% 2.0% 2.0% 2.7% 3.1% 2.0%	2.08 [1.16, 3.72] 2.63 [0.06, 7.22] 2.64 [1.88, 3.62] Modified by Random-effects model 66.63 [5.41, 1366.75] 7.83 [5.21, 11.75] 9.72 [4.05, 23.31] 2.04 [1.73, 2.40] 7.65 [4.15, 14.10] 2.66.7 [8.61, 82.61] 99.14 [6.10, 1757.75] 11.70 [3.76, 36.36] = 96% Modified by Random-effects model 197.06 [12.37, 3140.36] 1.95 [1.68, 2.25] 10.53 [3.95, 28.10] 5.97 [3.54, 10.07] 1.61 [1.56, 1.9857.06] 5.67 [2.51, 24.31]	
ALOMA-2 ALOMA-2 ALOMA-4 ValLOMA-4 (95% CI) otal events leterogeneity: Chi <sup>2</sup> = 7. 'est for overall effect: Z JAWNA-2 AONALEESA-3 (ONALEESA-3 (ONALEESA-3 (ONARCH 3 'ALOMA-2 'A	54 43 178 42, df = { 5, 76 (F 85 180 90 90 219 152 180 934 489; Chi <sup>2</sup> F 160 257 160 257 78 89 937 119 1034	444 169 2103 5 (P = 0.2 0 0.000 dose rec 303 334 237 288 328 244 169 2103 = 141.69 > < 0.000 dose int 303 334 444 169 1775	$\begin{array}{c} 13\\ 5\\ 44\\ 8); \  ^{2}=1\\ 01)\\ \begin{array}{c} 1\\ 10\\ 23\\ 5\\ 108\\ 10\\ 3\\ 0\\ 149\\ 9\\ 0\\ 149\\ 15\\ 10\\ 132\\ 4\\ 15\\ 92\\ 0\\ 0\\ 243\\ \end{array}$	222 171 1463 9% 153 334 128 290 165 222 171 1463 P < 0.0 n 153 334 128 290 222 171 1298	0.6% 0.2% 1.9% 1.9% 2.9% 2.1% 3.1% 2.6% 1.7% 0.5% 3.1% 2.0% 2.7% 3.1% 2.0%	2.08 [1.16, 3.72] 2.63 [0.06, 7.22] 2.61 [1.88, 3.62] Modified by Random-effects model 86.63 [5.41, 1386.75] 7.83 [5.21, 11.75] 9.72 [405, 23.31] 2.04 [1.73, 2.40] 7.65 [4.15, 14.10] 26.67 [26.1, 82.21] 88.14 [6.10, 1578.75] 11.70 [3.76, 36.36] = 96% Modified by Random-effects model 197.06 [12.37, 3140.36] 1.95 [1.88, 2.25] 10.53 [3.85, 28.10] 5.97 [3.54, 10.07] 1.61 [1.36, 1.91] 24.181 [15.16, 3857.06] 5.67 [2.59, 12.43]	
ALOMA-2 ALOMA-2 ALOMA-4 ALOMA-4 leterogeneity: Chi <sup>2</sup> = 7. est for overall effect: Z set for overall effect: Z interfection and a total events leterogeneity: Tau <sup>2</sup> = 1. est for overall effect: Z interfection ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 interfection	54 13 13 13 14 13 15 15 18 180 219 152 180 219 152 160 219 152 160 48 934 489;Chi <sup>2</sup> 152 160 194 48 257 78 89 297 7119	444 169 2103 3 (P = 0.2 0.000 dose rec 303 334 169 2103 328 241 328 = 141.69 2103 334 444 169 2103 334 288 328 = 141.69 2103 334 169 2103 288 334 169 2103 210 210 210 210 210 210 210 210	13 5 44 48); $l^2 = 11$ 101) 101) 101 101 101 101 101 1	222 171 1463 9% 153 334 128 290 165 222 171 1463 0 165 222 171 1463 0 9 8 0 0 0 222 171 128 8 290 0 171 128 8 290 8 200 171 1463 128 200 171 1463 200 171 1463 200 171 1463 200 171 1463 200 171 1463 200 171 1463 200 171 1463 200 171 1463 200 171 1463 200 171 1463 200 171 1463 200 171 1463 200 171 171 1463 200 171 171 1463 200 171 171 1463 200 171 171 1463 200 171 171 171 171 171 171 171 171 171 1	0.6% 0.2% 1.9% 0.5% 2.9% 2.1% 3.1% 2.6% 0.5% 3.1% 0.5% 3.1% 2.0% 3.1% 2.0% 2.1% 0.5% 2.12.7% 3.1% 2.0% 0.05% 2.1% 0.5% 0.2%	2.08 [1.16, 3.72] 2.63 [0.66, 7.22] 2.61 [1.86, 3.62] Modified by Random-effects model 86, 63 [6, 41, 1386, 75] 7.83 [5.21, 11.73] 9.72 [4.05, 223, 31] 2.04 [1.73, 2.40] 7.65 [4.15, 14, 10] 26.67 [6.6, 82, 61] 98.14 [6.10, 1578, 75] 11.70 [3.76, 36, 36] = 96% Modified by Random-effects model 197.06 [12, 37, 3140, 36] 1.55 [168, 2.25] 10.53 [3.95, 28, 10] 5.67 [2.59, 12.43] = 96%	
ALOMA-2 ALOMA-2 ALOMA-4 ALOMA-4 leterogeneity: Chi <sup>2</sup> = 7. est for overall effect: Z 1.5 Adverse event lez WWA-2 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONARCH 3 ALOMA-4 ALOMA-4 ALOMA-4 ALOMA-4 ALOMA-2 ALOMA-4 Steterogeneity: Tau <sup>2</sup> = 1. est for overall effect: Z .1.6 Adverse event lez MWNA-2 IONALEESA-3 IONALEAE ION	54 13 178 42, df = 6 576 (F 85 180 90 219 152 160 48 934 488; Chi <sup>2</sup> (F 848; Chi <sup>2</sup> (F 840) 194 257 78 840) 257 78 840) 297 119 104 48 257 78 297 119 207 247 247 257 297 119 257 247 257 267 267 267 278 267 278 267 278 278 278 278 278 278 278 27	444 169 2103 3 (P = 0.2 0.000 dose rec 303 334 288 328 2103 = 141.69 2 0.000 dose int 303 334 2103 = 141.63 334 237 288 328 = 141.63 109 2 103	$\begin{array}{c} 13\\ 5\\ 44\\ 48); \ l^{2}=1\\ 101)\\ luction\\ 0\\ 23\\ 5\\ 108\\ 10\\ 3\\ 10\\ 3\\ 10\\ 3\\ 10\\ 3\\ 10\\ 10\\ 13\\ 2\\ 4\\ 4\\ 15\\ 92\\ 0\\ 0\\ 243\\ 3\\ df=6(6\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10$	222 171 1463 9% 153 334 128 290 165 222 171 1463 290 222 171 1463 153 334 128 290 222 171 1298 P < 0.0	0.6% 0.2% 1.9% 0.5% 2.9% 2.1% 3.1% 2.9% 0.5% 0.00001); l <sup>2</sup> 13.5% 0.05% 2.7% 3.1% 2.0% 0.5% 2.2%	2.08 [1.16, 3.72] 2.63 [0.66, 7.22] 2.64 [1.88, 3.62] Modified by Random-effects model 86.63 [5.41, 1386,75] 7.83 [5.21, 11.75] 9.72 [4.05, 23.31] 2.04 [1.73, 2.40] 7.65 [4.51, 41.0] 26.67 [8.61, 82.251] 11.70 [3.76, 36.36] = 96% Modified by Random-effects model 197.06 [12.37, 3140.36] 1.957 (168, 2.25] 1.053 [3.96, 28.10] 5.97 [3.54, 10.07] 1.597 [3.54, 10.07] 1.597 [3.54, 10.07] 5.577 [2.59, 12.43] = 96%	
ALOMA-2 ALOMA-2 ALOMA-4 ALOMA-4 otal events leterogeneity: Chi <sup>2</sup> = 7. est for overall effect: Z .1.5 Adverse event lez AWNA-2 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONACA Leterogeneity: Tau <sup>2</sup> = 1. est for overall effect: Z .1.6 Adverse event lez AWNA-2 IONALEESA-3 IONALESA-3 IONALESA	54 13 178 ef 42, df = 6 5, 6 (F) 42, df = 6 85 180 90 90 919 119 192 160 48 934 48 938; Chi <sup>2</sup> ef 48 938; Chi <sup>2</sup> ef 194 257 78 89 297 119 1034 466; Chi <sup>2</sup> ef 43, 78 46, 78 1034 119 119 119 119 119 119 119 11	444 169 2103 5 (P = 0.2 0.000 dose rec 303 334 227 288 227 288 444 169 2 103 22103 2103 2114 303 334 2103 2114 50 2000 2000 2000 2000 2000 2000 2000	$\begin{array}{c} 13\\ 3\\ 44\\ 8); \ l^{2}=11\\ 01)\\ \begin{array}{c} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$	222 171 1463 9% 153 334 128 290 165 222 171 1463 P < 0.0 153 334 128 290 222 171 1463 290 222 171 1298 P < 0.0	0.6% 0.2% 1.9% 0.5% 2.9% 2.1% 2.6% 1.7% 2.6% 1.7% 3.1% 2.0% 3.1% 2.0% 3.1% 2.0% 3.1% 2.2,7% 3.1% 2.0% 3.1% 0.55% 2.2,7% 2.3,7% 2	2.08 [1.16, 3.72] 2.63 [0.06, 7.22] 2.61 [1.88, 3.62] Modified by Random-effects model 86.63 [5.41, 1386, 75] 7.83 [5.21, 11.75] 9.72 [4.05, 23.31] 2.04 [1.73, 2.40] 7.65 [4.15, 14.10] 2.66 7 [6.6, 82.61] 98.14 [6.10, 1578.75] 11.70 [3.76, 36.36] = 96% Modified by Random-effects model 195.70 [12.37, 3140.36] 1.95 [12.37, 3140.36] 2.96%	
ALOMA-2 ALOMA-2 ALOMA-4 ALOMA-4 leterogeneity: Chi <sup>2</sup> = 7. est for overall effect: Z 1.5 Adverse event lez WWA-2 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONACH 3 ALOMA-4 ALOMA-4 ALOMA-4 ALOMA-4 ALOMA-4 Chal events leterogeneity: Tau <sup>2</sup> = 1. est for overall effect: Z 1.6 Adverse event lez MVMA-2 IONALEESA-3 IO	54 13 178 42, df = 6 5, 6 (F) 42, df = 6 5, 180 90 90 219 915 160 48 89; Chi <sup>2</sup> 194 489; Chi <sup>2</sup> 194 489; Chi <sup>2</sup> 194 257 78 89 297 119 103 466; Chi <sup>2</sup> 103 466; Chi <sup>2</sup> 103 466; Chi <sup>2</sup> 103 467 103 467 103 467 103 467 103 103 103 103 103 103 103 103	444 169 2103 5 (P = 0.2, 0.000 dose rec 303 334 237 288 22103 = 141.69 > < 0.000 dose int 303 444 169 = 2288 444 169 = 2288 444 169 = 2, 0.000 dose int 303 288 444 169 = 2, 0.000 dose int 303 288 248 248 248 248 248 258 26 26 27 288 288 288 288 288 288 288 288 288	13 5 44 8); I <sup>2</sup> = 1 101) 1uction 0 23 5 108 10 149 9, df = 6 ( 1) 132 4 15 92 0 243 3, df = 5 ( 1)	222 171 1463 99% 153 334 128 290 165 222 171 1463 P < 0.0 n 153 334 128 290 0 222 171 1298 P < 0.0	0.6% 0.2% 1.9% 0.5% 2.1% 3.1% 2.6% 1.7% 0.5% 13.5% 13.5% 12.0%	2.08 [1.16, 3.72] 2.63 [0.06, 7.22] 2.64 [1.88, 3.62] Modified by Random-effects model 86.63 [5.41, 1386.75] 7.83 [5.21, 11.75] 9.72 [4.05, 23.31] 2.04 [1.73, 2.40] 7.65 [4.51, 41.01] 2.66, 7 [8.61, 82.61] 98.14 [6.10, 1578.75] 11.70 [3.76, 36.36] = 96% Modified by Random-effects model 197.06 [12.37, 3140.36] 197.06 [2.37, 3140.36] 10.53 [3.62, 28.10] 5.97 [3.54, 10.07] 1.63 [1.36, 1291] 241.81 [15.16, 3257.06] 5.67 [2.59, 12.43] = 96%	
ALOMA-2 ALOMA-2 ALOMA-4 ALOMA-4 otal events leterogeneity: Chi <sup>2</sup> = 7. est for overall effect: Z .1.5 Adverse event lea AVMA-2 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONACA Leterogeneity: Tau <sup>2</sup> = 1. est for overall effect: Z .1.6 Adverse event lea AVMNA-2 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-7 ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 IONALEESA-7 IONALESA-7 ION	544 $13$ 178 e42, df = 6 = 5.76 (F 85 = 5.76 (F 180 g = 5.76 (F 180 g = 5.76 (F 180 g = 5.76 (F 180 g = 5.76 (F) = 5.76	444 169 2103 5 (P = 0.2, 0,000 dose rec 303 237 288 2103 2113 2141.69 2103 2103 2113 2141.69 2175 288 2103 2113 2141.69 2175 20,000 dose int 303 217 288 219 2103 219 219 219 219 219 219 219 219 219 219	$\begin{array}{c} 13\\ 3\\ 44\\ 8); \  ^{2}=11\\ 101) \end{array}$	222 171 1463 99% 153 334 128 290 165 222 171 1463 290 202 171 1298 P < 0.0 153	0.6% 0.2% 1.9% 0.5% 2.9% 2.1% 2.6% 1.7% 2.6% 1.3.5% 0.5% 2.7% 3.1% 2.6% 1.3.5% 0.5% 2.7% 2.1% 0.5% 2.1% 0.5% 2.1% 0.5% 2.1% 2.6% 2.6% 2.6% 2.6% 2.6% 2.6% 2.6% 2.6	2.08 [1.16, 3.72] 2.63 [0.06, 7.22] 2.61 [1.88, 3.62] Modified by Random-effects model 86.63 [5.41, 1386,75] 7.83 [5.21, 11.75] 9.72 [405, 22.33] 2.04 [1.73, 2.40] 7.65 [4.15, 4.40] 26.67 [8.61, 82.41] 98.14 [6.10, 1578.76] 11.70 [3.76, 36.36] = 96% Modified by Random-effects model 197.06 [12.37, 3140.36] 1.95 [1.88, 2.25] 10.53 [3.95, 28.10] 5.97 [3.54, 10.07] 1.95 [1.88, 2.25] 10.53 [3.95, 28.10] 5.97 [3.54, 10.07] 1.95 [1.88, 2.25] 1.35 [3.857.06] 5.67 [2.59, 12.43] = 96%	
ALOMA-2 ALOMA-2 ALOMA-4 ALOMA-4 leterogeneity: Chi <sup>2</sup> = 7. est for overall effect: Z ist for overall effect: Z invalues: AUNALEESA-3 IONALEESA-3 IONALEESA-3 IONARCH 3 ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 ist for overall effect: Z i.1.6 Adverse event lea AVWA-2 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 ALOMA-4 ubtotat (95% CI) otal events leterogeneity: Tau <sup>2</sup> = 0, est for overall effect: Z i.1.7 Adverse event lea AVMA-2 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-2	54 13 178 ef = 6 42, df = 6 5, 76 (f 80 90 90 90 91 152 160 48 934 ef 89; Chi <sup>2</sup> H 934 489; Chi <sup>2</sup> H 934 489; Chi <sup>2</sup> H 934 489; Chi <sup>2</sup> H 934 194 257 78 89 297 1194 109 297 1194 109 297 1194 257 78 89 297 1194 109 207 78 89 297 1194 257 78 89 297 1194 209 209 209 209 209 209 209 209 209 209	444 169 2103 5 (P = 0.2, 0.000 dose rec 303 334 237 288 328 444 169 2103 = 141.69 < 0.000 dose int 303 334 237 = 124.63 334 169 2103 = 124.63 303 334 334 334 334 334 334	$\begin{array}{c} 13\\ 3\\ 5\\ 44\\ 8); l^{2}=1\\ 001\\ 0\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 1$	222 171 171 171 1463 199% 153 334 128 290 165 222 171 1463 P < 0.0 n 153 334 1298 P < 0.0 222 171 1298 P < 0.0 153 334	0.6% 0.2% 0.2% 2.9% 2.1% 3.1% 2.6% 0.5% 13.5% 13.5% 0.5% 13.5% 12.0% 0.5% 12.0% 0.5%	2.08 [1.16, 3.72] 2.63 [0.06, 7.22] 2.64 [1.88, 3.62] Modified by Random-effects model 66.63 [5.41, 1366.75] 7.83 [5.21, 11.75] 9.72 [4.05, 23.31] 2.04 [1.73, 2.40] 7.65 [4.5, 41.01] 26.67 [8.61, 82.61] 98.14 [61.0, 178.75] 11.70 [3.76, 36.36] = 96% Modified by Random-effects model 197.06 [12.37, 3140.36] 1.95 [1.88, 2.25] 10.53 [3.95, 28.10] 5.67 [2.59, 12.43] 5.67 [2.59, 12.43] = 96%	
ALOMA-2 ALOMA-2 ALOMA-4 ALOMA-4 Cotal events leterogeneity: Chi <sup>2</sup> = 7. est for overall effect: Z .1.5 Adverse event lea AWNA-2 IONALEESA-3 IONALEESA-3 IONACESA-3 IONACESA-3 IONACESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-7 ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 ALOMA-2 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3	54 13 178 ef 42, df = 6 85 180 90 90 91 92 19 152 160 48 934 489; Chi <sup>2</sup> 152 160 48 934 489; Chi <sup>2</sup> 152 160 48 934 489; Chi <sup>2</sup> 152 160 48 934 489; Chi <sup>2</sup> 152 160 48 934 489; Chi <sup>2</sup> 152 160 152 160 152 160 152 160 152 160 152 160 152 160 152 160 160 160 160 160 160 160 160 160 160	444 169 2103 5 (P = 0.2.0 0 < 0.000 0 dose ret 303 324 227 2103 = 141.69 2103 = 2103 334 2103 = 2 < 0.000 dose int 303 324 1775 = 124.63 324 169 217 208 209 200 209 200 200 200 200 200	$\begin{array}{c} 13\\ 3\\ 5\\ 44\\ 8); \ l^{2}=1\\ 01)\\ luction\\ 0\\ 23\\ 5\\ 108\\ 10\\ 3\\ 0\\ 13\\ 0\\ 149\\ 4\\ 15\\ 12\\ 0\\ 243\\ 4\\ 15\\ 12\\ 0\\ 0\\ 243\\ 15\\ 12\\ 0\\ 0\\ 243\\ 10\\ 12\\ 1\\ 1\\ 0\\ 0\\ 21\\ 1\\ 1\\ 0\\ 0\\ 1\\ 1\\ 0\\ 0\\ 1\\ 0\\ 1\\ 0\\ 1\\ 0\\ 0\\ 1\\ 0\\ 1\\ 0\\ 0\\ 1\\ 0\\ 1\\ 0\\ 0\\ 0\\ 1\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\$	222 171 171 1463 99% 153 334 128 280 165 222 171 1463 0 165 222 171 1463 0 165 222 171 1463 0 165 222 171 11463 0 175 171 128 P<0.0 C	0.6% 0.2% 1.9% 1.9% 0.5% 2.9% 0.5% 0.5% 13.5% 0.5% 0.5% 0.5% 0.5% 0.5% 0.5% 0.5% 0	2.08 [1.16, 3.72] 2.63 [0.06, 7.22] 2.64 [1.88, 3.62] Modified by Random-effects model 86.63 [5.41, 1386.75] 7.83 [5.21, 11.75] 9.72 [405, 23.31] 2.04 [1.73, 2.40] 7.65 [4.15, 14.10] 7.65 [4.15, 14.10] 1.96 [1.68, 2.25] 10.53 [3.95, 28.10] 5.97 [3.54, 10.07] 1.95 [1.58, 7.06] 5.67 [2.59, 12.43] = 96%	
ALOMA-2 ALOMA-2 ALOMA-4 ALOMA-4 leterogeneity: Chi <sup>2</sup> = 7. est for overall effect: Z set for overall effect: Z ional EESA-2 ional EESA-2 ional EESA-3 ional EESA-3 ional EESA-3 ional events leterogeneity: Tau <sup>2</sup> = 1. 6 Adverse event lea WWA-2 ional EESA-3 ional EESA-3	54 13 178 42, df = 6 85 180 90 91 152 160 934 48 934 48 934 48 934 48 934 48 934 48 934 48 934 194 257 78 89 297 78 89 297 194 194 257 78 80 194 194 257 78 80 194 194 257 78 80 194 194 257 78 80 194 194 257 78 80 194 194 257 78 80 194 194 194 257 78 194 194 194 257 78 80 194 194 257 78 80 194 194 257 78 80 219 194 257 78 80 219 194 257 78 80 294 194 257 78 80 295 194 297 78 80 297 78 119 103 4 119 103 103 103 103 103 103 103 103	444 169 2103 8 (P = 0.2 < 0.000 303 334 288 328 328 237 241 2103 = 141.69 > < 0.000 dose int 303 334 444 169 > < 0.000 dose int 303 324 2175 = = 124.63 304 227 228 228 228	$\begin{array}{c} 13\\ 3\\ 5\\ 44\\ 8); l^{2}=1\\ 001\\ 0\\ 0\\ 23\\ 3\\ 0\\ 149\\ 9\\ df=6\\ (c)\\ 11\\ 0\\ 132\\ 4\\ 15\\ 9\\ 243\\ df=5\\ (c)\\ 11\\ 0\\ 243\\ df=5\\ (c)\\ 11\\ 0\\ 243\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\$	222 171 171 1463 99% 153 334 128 290 165 222 171 1463 165 222 171 1463 0 165 222 171 1463 0 165 222 171 1298 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	0.6% 0.2% 1.9% 0.5% 2.9% 2.1% 3.1% 0.5% 13.5% 0.5% 13.5% 0.5% 13.5% 0.5% 13.5% 0.5% 0.5% 0.5% 0.0% 0.0%	2.08 [1.16, 3.72] 2.63 [0.06, 7.22] 2.61 [1.86, 7.22] 2.61 [1.88, 3.62] Modified by Random-effects model 86.63 [6.41, 1386, 75] 7.83 [5.21, 41.75] 9.72 [4.05, 23.31] 2.04 [1.73, 2.40] 7.65 [4.15, 14.10] 2.65 7 [6.5, 82.61] 98.14 [6.10, 1578.75] 11.70 [3.76, 36.36] = 96% Modified by Random-effects model 197.06 [12.37, 3140.36] 1.55 [12.37, 3140.36] 5.57 [254, 10.07] 1.61 [1.36, 121] 5.57 [254, 10.07] 1.61 [1.56, 3257.06] 5.57 [2.54, 10.07] 1.61 [1.56, 3257.06] 5.57 [2.54, 10.07] 1.61 [1.56, 3257.06] 5.57 [2.54, 10.07] 1.61 [1.56, 3257.06] 5.57 [2.54, 10.07] 1.61 [1.56, 3257.06] 5.57 [2.56, 10.07] 1.63 [1.57, 2.56, 2.57] 1.63 [1.57, 2.56, 2.57] 1.53 [1.57, 2.56, 2.57] 1.55 [1.57, 2	
ALOMA-2 ALOMA-2 ALOMA-4 ALOMA-4 Valobat (95% CI) otal events rest for overall effect Z avwards (16% CI) otal events (15, 54/verse event lea bawka-2 (0NALEESA-3 (0NALEESA-3 (0NALEESA-3 (0NALEESA-3 (0NALEESA-3 (0NALEESA-3 (0NALEESA-3 (0NALEESA-3 (0NALEESA-3 (0NALEESA-3 (0NALEESA-3 (0NALEESA-3 (0NALEESA-3 (0NALEESA-3 (0NALEESA-3 (0NALEESA-3 (0NALEESA-3 (0NALEESA-3 (0NALEESA-2 (0NALEESA-2 (0NALEESA-2 (0NALEESA-2 (0NALEESA-3 (0NACH 3)	54 4 13 178 42, df = 6, f = 6, f = 5, f = 6, f = 18, f = 18	444 169 2103 8 (P = 0.2 < < 0.000 dose ret 28 288 328 288 328 288 328 2103 = 141.69 2103 334 169 2103 334 169 2103 334 2103 334 2175 = 124.63 33 34 1775 = 124.63 33 33 444 169 207 287 288 203 203 203 203 203 203 203 203 203 203	$\begin{array}{c} 13\\ 3\\ 5\\ 44\\ 8); \ l^{p}=1\\ 101) \\ luction\\ 0\\ 3\\ 5\\ 108\\ 10\\ 3\\ 0\\ 13\\ 1\\ 9\\ 132\\ 4\\ 4\\ 5\\ 92\\ 20\\ 3\\ 4\\ 5\\ 92\\ 20\\ 3\\ 4\\ 5\\ 11) \\ 2\\ 2\\ 1\\ 0\\ 0\\ 2 \end{array}$	2222 171 171 1463 9% 153 334 290 165 222 272 171 1463 9 0 165 334 128 290 165 334 128 290 171 1298 9 0 0 0 153 334 128 290 153 334 128 290 153 171 171 171 171 171 171 171 171 171 17	0.6% 1.9% 0.5% 2.9% 2.9% 2.6% 1.7% 0.5% 3.1% 2.0% 0.5% 3.1% 2.0% 0.5%	2.08 [1.16, 3.72] 2.63 [0.06, 7.22] 2.64 [1.88, 3.62] Modified by Random-effects model 86.63 [5.41, 1386.75] 7.83 [5.21, 11.75] 9.72 [4.05, 23.31] 2.04 [1.73, 2.40] 7.65 [4.16, 14.10] 26.67 [8.61, 82.261] 80.14 [6.10, 1578.75] 11.70 [12.37, 34.0.36] 197.06 [12.37, 3140.36] 197.06 [12.37, 3140.36] 195.[1.88, 2.25] 10.53 [3.95, 28.10] 5.97 [3.54, 10.07] 1.57 [1.54, 1.31] 24.18 [1.51, 63, 867.06] 5.67 [2.59, 12.43] = 96%	
ALOMA-2 ALOMA-4 ALOMA-4 ALOMA-4 Iderogeneity: Chi = 7.7. est for overall effect: Z stronoverall effect: Z J.1.5 Adverse event lea XWWA-2 IONALEESA-2 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALESA-2 ALOMA-4 VALOMA-4 VALOMA-4 VALOMA-4 VALOMA-2 IONALEESA-3 IONALEESA-7 IONACH 3 XLOMA-2	54 4 13 178 822, df = (F 827 = (F 827 = (F 827 = (F 828 - 200 - 20	444 169 2103 8 (P = 0.2 < 0.000 0 dose rec 288 328 328 288 328 22103 = 141.69 > < 0.000 dose int 303 334 444 169 = 124.63 328 288 288 328 = 124.63 334 169 1775 = = 124.63 334 444	$\begin{array}{c} 13\\ 3\\ 5\\ 44\\ 8); \  ^{2}=1\\ 101\\ 0\\ 23\\ 5\\ 108\\ 100\\ 23\\ 5\\ 108\\ 100\\ 0\\ 23\\ 108\\ 100\\ 0\\ 132\\ 4\\ 15\\ 92\\ 0\\ 0\\ 243\\ 3\\ df=5(\\ 1)\\ 1\\ 2\\ 1\\ 1\\ 0\\ 0\\ 2\\ 4\\ 4\end{array}$	2222 171 171 1463 99% 153 334 128 290 165 222 171 1463 P < 0.0 153 334 290 222 171 1298 P < 0.0 153 334 128 290 222 171 1298 290 222	0.6% 0.2% 1.9% 0.5% 2.9% 2.1% 3.1% 0.5% 13.5% 0.5% 13.5% 0.5% 13.5% 0.5% 13.5% 0.5% 13.5% 0.5% 0.0% 0.0% 0.0% 0.0%	2.08 [1.16, 3.72] 2.63 [0.06, 7.22] 2.64 [1.86, 7.22] 2.64 [1.88, 3.62] Modified by Random-effects model 86.63 [5.41, 1386, 75] 7.78 [5.21, 11.75] 9.72 [4.05, 23.31] 2.04 [1.73, 2.40] 7.65 [4.15, 14.10] 2.66 7 [6.6, 82.61] 98.14 [6.10, 1578.75] 11.70 [3.76, 36.36] = 96% Modified by Random-effects model 195.06 [12.37, 3140.36] 1.95 [12.37, 3140.36]	
ALOMA-2 ALOMA-2 ALOMA-4 ValOMA-4 Iderogeneity: Chi <sup>2</sup> = 7. est for overall effect: Z .1.5 Adverse event lez XWNA-2 IONALEESA-3 (ONALEESA-3 (ONALEESA-3 (ONALEESA-3 (ONACESA-3 ALOMA-2 ALOMA-4 VaLOMA-4 VaLOMA-4 VaLOMA-4 VaLOMA-4 VaLOMA-4 VaLOMA-4 VaLOMA-4 VaLOMA-4 VaLOMA-2 ALOMA-4 VaLOMA-2 VaLOMA-2 VaLOMA-2 VaLOMA-2 VaLOMA-2 VaLOMA-2 VaLOMA-2 VaLOMA-2 VaLOMA-2 VaLOMA-2 VALOMA-4 VALOMA-2 VALOMA-2 VALOMA-2 VALOMA-2 VALOMA-2 VALOMA-2 VALOMA-2 VALOMA-2 VALOMA-2 VALOMA-2 VALOMA-2 VALOMA-2 VALOMA-2 VALOMA-2 VALOMA-2 VALOMA-2 VALOMA-4 VALOMA-4 VALOMA-4	54 4 13 178 842, df = 5, 6 (f) 4 42, df = 5, 6 (f) 4 42, df = 5, 7 (e) (f) 4 42, df = 5, 7 (e) 4 42, df = 1, 6 (f) 4 934 4 934 4 934 4 934 4 934 4 199 7 119 1034 7 119 1035 7 119 1036 (Chi <sup>2</sup> ) 4 297 7 119 1036 (Chi <sup>2</sup> ) 4 297 7 119 1036 (Chi <sup>2</sup> ) 4 297 7 119 1037 4 297 7 119 1038 7 119 10 10 11 11 10 11 10 10 10 10	444 169 2103 3 (P = 0.20 dose rec 303 334 423 2103 = 141.69 2103 = 141.69 2103 = 2.0000 dose int 303 324 444 169 2103 = 2.0000 dose rec 237 288 444 169 2103 303 303 444 169 200 200 200 200 200 200 200 20	$\begin{array}{c} 13\\ 3\\ 5\\ 44\\ 8); \ l^{2}=1\\ 101)\\ luction\\ 0\\ 0\\ 23\\ 5\\ 108\\ 10\\ 3\\ 0\\ 10\\ 3\\ 0\\ 132\\ 4\\ 4\\ 15\\ 92\\ 92\\ 92\\ 3\\ df=6\\ (1)\\ 1)\\ 243\\ df=5\\ 1\\ 0\\ 0\\ 243\\ df=5\\ 1\\ 0\\ 0\\ 2\\ 4\\ 0\\ 0\\ 2\\ 4\\ 0\\ 0\\ 2\\ 4\\ 0\\ 0\\ 2\\ 4\\ 0\\ 0\\ 0\\ 2\\ 4\\ 0\\ 0\\ 0\\ 2\\ 4\\ 0\\ 0\\ 0\\ 0\\ 0\\ 2\\ 4\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\$	2222 171 171 1463 9% 153 334 128 290 165 222 171 1463 178 290 0 175 334 128 290 222 171 1298 128 290 222 171 153 334 128 290 153 334 128 290 175 175 176 176 176 176 176 176 176 176 176 176	0.6% 0.2% 1.9% 0.5% 2.9% 2.7% 3.1% 2.6% 1.7% 2.6% 1.7% 2.6% 1.7% 2.6% 0.5% 3.1% 0.5% 2.0% 0.0% 0.0% 0.0%	2.08 [1.16, 3.72] 2.63 [0.06, 7.22] 2.64 [1.88, 3.62] Modified by Random-effects model 86.63 [5.41, 1386, 75] 7.83 [5.21, 11.75] 9.72 [4.05, 23.31] 2.04 [1.73, 2.40] 7.65 [4.51, 41.0] 26.67 [8.61, 82.21] 11.70 [3.76, 36.36] 11.70 [3.76, 36.36] 11.70 [12.37, 3140.36] 197.06 [12.37, 3140.36] 197.06 [12.37, 3140.36] 1.55 [1.58, 2.25] 1.55 [3.65, 28.10] 5.57 [2.59, 12.43] 241.81 [15.16, 3637.06] 5.67 [2.59, 12.43] 2 96%	
ALOMA-2 ALOMA-2 ALOMA-4 ALOMA-4 Valtottat (95% CI) otal events leterogeneity: Chi <sup>2</sup> = 7. est for overall effect Z J.1.5 Adverse event let XWWA-2 IONALEESA-2 IONALEESA-3 IONALEESA-7 IONALEESA-7 IONALESA-2 IONALEESA-2 IONALEESA-2 IONALEESA-3 IONACH 3 IONACH 3 IONAC	544 13 178 842, df = (F adding to 85 180 90 90 90 90 90 90 90 90 90 90 90 90 90	$\begin{array}{l} 444\\ 444\\ 169\\ 2103\\ \hline\\ 6(P=0.2\\ <0.000\\ \hline\\ 303\\ 334\\ 237\\ 238\\ 328\\ 328\\ 328\\ 328\\ 22103\\ \hline\\ 2103\\ \hline\\ 2103\\ \hline\\ 2103\\ \hline\\ 2103\\ \hline\\ 237\\ 238\\ 334\\ 444\\ 169\\ -0.000\\ \hline\\ 303\\ 334\\ 464\\ 169\\ 1775\\ \hline\\ 237\\ 288\\ 328\\ 444\\ 169\\ 237\\ 238\\ 334\\ 444\\ 169\\ 237\\ 238\\ 334\\ 444\\ 169\\ 237\\ 288\\ 333\\ 444\\ 169\\ 2103\\ \hline\\ 333\\ 444\\ 169\\ 2103\\ \hline\\ 2$	$\begin{array}{c} 13\\ 3\\ 5\\ 44\\ 8); \  ^{2}=1\\ 101\\ 0\\ 23\\ 5\\ 108\\ 108\\ 10\\ 0\\ 23\\ 5\\ 108\\ 10\\ 0\\ 132\\ 0\\ 149\\ 0\\ 149\\ 0\\ 149\\ 0\\ 149\\ 0\\ 149\\ 0\\ 243\\ 3\\ df=5\\ (1\\ 1\\ 1\\ 1\\ 0\\ 2\\ 4\\ 1\\ 0\\ 0\\ 2\\ 4\\ 0\\ 0\\ 2\\ 4\\ 0\\ 0\\ 2\\ 4\\ 0\\ 0\\ 0\\ 2\\ 4\\ 0\\ 0\\ 0\\ 2\\ 4\\ 0\\ 0\\ 0\\ 0\\ 2\\ 4\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\$	222 171 171 1463 9% 153 334 128 290 165 222 171 1463 P < 0.0 n 153 334 128 290 222 171 1298 P < 0.0 N 153 334 128 290 2171 11463 P < 0.0 N 153 334 128 290 153 334 128 290 153 334 128 290 153 334 128 290 153 334 128 290 1290 1290 1290 1290 1290 1290 1290	0.6% 0.2% 1.9% 0.5% 2.9% 2.1% 3.1% 2.6% 0.5% 3.1% 2.6% 0.5% 3.1% 2.0% 0.5% 0.5% 0.5% 0.0% 0.0% 0.0% 0.0%	2.08 [1.16, 3.72] 2.63 [0.06, 7.22] 2.64 [1.88, 3.62] Modified by Random-effects model 86.63 [5.41, 1386, 75] 7.83 [5.21, 11.75] 9.72 [405, 223 31] 2.04 [1.73, 2.40] 7.65 [4.15, 14, 10] 2.65 7 [8.61, 82.61] 98.14 [6.10, 1578.75] 11.70 [3.76, 36.36] = 96% Modified by Random-effects model 197.06 [1.237, 3140.36] 1.95 [1.88, 2.25] 10.53 [3.95, 28.10] 5.97 [3.54, 10.07] 1.85 [1.86, 2.25] 10.53 [3.95, 28.10] 5.97 [3.54, 10.07] 1.85 [1.36, 1.91] 241.81 [151, 635.706] 5.67 [2.59, 12.43] = 96%	
ALOMA-2 ALOMA-2 ALOMA-4 ALOMA-4 (storest) leterogeneity: Chi <sup>2</sup> = 7. est for overall effect: Z .1.5 Adverse event lez XWWA-2 IONALEESA-3 (ONALEESA-3 (ONALEESA-3 (ONALEESA-3 (ONARCH 3 ALOMA-4 XLOMA-4 XLOMA-4 XLOMA-4 Storese event lez XWWA-2 IONALEESA-3 (ONALEESA-3 (ONALEESA-3 (ONALEESA-3 IONALEESA-3 (ONALEESA-3 (ONALEESA-3 (ONALEESA-3 ALOMA-4 XLOMA-2 XLOMA-4 XLOMA-2 XLOMA-4 XLOMA-4 XLOMA-4 XLOMA-4 XLOMA-4 XLOMA-4 XLOMA-2 XLOMA-4 XLOMA-4 XLOMA-4 XLOMA-2 XLOMA-4 XLOMA-4 XLOMA-4 XLOMA-2 XLOMA-4 XLOMA-4 XLOMA-4 XLOMA-2 XLOMA-4 XLOMA-2 XLOMA-4 XLOMA-2 XLOMA-4 XLOMA-2 XLOMA-4 XLOMA-2 XLOMA-4 XLOMA-2 XLOMA-4 XLOMA-4 XLOMA-4 XLOMA-2 XLOMA-4 XLOMA-	544 13 178 842, df = (F 85 180 90 90 90 90 90 90 90 90 90 9	444 169 2103 3 (P = 0.20 dose rec 303 334 237 288 328 444 169 2103 = 141.69 2103 = 141.69 2103 = 141.69 2103 334 469 2175 = 124.63 303 334 469 2175 = 124.63 303 324 1775 = 124.63 324 1775 = 124.63 324 1775 = 124.63 324 1775 = 124.63 324 1775 = 124.63 324 1775 = 124.63 324 1775 = 124.63 2277 288 328 247 247 247 247 247 247 247 247	$\begin{array}{c} 13\\ 3\\ 5\\ 44\\ 8); \  ^{2}=1\\ 101\\ 0\\ 23\\ 3\\ 108\\ 10\\ 0\\ 23\\ 3\\ 0\\ 108\\ 10\\ 0\\ 108\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10\\ 10$	2222 171 171 1463 9% 153 334 128 290 165 2222 171 1463 9 P < 0.0 153 334 128 290 222 171 1298 P < 0.0 153 334 128 290 165 128 291 171 1298 P < 0.0 129 171 171 171 171 171 171 171 171 171 17	0.6% 0.2% 1.9% 0.5% 2.9% 2.7% 3.1% 0.5% 2.7% 3.1% 0.5% 2.7% 3.1% 0.5% 0.5% 0.5% 0.0% 0.0% 0.0% 0.5%	2.08 [1.16, 3.72] 2.63 [0.06, 7.22] 2.64 [1.88, 3.62] Modified by Random-effects model 86.63 [5.41, 1386.75] 7.83 [5.21, 11.75] 9.72 [4.05, 23.31] 2.04 [1.73, 2.40] 7.65 [4.15, 14.10] 26.67 [8.61, 82.61] 98.14 [6.10, 1757.75] 91.72 [0.1757.75] 91.70 [12.37, 3140.36] 197.06 [12.37, 3140.36] 197.06 [12.37, 3140.36] 195.05 [3.95, 28.10] 5.67 [2.59, 12.43] 241.81 [15.16, 3957.06] 5.67 [2.59, 12.43] 241.81 [15.16, 3957.06] 5.67 [2.59, 12.43] 241.81 [0.13, 14.49] 4.00 [0.45, 35.60] 1.63 [0.07, 39.63] Not estimable 2.77 [0.62, 12.34] 1.25 [0.40, 3.94] 3.04 [0.12, 73.99] 1.77 [0.86, 3.55]	
ALOMA-2 ALOMA-2 ALOMA-4 ALOMA-4 Valobat (95% CI) otal events leterogeneity: Chi <sup>2</sup> = 7. 'est for overall effect Z J. 5. Adverse event lea DAWNA-2 NONALEESA-3 (ONALEESA-3 (ONALEESA-3 (ONALEESA-3 (ONACA) leterogeneity: Tau <sup>2</sup> = 0. 'est for overall effect Z J.6. Adverse event lea DAWNA-2 NONALEESA-3 (ONACA) J. 200MA-2 'ALOMA-4 'ALOMA-4 'ALOMA-4 'ALOMA-4 'ALOMA-4 'ONACA' CH <sup>2</sup> = 2.	544 13 178 842, df = (F 85 180 90 90 219 9152 160 219 934 934 934 934 934 934 934 934 934 93	444 169 2103 6 (P = 0.2 4 < 0.000 dose rec 303 334 22103 = 141.69 > < 0.000 dose int 322 444 169 = 0.2 2103 334 227 288 444 169 = 0.2 2103 334 227 288 444 169 = 0.2 2103 334 228 444 169 = 0.2 2103 334 228 247 288 444 169 200 200 2103 200 2103 200 2103 200 200 200 200 200 200 200 2	$\begin{array}{c} 13\\ 3\\ 5\\ 44\\ 8); \  ^{2}=1\\ 001)\\ 0\\ 23\\ 3\\ 5\\ 108\\ 10\\ 0\\ 23\\ 5\\ 108\\ 10\\ 0\\ 23\\ 5\\ 108\\ 10\\ 0\\ 149\\ 9\\ 10\\ 11\\ 1\\ 1\\ 1\\ 2\\ 4\\ 4\\ 15\\ 92\\ 0\\ 0\\ 243\\ 4\\ 15\\ 92\\ 0\\ 0\\ 2\\ 243\\ 1\\ 1\\ 1\\ 1\\ 0\\ 0\\ 2\\ 2\\ 4\\ 0\\ 2\\ 2\\ 4\\ 0\\ 2\\ 2\\ 4\\ 0\\ 2\\ 2\\ 4\\ 0\\ 0\\ 2\\ 2\\ 4\\ 0\\ 0\\ 2\\ 2\\ 4\\ 0\\ 0\\ 2\\ 2\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\$	222 171 171 1463 9% 153 334 128 290 165 222 171 1463 P < 0.0 153 334 128 290 222 171 1298 P < 0.0 153 334 128 290 202 171 11463	0.6% 0.2% 1.9% 0.5% 2.9% 2.1% 3.1% 2.6% 3.1% 2.1% 3.1% 2.6% 3.1% 2.1% 3.1% 2.1% 3.1% 2.1% 3.1% 0.5% 3.1% 0.5% 3.1% 0.5% 3.1% 0.5%	2.08 [1.16, 3.72] 2.63 [0.06, 7.22] 2.64 [1.88, 3.62] Modified by Random-effects model 86.63 [5.41, 1386.75] 7.83 [5.21, 11.75] 9.72 [4.05, 23.31] 2.04 [1.73, 2.40] 7.65 [4.15, 14.10] 7.65 [4.15, 14.10] 1.95 [1.88, 2.25] 10.53 [3.95, 28.10] 1.95 [1.88, 7.66] 5.67 [2.59, 12.43] = 96% 0.76 [0.13, 4.49] 4.00 [0.45, 35.60] 1.63 [0.07, 39.63] Net estimable 2.77 [0.62, 12.34] 1.25 [0.40, 3.34] 3.04 [0.17, 73.99] 1.77 [0.88, 3.55]	
ALOMA-2 ALOMA-4 ALOMA-4 ALOMA-4 Cotal events leterogeneity: Chi <sup>2</sup> = 7. est for overall effect: Z st for overall effect: Z ioNALEESA-2 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONACESA-2 ALOMA-2 ALOMA-4 ubtotal (95% CI) otal events leterogeneity: Tau <sup>2</sup> = 1. 6 Adverse event lea WWNA-2 IONALEESA-3 IONALEESA-7 IONACH 3 ALOMA-4 ubtotal (95% CI) otal events leterogeneity: Chi <sup>2</sup> = 0. est for overall effect: Z iest for overall effect: Z	544 13 178 842, df = (f = 5.76 (f) = (f) 90 90 90 219 9152 1600 90 9152 152 1600 48 893, CH <sup>2</sup> (f) 48 894, CH <sup>2</sup> (f) 48 894, CH <sup>2</sup> (f) 48 894, CH <sup>2</sup> (f) 48 897 119 1034, CH <sup>2</sup> (f) 48 89, CH <sup>2</sup> (f) 48 89, CH <sup>2</sup> (f) 48 89, CH <sup>2</sup> (f) 48 110 111 111 12 22, df = (f) 48 110 (f) 48 1	444 169 2103 3 (P = 0.20 dose rec 303 324 237 288 2103 = 141.68 < 0.000 dose int 303 324 169 2103 = 124.63 323 444 169 2 0.000 dose int 303 324 169 2 0.000 dose rec 2103 = 124.63 237 288 328 444 169 2 0.000 dose int 303 324 169 2 0.000 dose int 303 324 444 169 2 0.000 dose int 303 324 444 169 2 217 2 88 328 2 84 2 82 2 82 2 82 2 84 2 84 2 84 3 84 4 44 169 2 217 2 87 2 88 3 24 4 44 169 2 210 3 54 4 44 169 2 210 3 54 4 44 169 2 210 3 54 2 87 2 88 3 28 2 83 2 86 3 54 4 44 169 2 87 2 88 3 54 4 44 169 2 87 2 88 3 54 3 54 3 54 2 103 2 107 2 1	$\begin{array}{c} 13\\ 3\\ 5\\ 44\\ 8); \  ^{2}=1\\ 1001\\ 0\\ 23\\ 3\\ 5\\ 108\\ 100\\ 3\\ 0\\ 23\\ 5\\ 108\\ 100\\ 3\\ 0\\ 10\\ 3\\ 0\\ 10\\ 11\\ 0\\ 0\\ 24\\ 4\\ 11\\ 1\\ 1\\ 2\\ 2\\ 1\\ 1\\ 0\\ 0\\ 2\\ 4\\ 0\\ 0\\ 9\\ 9; \  ^{2}=0\\ 1\\ 1^{2}=0\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\$	222 222 171 171 1463 9% 153 334 128 290 165 222 171 1463 P < 0.0 7 153 334 128 290 222 171 153 334 128 290 222 171 1463 334 128 290 05 222 171 145 153 334 145 153 153 153 153 153 153 153 153 153 15	0.6% 0.5% 1.9% 0.5% 2.9% 2.1% 3.1% 2.6% 13.5% 13.5% 0.5% 2.7% 3.13% 0.5	2.08 [1.16, 3.72] 2.63 [0.66, 7.22] 2.61 [1.88, 3.62] Modified by Random-effects model 86.63 [5.41, 1386, 75] 7.78 [5.21, 11.75] 9.72 [4.05, 23.31] 2.04 [1.73, 2.40] 7.65 [4.15, 14.10] 2.66 7 [6.6, 82.61] 98.14 [6.10, 1578.75] 11.70 [3.76, 36.36] = 96% Modified by Random-effects model 195.06 [12.37, 3140.36] 1.95 [12.37, 3140.36] 1.95 [12.37, 3140.36] 1.95 [12.37, 3140.36] 5.97 [3.54, 10.07] 1.16 [1.36, 1.91] 2.41.38 [1.51 [6, 3857.06] 5.67 [2.59, 12.43] = 96%	
ALOMA-2 ALOMA-2 ALOMA-4 ValLOMA-4 Iderogeneity: Ch <sup>2</sup> = 7. est for overall effect: Z .1.5 Adverse event lez XWNA-2 IONALEESA-3 (ONALEESA-3 (ONALEESA-3 (ONALEESA-3 (ONALEESA-3 (ONALEESA-3 (ONACA) aloma-2 (ALOMA-4 (ALOMA-4 (ALOMA-4) (Iderogeneity: Tau <sup>2</sup> = 1. est for overall effect: Z .1.6 Adverse event lez XWNA-2 IONALEESA-3 (IONALEESA-3 IONALEESA-3 (IONALEESA-3 IONALEESA-3 (IONALEESA-3 IONALEESA-2 (IONALEESA-3 IONALEESA-2 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-3 IONALEESA-7 IONALEESA-3 IONALEESA-7 IONALEESA-3 IONALEESA-7 IONACH 3 ALOMA-4 ALOMA-4 ALOMA-4 IONACH 3 ALOMA-2 IONACH 3 ALOMA-4 IONACH 3 ALO	544 13 178 842, df = 6 85 1800 90 900 219 9152 16 1800 90 9152 16 1800 90 9152 16 1800 90 9152 16 1800 90 9152 16 1800 90 934 89 934 194 257 78 89 9297 119 1034 66; Chi <sup>2</sup> 194 257 78 89 9297 119 1034 66; Chi <sup>2</sup> 193 4 257 78 89 9297 119 1034 103 103 103 103 103 103 103 103 103 103	444 169 2103 3 (P = 0.2, 0 303 334 423 2103 = 141.69 2103 = 2.000 dose rec 303 324 213 = 141.69 ≥ 0.000 dose int 303 324 444 169 2103 = 2.000 dose rec 2103 324 217 288 444 169 2103 334 444 169 2103 303 303 217 288 444 169 2103 303 303 217 288 444 169 2103 303 303 217 288 444 169 2103 303 303 217 288 444 169 2103 303 303 303 217 288 444 169 217 288 444 169 217 288 444 169 217 288 444 169 217 288 444 169 217 288 444 169 217 288 444 169 217 288 444 169 217 217 288 444 169 217 217 288 444 169 217 217 217 218 217 217 218 218 219 219 219 219 219 219 219 219	$\begin{array}{c} 13\\ 3\\ 5\\ 44\\ 8); \ l^{2}=1\\ 001)\\ 1\\ 1\\ 1\\ 0\\ 2\\ 3\\ 5\\ 108\\ 1\\ 0\\ 1\\ 3\\ 0\\ 1\\ 3\\ 0\\ 1\\ 1\\ 1\\ 1\\ 1\\ 0\\ 0\\ 2\\ 4\\ 1\\ 1\\ 1\\ 0\\ 0\\ 2\\ 2\\ 1\\ 1\\ 1\\ 0\\ 0\\ 2\\ 2\\ 1\\ 1\\ 1\\ 0\\ 0\\ 2\\ 2\\ 1\\ 1\\ 1\\ 1\\ 0\\ 0\\ 2\\ 2\\ 1\\ 1\\ 1\\ 1\\ 0\\ 0\\ 0\\ 2\\ 2\\ 1\\ 1\\ 1\\ 1\\ 0\\ 0\\ 0\\ 2\\ 2\\ 1\\ 1\\ 1\\ 0\\ 0\\ 0\\ 2\\ 2\\ 1\\ 1\\ 1\\ 0\\ 0\\ 0\\ 2\\ 1\\ 1\\ 0\\ 0\\ 0\\ 2\\ 1\\ 0\\ 1\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\$	222 212 2171 171 1463 9% 153 334 128 280 0165 222 171 1463 0165 222 171 1463 020 290 290 153 334 128 P < 0.00 153 334 128 P < 0.00 153 334 128 290 171 1463 153 153 154 171 1463 153 154 154 154 154 154 154 154 154	0.6% 1.9% 0.2% 1.9% 0.5% 2.9% 2.7% 1.7% 0.5% 3.1% 0.5% 3.1% 0.5% 3.1% 0.5%	2.08 [1.16, 3.72] 2.63 [0.06, 7.22] 2.64 [1.88, 3.62] Modified by Random-effects model 86.63 [5.41, 1386.75] 7.83 [5.21, 11.75] 9.72 [4.05, 23.31] 2.04 [1.73, 2.40] 7.65 [4.5, 14.10] 26.67 [8.61, 82.21] 98.14 [6.10, 1578.75] 11.70 [3.76, 38.36] 11.70 [12.37, 34.0.36] 1.97.06 [12.37, 34.0.36] 1.95.76 [12.37, 34.0.36] 1.95.76 [2.58, 22.5] 1.053 [3.95, 28.10] 5.87 [2.59, 12.43] 24.18 [15.16, 3857.06] 5.67 [2.59, 12.43] = 96% 0.76 [0.13, 4.49] 4.00 [0.45, 35.60] 1.63 [0.07, 39.63] Not estimable 2.77 [0.62, 12.34] 1.26 [0.40, 3.34] 3.04 [0.17, 73.99] 1.77 [0.88, 3.55]	
ALOMA-2 ALOMA-4 ALOMA-4 ALOMA-4 Cotal events leterogeneity: Chi <sup>2</sup> = 7. est for overall effect Z 1.5 Adverse event lea MWAA-2 10NALEESA-3 10NALEESA-3 10NALEESA-3 10NALEESA-3 10NALEESA-3 10NALESA-2 10NALESA-2 10NALESA-2 10NALESA-2 10NALESA-2 10NALEESA-3 10NALEESA-7 10NAECH 3 ALOMA-4 ubtotal (95% CI) otal events leterogeneity: Chi <sup>2</sup> = 2. est for overall effect: Z otal events	544 13 178 842, df = (F 85 180 90 90 90 91 91 152 152 160 93 48 934 48 934 48 934 194 257 78 89 934 194 257 195 195 195 195 195 195 195 195	$\begin{array}{l} 444\\ 169\\ 2103\\ \delta(P=0.2\\ 0<0,000\\ 0\\ 0\\ 303\\ 334\\ 169\\ 237\\ 237\\ 238\\ 328\\ 328\\ 328\\ 22103\\ 2103\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\$	$\begin{array}{c} 13\\ 3\\ 5\\ 44\\ 48); \  ^{2}=1\\ 001) \\ 0\\ 23\\ 3\\ 108\\ 10\\ 0\\ 23\\ 3\\ 0\\ 0\\ 10\\ 10\\ 10\\ 132\\ 4\\ 4\\ 1\\ 1\\ 1\\ 1\\ 2\\ 2\\ 1\\ 0\\ 0\\ 22\\ 3\\ 2\\ 1\\ 1\\ 1\\ 1\\ 2\\ 2\\ 1\\ 0\\ 0\\ 2\\ 2\\ 3\\ 2\\ 0\\ 0\\ 2\\ 2\\ 3\\ 2\\ 0\\ 0\\ 0\\ 2\\ 3\\ 2\\ 3\\ 2\\ 0\\ 0\\ 0\\ 2\\ 2\\ 3\\ 2\\ 0\\ 0\\ 0\\ 2\\ 2\\ 3\\ 2\\ 0\\ 0\\ 0\\ 0\\ 2\\ 2\\ 3\\ 0\\ 0\\ 0\\ 0\\ 2\\ 2\\ 3\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 2\\ 3\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\ 0\\$	222 171 171 1463 9% 153 334 128 290 165 222 171 1463 9 7 153 334 128 290 0 153 334 128 290 0 122 171 1298 P < 0.0 153 334 128 290 9740	0.6% 0.5% 1.9% 0.5% 2.9% 2.1% 3.1% 2.6% 0.5% 0.5% 12.0% 0.5% 0.5% 100.0%	2.06 [1.16, 3.72] 2.63 [0.06, 7.22] 2.64 [1.88, 3.62] Modified by Random-effects model 86.63 [5.41, 1386, 75] 7.83 [5.21, 11.75] 9.72 [405, 223 31] 2.04 [1.73, 2.40] 7.66 [4.15, 14, 10] 2.66 7 [8.6], 82.61] 98.14 [6.10, 1578.75] 11.70 [3.76, 36.36] = 96% Modified by Random-effects model 197.06 [1.237, 3140.36] 1.95 [1.287, 240] 1.35 [3.95, 28.10] 5.97 [3.54, 10.07] 1.95 [1.88, 2.25] 10.53 [3.95, 28.10] 5.97 [3.54, 10.07] 1.95 [1.136, 1.91] 241.81 [151, 635.706] 5.67 [2.59, 12.43] = 96% 0.76 [0.13, 4.49] 4.00 [0.45, 35.60] 1.85 [0.7, 98.63] Not estimable 2.77 [0.62, 12.34] 3.04 [0.12, 73.39] 1.77 [0.88, 3.55]	

Fig. 5 Forest plots of adverse events summary associated with CET group versus PET group

In exploratory analyses of other secondary factors, this study found that CET significantly improved the ORR in the Intent-to-Treat (ITT) population. Incorporating data from MONALEESA-7 and MONALEESA-3 did not alter the overall conclusions of the study, and the consistency between these study results increased the reliability of the research. Furthermore, the analysis also confirmed that combined medication can increase the clinical benefit rate, with statistically significant differences observed [26, 32]. This contrasts with another meta-analysis, which indicated no significant differences, suggesting that the variation between the two study outcomes may be related to more comprehensive data updates. As of now, the MONALEESA-3 study, which has enrolled the

Adverse events	Studies involved	CET group		PET group		Risk ratio [95% CI]	Р
		Event/total	%	Event/total	%	-	
Neutropenia	7	1570/2103	74.66%	106/1463	7.25%	10.92 [7.62, 15.65]	< 0.00001
White blood cell count decreased	2	328/662	49.55%	50/499	10.02%	4.93 [1.74, 13.99]	0.003
Leukopenia	7	900/2103	42.80%	79/1463	5.40%	7.41 [5.69, 9.66]	< 0.00001
Nausea	6	726/1934	37.54%	301/1292	23.30%	1.67 [1.47, 1.90]	< 0.00001
Fatigue	6	604/1800	33.56%	359/1310	27.40%	1.18 [1.05, 1.32]	0.003
Diarrhea	7	697/2103	33.14%	288/1463	19.69%	1.51 [1.16, 1.96]	0.002
Anemia	7	670/2103	31.86%	122/1463	8.34%	3.64 [2.57, 5.14]	< 0.00001
Hypercalcemia	1	96/328	29.27%	50/165	30.30%	0.97 [0.73, 1.29]	0.81
Hyponatremia	1	90/328	27.44%	37/165	22.42%	1.22 [0.88, 1.71]	0.24
Thrombocytopenia	4	328/1204	27.24%	27/836	3.23%	7.59 [4.86, 11.86]	< 0.00001
Alopecia	6	472/1800	26.22%	159/1310	12.14%	2.10 [1.78, 2.48]	< 0.00001
Arthralgia	7	550/2103	26.15%	409/1463	27.96%	0.98 [0.88, 1.09]	0.61
Hot flush	4	305/1303	23.41%	275/974	28.23%	0.86 [0.71, 1.05]	0.05
Headache	5	375/1631	22.99%	257/1139	22.56%	1.05 [0.87, 1.26]	0.50
Vomiting	6	436/1934	22.54%	192/1292	14.86%	1.63 [1.18, 2.25]	0.003
Hypokalemia	2	110/497	22.13%	29/336	8.63%	2.25 [1.51, 3.35]	< 0.0001
Hypocalcemia	1	72/328	21.95%	28/165	16.97%	1.29 [0.87, 1.92]	0.20
Cough	5	320/1472	21.74%	201/1145	17.55%	1.21 [1.03, 1.42]	0.02
Aspartate aminotransferase increased	5	308/1422	21.66%	167/1113	15.00%	1.50 [0.94, 2.41]	0.0002
Constipation	5	349/1631	21.40%	182/1139	15.98%	1.37 [1.16, 1.62]	0.0001
Alanine aminotransferase increased	5	301/1422	21.17%	165/1113	14.82%	1.55 [0.90, 2.66]	0.11
Back pain	5	331/1631	20.29%	229/1139	20.11%	1.04 [0.89, 1.21]	0.64

# Table 3 Any grade adverse events (> 20% in the CET group)

Abbreviations CET: CDK4/6 inhibitors plus endocrine therapy; CI: Confidence interval; PET: Placebo plus endocrine therapy; RR: Risk ratio

Tab	le 4	Grac	le 3–5	i ac	lverse	events	(>	1%	in	the	CET	group)	)
-----	------	------	--------	------	--------	--------	----	----	----	-----	-----	--------	---

Adverse events	Studies involved	CET group		PET group		Risk ratio [95% CI]	Р
		Event/total	%	Event/total	%	-	
Neutropenia	7	1249/2103	59.39%	20/1463	1.37%	42.16 [20.45, 86.90]	< 0.00001
Leukopenia	7	507/2103	24.11%	7/1463	0.48%	27.95 [12.00, 65.11]	< 0.00001
White blood cell count decreased	2	86/662	12.99%	3/499	0.60%	21.99 [6.99, 69.19]	< 0.00001
Hypertension	3	65/925	7.03%	57/777	7.34%	1.11 [0.79, 1.54]	0.55
Alanine aminotransferase increased	5	84/1422	5.91%	15/1113	1.35%	3.51 [1.31, 9.44]	0.01
Hypokalemia	2	25/497	5.03%	4/336	1.19%	3.06 [0.04, 240.13]	0.62
Anemia	7	105/2103	4.99%	25/1463	1.71%	2.45 [1.54, 3.89]	< 0.00001
Hyponatremia	1	16/328	4.88%	0/165	0.00%	16.65 [1.01, 275.82]	0.05
Aspartate aminotransferase increased	5	54/1422	3.80%	13/1113	1.17%	3.38 [1.84, 6.21]	< 0.0001
Thrombocytopenia	4	33/1204	2.74%	4/836	0.48%	4.45 [1.41, 14.02]	0.001
Diarrhea	7	51/2103	2.43%	10/1463	0.68%	2.53 [1.16, 5.53]	0.0008
Electrocardiogram QT prolonged	3	18/760	2.37%	3/614	0.49%	2.85 [0.81, 9.95]	0.03
Pneumonia	1	6/303	1.98%	1/153	0.65%	3.03 [0.37, 24.94]	0.30
Fatigue	6	33/1800	1.83%	5/1310	0.38%	3.76 [1.62, 8.76]	0.002
Dyspnea	2	13/778	1.67%	5/556	0.90%	1.77 [0.38, 8.34]	0.20
Back pain	5	27/1631	1.66%	9/1139	0.79%	2.10 [0.97, 4.52]	0.03
γ-Glutamyltransferase increased	3	12/760	1.58%	13/614	2.12%	0.72 [0.33, 1.61]	0.52
Vomiting	6	27/1934	1.40%	12/1292	0.93%	1.39 [0.49, 3.91]	0.14
Hypokalaemia	1	4/303	1.32%	0/153	0.00%	4.56 [0.25, 84.14]	0.31
Asthenia	3	13/1035	1.26%	0/665	0.00%	4.66 [0.82, 26.49]	0.04
Abdominal pain	3	13/1060	1.23%	3/677	0.44%	2.19 [0.67, 7.18]	0.16
Blood creatinine increased	2	7/631	1.11%	0/318	0.00%	7.57 [0.43, 131.71]	0.16
Dyspnoea	1	3/288	1.04%	1/290	0.34%	3.02 [0.32, 28.87]	0.34

Abbreviations: CET: CDK4/6 inhibitors plus endocrine therapy; CI: Confidence interval; PET: Placebo plus endocrine therapy; RR: Risk ratio



Fig. 6 Funnel plots of survival summary (A), OSR (B), responses (C), and AEs summary (D) associated with CET group versus PET group

most patients, indicates that Ribociclib combined with fulvestrant, compared to fulvestrant alone, offers a higher ORR and a clear PFS benefit advantage, consistent with the results of this study [26]. These findings underscore the significant impact of CET on the efficacy for patients with HR+/HER2- breast cancer.

The subgroup analysis indicate consistent improvement in OS and PFS prognosis across the included subgroups, even though some subgroups did not show statistically significant differences in OS. A systematic review conducted by Piezzo et al. demonstrated that CDK4/6 inhibitors improved PFS prognosis regardless of the presence of metastases, including bone metastases [43]. This result aligns with our findings, suggesting that CET is particularly effective for patients with visceral metastases. However, when considering OS outcomes, the study by Lin et al. suggested OS benefits for patients with visceral metastases [44]. In contrast, our study's results indicated that patients with bone metastases also experienced improved OS prognosis. Nonetheless, it's essential to acknowledge that the number of studies and total patient numbers varied across subgroups, suggesting potential bias. Therefore, further expansion of the study population is warranted to validate these findings. Importantly, our study found that patients who had previously received ET exhibited similar OS and PFS benefits compared to those who had not undergone adjuvant or neoadjuvant ET. Preclinical research suggested cyclin D-CDK4/6-retinoblastoma pathway changes link to breast cancer's endocrine resistance. Thus, the CET could potentially offer clinical efficacy to the patients with HR+/HER2- breast cancer experiencing progression after ET [38].

In terms of safety, our results suggested that CET increased the incidence rates of neutropenia, decreased white blood cell count, leukopenia, and anemia in both any grade and grade 3-5 AEs. This suggests that CDK4/6 inhibitors may contribute to a higher frequency of hematotoxic AEs, with neutropenia being the most common, occurring at rates of 74.66% in any grade and 59.39% in grade 3-5, significantly higher than other adverse event rates. However, unlike chemotherapy drugs that induce DNA damage and cell apoptosis, CDK4/6 inhibitors primarily inhibit progenitor cells of neutrophils, thereby arresting the cell cycle and causing neutropenia, which often resolves quickly upon discontinuation of the CDK4/6 inhibitors [45]. This highlights the controllability of Neutropenia risk associated with CDK4/6 inhibitors, with no severe death events reported due to Neutropenia. Nonetheless, close monitoring of patients' blood counts is still essential during CDK4/6 inhibitor use to promptly prevent or manage serious AEs [46]. The incidence of Grade 3-5 hypertension is higher in the CET group, highlighting the importance of monitoring blood pressure, managing thromboembolic risks, and addressing cardiovascular health in patients undergoing CDK4/6 inhibitor therapy. Meanwhile, in CDK4/6 inhibitor therapy, interstitial lung disease (ILD) is a rare but serious adverse event that requires close monitoring. In our analysis, the incidence of ILD is higher in the CET group (without statistical significance). To effectively manage ILD, it is recommended to conduct baseline lung function assessments and high-resolution chest CT scans before treatment, and regularly monitor respiratory symptoms and lung function changes during treatment [47]. If suspected ILD symptoms occur, treatment should be immediately paused, and further lung evaluations and appropriate medical interventions should be carried out [48].

Limitations of this study: (1) Including only English articles may introduce language bias; (2) The research includes fewer than 10 studies, and although a funnel plot test did not show significant publication bias, accurately determining publication bias results remains challenging. (3) No individual patient data hindered patient-level meta-analysis, possibly reducing clinical value. (4) Differences in follow-up times among RCTs may increase data heterogeneity.

#### Conclusion

CET appears to outperform PET in HR+/HER2advanced breast cancer, demonstrating improved survival (OS and PFS) and responses. Survival benefits were consistent across most subgroups. However, the increased incidence of AEs, particularly hematologic AEs, requires careful consideration. Due to the limited number and quality of included studies, these conclusions require further validation through high-quality research.

#### Abbreviations

AEs	Adverse effects
CBR	Clinical benefit rate
CET	CDK4/6 inhibitors plus endocrine therapy
CDK4/6	Cyclin-dependent kinase 4/6
CI	Confidence interval
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ER+	Estrogen receptor-positive
ET	Endocrine therapy
GRADE	Grading of Recommendations, Assessment, Development, and
	Evaluation
HER2-	Human epidermal growth factor receptor 2-negative
HR	Hazard ratio
HR+	Hormone receptor-positive
ITT	Intent-to-Treat
ORR	Objective response rate
OS	Overall survival
OSR	Overall survival rate
PFS	Progression-free survival
PFSR	Progression-free survival rate
PET	Placebo plus endocrine therapy
PICOS	Participants, Intervention, Control, Outcome and Study design
PRISMA	Preferred Reporting Items for Systematic Reviews and
	Meta-Analysis
PR	Partial response
PR+	Progesterone receptors-positive
SD	Stable disease
RCT	randomized controlled trial
RR	Risk ratio

#### **Supplementary Information**

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-12782-w.

Supplementary Material 1
Supplementary Material 2
Supplementary Material 3
Supplementary Material 4
Supplementary Material 5
Supplementary Material 6
Supplementary Material 7
Supplementary Material 8
Supplementary Material 9
Supplementary Material 10
Supplementary Material 11
Supplementary Material 12

#### Acknowledgements

The authors thank professor Wenxiong Zhang, MD (Department of Thoracic Surgery, The second affiliated hospital of Nanchang University) for his data collection and statistical advice.

#### Author contributions

Zhongkui Jin had full access to all of the data in the manuscript and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Cailu Luo, Kunlin Yu, Xiaodan Luo, Tao Lian, Xuejuan Liu, Wang Xu, and Zhongkui Jin. Acquisition, analysis, or interpretation of data: Cailu Luo, Kunlin Yu, Xiaodan Luo, Tao Lian, Xuejuan Liu, Wang Xu, and Zhongkui Jin. Drafting of the manuscript: Cailu Luo, Kunlin Yu and Zhongkui

Jin. Critical revision of the manuscript for important intellectual content: Cailu Luo, Kunlin Yu, and Zhongkui Jin. Statistical analysis: Cailu Luo, Kunlin Yu, and Xiaodan Luo. Supervision: Cailu Luo, Kunlin Yu, and Zhongkui Jin.

#### Funding

This study was supported by Natural Science Foundation of Jiangxi Province (Grant number: 20212BAB206050). Role of the Funding: The funding had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

#### Data availability

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## Declarations

#### Consent for publication

Not Applicable.

#### Ethical approval

Due to the nature of this study no ethical approval was required.

#### Informed consent

For this type of study formal consent is not required.

#### **Competing interests**

The authors declare no competing interests.

Received: 24 April 2024 / Accepted: 8 August 2024 Published online: 21 August 2024

#### References

- Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74(1):12–49.
- García-Sáenz JA, Marmé F, Untch M, Bonnefoi H, Kim SB, Bear H, et al. Patientreported outcomes in high-risk HR+ /HER2- early breast cancer patients treated with endocrine therapy with or without palbociclib within the randomized PENELOPEB study. Eur J Cancer. 2024;196:113420.
- Wang QL, Zhang Y, Zeng E, Grassmann F, He W, Czene K. Risk of estrogen receptor-specific breast cancer by family history of estrogen receptor subtypes and other cancers. J Natl Cancer Inst. 2023;115(9):1020–8.
- Woolpert KM, Schmidt JA, Ahern TP, Hjorth CF, Farkas DK, Ejlertsen B, et al. Clinical factors associated with patterns of endocrine therapy adherence in premenopausal breast cancer patients. Breast Cancer Res. 2024;26(1):59.
- Burstein HJ, DeMichele A, Fallowfield L, Somerfield MR, Henry NL. Endocrine and targeted therapy for hormone Receptor-Positive, human epidermal growth factor receptor 2-Negative metastatic breast Cancer-Capivasertib-Fulvestrant: ASCO Rapid Recommendation Update. J Clin Oncol. 2024;42(12):1450–3.
- Wekking D, Leoni VP, Lambertini M, Dessi M, Pretta A, Cadoni A, et al. CDK4/6 inhibition in hormone receptor-positive/HER2-negative breast cancer: Biological and clinical aspects. Cytokine Growth Factor Rev. 2024;75:57–64.
- Roberts EL, Greenwood J, Kapadia N, Auchynnikava T, Basu S, Nurse P. CDK activity at the centrosome regulates the cell cycle. Cell Rep. 2024;43(4):114066.
- Morrison L, Loibl S, Turner NC. The CDK4/6 inhibitor revolution-a game-changing era for breast cancer treatment. Nat Rev Clin Oncol. 2024;21(2):89–105.
- Zhang P, Zhang Q, Tong Z, Sun T, Li W, Ouyang Q, et al. Dalpiciclib plus letrozole or anastrozole versus placebo plus letrozole or anastrozole as firstline treatment in patients with hormone receptor-positive, HER2-negative advanced breast cancer (DAWNA-2): a multicentre, randomised, doubleblind, placebo-controlled, phase 3 trial. Lancet Oncol. 2023;24(6):646–57.
- Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Ribociclib as First-Line therapy for HR-Positive, advanced breast Cancer. N Engl J Med. 2016;375(18):1738–48.

- 11. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, et al. Phase III randomized study of Ribociclib and Fulvestrant in hormone Receptor-Positive, human epidermal growth factor receptor 2-Negative advanced breast Cancer: MONALEESA-3. J Clin Oncol. 2018;36(24):2465–72.
- Tripathy D, Im SA, Colleoni M, Franke F, Bardia A, Harbeck N, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptorpositive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol. 2018;19(7):904–15.
- Goetz MP, Toi M, Campone M, Sohn J, Paluch-Shimon S, Huober J, et al. MONARCH 3: Abemaciclib as initial therapy for advanced breast Cancer. J Clin Oncol. 2017;35(32):3638–46.
- 14. Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, et al. Palbociclib and Letrozole in Advanced breast Cancer. N Engl J Med. 2016;375(20):1925–36.
- Xu B, Hu X, Li W, Sun T, Shen K, Wang S, et al. Palbociclib plus Letrozole versus placebo plus letrozole in Asian postmenopausal women with oestrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: primary results from PALOMA-4. Eur J Cancer. 2022;175:236–45.
- Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1–12.
- Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
- Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011;64(4):380–2.
- Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. Ann Oncol. 2018;29(7):1541–7.
- O'Shaughnessy J, Petrakova K, Sonke GS, Conte P, Arteaga CL, Cameron DA, et al. Ribociclib plus Letrozole versus letrozole alone in patients with de novo HR+, HER2- advanced breast cancer in the randomized MONALEESA-2 trial. Breast Cancer Res Treat. 2018;168(1):127–34.
- Sonke GS, Hart LL, Campone M, Erdkamp F, Janni W, Verma S, et al. Ribociclib with letrozole vs letrozole alone in elderly patients with hormone receptorpositive, HER2-negative breast cancer in the randomized MONALEESA-2 trial. Breast Cancer Res Treat. 2018;167(3):659–69.
- Yardley DA, Hart L, Favret A, Blau S, Diab S, Richards D, et al. Efficacy and safety of Ribociclib with Letrozole in US patients enrolled in the MONA-LEESA-2 study. Clin Breast Cancer. 2019;19(4):268–e2771.
- Slamon D, Lipatov O, Nowecki Z, McAndrew N, Kukielka-Budny B, Stroyakovskiy D, et al. Ribociclib plus Endocrine Therapy in early breast Cancer. N Engl J Med. 2024;390(12):1080–91.
- Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, et al. Overall survival with Ribociclib plus Fulvestrant in Advanced breast Cancer. N Engl J Med. 2020;382(6):514–24.
- Slamon DJ, Neven P, Chia S, Jerusalem G, De Laurentiis M, Im S, et al. Ribociclib plus fulvestrant for postmenopausal women with hormone receptorpositive, human epidermal growth factor receptor 2-negative advanced breast cancer in the phase III randomized MONALEESA-3 trial: updated overall survival. Ann Oncol. 2021;32(8):1015–24.
- Neven P, Fasching PA, Chia S, Jerusalem G, De Laurentiis M, Im SA, et al. Updated overall survival from the MONALEESA-3 trial in postmenopausal women with HR+/HER2- advanced breast cancer receiving first-line ribociclib plus fulvestrant. Breast Cancer Res. 2023;25(1):103.
- Im SA, Lu YS, Bardia A, Harbeck N, Colleoni M, Franke F, et al. Overall survival with Ribociclib plus endocrine therapy in breast Cancer. N Engl J Med. 2019;381(4):307–16.
- Lu YS, Im SA, Colleoni M, Franke F, Bardia A, Cardoso F, et al. Updated overall survival of Ribociclib plus endocrine therapy versus endocrine therapy alone in pre- and perimenopausal patients with HR+/HER2- advanced breast Cancer in MONALEESA-7: a phase III Randomized Clinical Trial. Clin Cancer Res. 2022;28(5):851–9.
- Johnston S, Martin M, Di Leo A, Im SA, Awada A, Forrester T, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. NPJ Breast Cancer. 2019;5:5.
- Toi M, Inoue K, Masuda N, Iwata H, Sohn J, Hae Park I, et al. Abemaciclib in combination with endocrine therapy for east Asian patients with HR+, HER2- advanced breast cancer: MONARCH 2 & 3 trials. Cancer Sci. 2021;112(6):2381–92.

- Goetz1 MP, Toi M, Huober J, Sohn J, Tredan O, Park IH et al. LBA15 MONARCH 3: interim overall survival (OS) results of abemaciclib plus a nonsteroidal aromatase inhibitor (NSAI) in patients (pts) with HR+, HER2- advanced breast cancer (ABC). Ann Oncol 33:S1384.
- 32. Takahashi M, Tokunaga E, Mori J, Tanizawa Y, van der Walt JS, Kawaguchi T, et al. Japanese subgroup analysis of the phase 3 MONARCH 3 study of abemaciclib as initial therapy for patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer. Breast Cancer. 2022;29(1):174–84.
- Mukai H, Shimizu C, Masuda N, Ohtani S, Ohno S, Takahashi M, et al. Palbociclib in combination with letrozole in patients with estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: PALOMA-2 subgroup analysis of Japanese patients. Int J Clin Oncol. 2019;24(3):274–87.
- Rugo HS, Finn RS, Gelmon K, Joy AA, Harbeck N, Castrellon A, et al. Progression-free survival outcome is Independent of Objective response in patients with estrogen Receptor-positive, human epidermal growth factor receptor 2-negative advanced breast Cancer treated with Palbociclib Plus Letrozole compared with letrozole: analysis from PALOMA-2. Clin Breast Cancer. 2020;20(2):e173–80.
- Im SA, Mukai H, Park IH, Masuda N, Shimizu C, Kim SB, et al. Palbociclib Plus Letrozole as First-Line therapy in postmenopausal Asian women with metastatic breast Cancer: results from the Phase III, Randomized PALOMA-2 study. J Glob Oncol. 2019;5:1–19.
- Gelmon K, Walshe JM, Mahtani R, Joy AA, Karuturi M, Neven P, et al. Efficacy and safety of palbociclib in patients with estrogen receptor-positive/ human epidermal growth factor receptor 2-negative advanced breast cancer with preexisting conditions: a post hoc analysis of PALOMA-2. Breast. 2021;59:321–6.
- Slamon DJ, Diéras V, Rugo HS, Harbeck N, Im SA, Gelmon KA, et al. Overall survival with Palbociclib Plus Letrozole in Advanced breast Cancer. J Clin Oncol. 2024;42(9):994–1000.
- Peurala E, Koivunen P, Haapasaari KM, Bloigu R, Jukkola-Vuorinen A. The prognostic significance and value of cyclin D1, CDK4 and p16 in human breast cancer. Breast Cancer Res. 2013;15(1):R5.
- Beaver JA, Amiri-Kordestani L, Charlab R, Chen W, Palmby T, Tilley A, et al. FDA approval: Palbociclib for the Treatment of Postmenopausal Patients with estrogen Receptor-Positive, HER2-Negative metastatic breast Cancer. Clin Cancer Res. 2015;21(21):4760–6.
- 40. Shah A, Bloomquist E, Tang S, Fu W, Bi Y, Liu Q, et al. FDA approval: Ribociclib for the Treatment of Postmenopausal Women with hormone

Receptor-Positive, HER2-Negative Advanced or metastatic breast Cancer. Clin Cancer Res. 2018;24(13):2999–3004.

- 41. Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, et al. The cyclindependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol. 2015;16(1):25–35.
- 42. Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, Masuda N, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol. 2016;17(4):425–39.
- Piezzo M, Chiodini P, Riemma M, Cocco S, Caputo R, Cianniello D, et al. Progression-free survival and overall survival of CDK 4/6 inhibitors plus endocrine therapy in metastatic breast Cancer: a systematic review and Meta-analysis. Int J Mol Sci. 2020;21(17):6400.
- Lin M, Chen Y, Jin Y, Hu X, Zhang J. Comparative overall survival of CDK4/6 inhibitors plus endocrine therapy vs. endocrine therapy alone for hormone receptor-positive, HER2-negative metastatic breast cancer. J Cancer. 2020;11(24):7127–36.
- Lai JI, Kuo TH, Huang KJ, Chai LMX, Lee MH, Liu CY, et al. Clinical and genotypic insights into higher prevalence of Palbociclib Associated Neutropenia in Asian patients. Oncologist. 2024;29(4):e455–66.
- 46. Lavery L, DiSogra K, Lea J, Trufan SJ, Symanowski JT, Roberts A, et al. Risk factors associated with palbociclib-induced neutropenia in patients with metastatic breast cancer. Support Care Cancer. 2022;30(12):9803–9.
- Birnhuber A, Egemnazarov B, Biasin V, Bonyadi Rad E, Wygrecka M, Olschewski H, Kwapiszewska G, Marsh LM. CDK4/6 inhibition enhances pulmonary inflammatory infiltration in bleomycin-induced lung fibrosis. Respir Res. 2020;21(1):167.
- Schlam I, Giordano A, Tolaney SM. Interstitial lung disease and CDK4/6 inhibitors in the treatment of breast cancer. Expert Opin Drug Saf. 2023;22(12):1149–56.

#### **Publisher's Note**

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.