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The impact of Pegylated liposomal doxorubicin in recurrent ovarian cancer: an updated meta-analysis of randomized clinical trials



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Abstract

Background: Previous meta-analysis studies suggested that pegylated liposomal doxorubicin (PLD) may improve the survival rate of patients with recurrent ovarian cancer. The aim of the present meta-analysis, then, was to further update the role of PLD in the treatment of recurrent ovarian cancer.

Methods: We performed a literature search using the electronic databases Medicine, EMBASE, Web of Science, and the Cochrane Library to 27 July 2020. We only restricted the randomized clinical trials. Study-specific hazard ratios and 95% confidence interval (HR/95% CI) and risk ratios and 95% confidence interval (RR/95% CI) were pooled using a random-effects model.

Results: Ten studies (12 trials) were included after screening 940 articles. We categorized the eligible studies into two groups: the doublet regimens (four trials, 1767 patients) showed that PLD plus carbo provided superior progression-free survival (PFS) (HR, 0.85; 95% Cl, 0.74–0.97) and similar overall survival (OS) (HR, 1.00; 95% Cl, 0.88–1.14) compared to paclitaxel (PAC) plus carboplatin (carbo). PLD plus carbo was associated with significantly more anemia and thrombocytopenia, and other side effects were well tolerated. The monotherapy regimens (eight trials, 1980 patients) showed that PLD possessed a similar PFS (HR, 1.02; 95% Cl, 0.90–1.16) and OS (HR, 0.88; 95% Cl, 0.77–1.01) relative to other monotherapies. PLD alone was also more associated with mucositis/stomatitis and hand-foot syndrome, while other side effects were well tolerated.

Conclusions: In platinum-sensitive recurrent ovarian cancer, PLD plus carbo was more effective than PAC plus carbo, while in platinum-resistant or -refractory recurrent ovarian cancer, PLD exhibited similar survival to other monotherapies. Regarding side effects, PLD plus carbo and mono chemotherapy were both well tolerated.

Keywords: Ovarian neoplasms, Pegylated liposomal doxorubicin, Progression-free survival, Overall survival, Meta-analysis

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Introduction

Ovarian cancer is one of the most common gynecologic malignancies, with the third highest incidence of gynecologic tumors and the highest mortality rate. Because ovarian cancer is not easy to detect at the early stages, it is usually diagnosed at an advanced stage, and its 5-year relative survival rate is comparatively low. The lifetime risk for ovarian cancer is approximately 1 in 75, and the likelihood of dying from this malignancy is 1 in 100 [1, 2]. Cytoreductive surgery followed by platinum-based chemotherapy remains the mainstay of treatment in ovarian cancer. Yet, despite complete remission through the very best treatments, approximately 70-80% of patients with International Federation of Gynecology and Obstetrics stage III to IV disease experience a relapse within 5 years [3, 4]. Thus, ovarian cancer remains a serious threat to women's health worldwide.

For patients with platinum-sensitive recurrent ovarian cancer, we usually choose carboplatin (carbo) in combination with paclitaxel (PAC) as the first-line standard chemotherapy regimen, but this regimen exhibits more non-hematologic toxicity, which results in early discontinuation of treatment. Specifically, this regimen imposes high rates of alopecia, hypersensitivity, and neurotoxicity [5], and platinum re-challenge therapy in platinumrefractory or -resistant patients usually results in low response rates and short survival. In this particular setting, chemotherapy with single agents shows activity and lower toxicity than combination chemotherapy [6]. Single-agent second-line treatments include non-platinum compounds such as PAC, topotecan, PLD, gemcitabine, etoposide, vinorelbine, and bevacizumab, and we typically choose sequential single chemotherapeutic agents depending upon the various conditions exhibited by patients. While treatment options for recurrent ovarian cancer have increased, the majority of these patients will still eventually die from ovarian cancer. Therefore, the goal of therapy in the recurrent setting should not only focus on improving the length of life but also include a thoughtful review of anticipated side effects and overall quality of life.

PLD—anthracycline chemotherapy derived from doxorubicin—was the first FDA-approved cancer nanomedicine [7], and was used as early as 2014 for the treatment of ovarian and breast cancer, multiple myeloma, and Kaposi sarcoma [8]. The 2017 NCCN Guidelines recommended that carbo combined with PLD be added as one of the initial chemotherapy regimens for ovarian cancer. Carbo combined with PLD was thus recommended for patients with recurrent platinum-sensitive ovarian cancer, and PLD monotherapy was recommended for relapsed platinum-resistant ovarian cancer patients. The 2018 NCCN Guidelines included PLD as a first-line chemotherapy regimen for ovarian cancer, and a regimen of carbo combined with PLD is recommended for initial treatment of stage-1 ovarian cancer. The 2019 NCCN Guidelines recommend that PLD plus bevacizumab be used as a potential treatment option for patients with platinum-resistant recurrent ovarian cancer. Clinical studies have shown that compared with other standard chemotherapy regimens, PLD possesses a non-inferior survival rate and is well tolerated, exhibiting reduced alopecia and neuro-toxicity [9].

Previous studies [10, 11] showed that PLD is effective and well tolerated in the treatment of ovarian cancer. However, because these two meta-analyses were published earlier and contained fewer trials, we added the most recent trials and performed an updated meta-analysis. We trust that our study results will soon facilitate the selection of chemotherapy regimens for recurrent ovarian cancer patients.

Methods

Search strategy

We conducted this meta-analysis framework under the guidance of PRISMA, and performed queries of the literature using the electronic databases Medicine, EMBASE, Web of Science, and the Cochrane Library to 27 July 2020. The search MeSH terms and free words used were 1) "Pegy-lated Liposomal Doxorubicin," "Caelyx," "Lipodox," "Doxil," 2) "ovarian cancer," "ovarian neoplasm," "ovarian carcinoma, " and 3) "Randomized Controlled Trial." We did not limit the language for our searches or the studies included in the present investigation. The details of the search strategy are presented in Supplementary Material 1.

Eligibility criteria

The abstracts of all articles retrieved in the initial search were independently screened by two authors (X.R.L and L.X.P). The procedures were executed by the independent reviewers according to the following criteria. The inclusion criteria were 1) patients with histologically confirmed recurrent ovarian cancer; 2) patients with interventions involving PLD alone versus other monotherapy, or PLD plus carboplatin versus paclitaxel plus carboplatin; 3) outcome measures that involved survival outcome and adverse events; and 4) all RCT studies. The exclusion criteria were 1) patients not having previously received PLD; 2) patients not having undergone any examinations for ovarian cancer; 3) pediatric populations (<18 years of age); 4) animal/laboratory studies; 5) review articles, case reports, letters, commentaries, or conference proceedings; and 6) no histologic confirmation of recurrent ovarian cancer. Disagreements were discussed with a third author (Prof. G.N.Z) to achieve consensus.

For the present study, the same two authors who performed full-text screening independently conducted data extraction, and all inconsistencies were resolved by consensus. Selected full-text manuscripts were reviewed in detail to determine their relevance. The exclusion criteria were 1) those studies not within the current research aims; 2) studies with missing data; and 3) overlapping studies.

Data extraction

Data were extracted from the studies that we ultimately used, and data included first author, journal, year of publication, number, age and characteristics of patients, study design, and outcomes.

Statistical analysis

For survival variables such as progression-free survival (PFS) and overall survival (OS), we used hazard ratios (HR) and 95% CI, which are presented as forest plots. For categorical variables, we used risk ratios (RR) and 95% CI, which are also presented as forest plots. Heterogeneity across studies was evaluated using the I² metric and Chi-squared test. We used the random-effects model to calculate the summary estimate if heterogeneity was shown (I² > 50%) across studies; otherwise, the fixed-effects model was used (I² \leq 50%). If heterogeneity was

uncovered across studies, we performed subgroup analyses based upon study design and then analyzed the subgroup results. If potential publication bias was shown across studies, we used Egger's linear regression test, as well as Begg's funnel plot. All statistical testing was conducted using the Review Manager 5.3 (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and Stata.15.0 (Stata-Corp, College Station, TX). All tests were two-sided with P < 0.05 considered statistically significant, except for the heterogeneity test (P < 0.1) and publication bias (P < 0.1) in our meta-analyses.

Results

Literature search

We designated for initial evaluation a total of 940 articles using our electronic database search. After removing duplicate articles and screening the study titles and abstracts, 56 articles meeting the inclusion criteria underwent full-text assessment, resulting in 10 relevant studies [12–22]. A flowchart of the selection procedure is shown in Fig. 1.



Study characteristics

We categorized the 12 eligible trials into two groups: PLD plus carbo vs. PAC plus carbo (four trials [12–15]: 851 PLD plus carbo and 916 PAC plus carbo), and PLD vs. other monotherapies (eight trials [16-21]: 963 PLD and 1017 other monotherapies). Vergote 2009 [18] was utilized in both trials-PLD vs topotecan and PLD vs canfosfamide, and Kave 2012 [21] was integrated into both trials-PLD vs. 200 mg of olaparib and PLD vs. 400 mg of olaparib. All features of the included studies are depicted in Table.1. We assessed the study quality based on the Cochrane Collaboration tool and the criteria specified in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions [23] (Table 2). Each study was evaluated for potential bias and quality by two independent and experienced authors, and disagreements were resolved by consensus.

Extraction of data

Overall analysis of doublet regimens: PLD plus carbo vs. PAC plus carbo

PLD plus carbo was associated with a significant improvement in PFS (HR, 0.85; 95% CI, 0.74–0.97; $I^2 = 28\%$; p = 0.02), while OS was similar to the standard chemotherapy regimen PAC plus carbo (HR, 1.00; 95% CI, 0.88–1.14; $I^2 = 0\%$; p = 0.99) (Fig. 2).

With respect to grade 3–4 toxicities, PLD plus carbo was associated with a decreased risk of an allergic reaction (RR, 0.38; 95% CI, 0.19–0.78; $I^2 = 0\%$; p < 0.01), arthralgia/myalgia (RR, 0.19; 95% CI, 0.05–0.68; $I^2 = 0\%$; p = 0.01), and neutropenia (RR, 0.76; 95% CI, 0.67–0.86; $I^2 = 0\%$; p < 0.01). PLD plus carbo was also associated with an increased risk of anemia (RR, 1.82; 95% CI, 1.22–2.71; $I^2 = 0\%$; p < 0.01) and thrombocytopenia (RR, 2.67; 95% CI,1.94–3.67; $I^2 = 0\%$; p < 0.01). There was no difference in the risk of fatigue/asthenia (RR, 1.10; 95% CI, 0.78–1.56; $I^2 = 0\%$; p = 0.57), mucositis/stomatitis (RR, 2.04; 95% CI, 0.90–4.66; $I^2 = 0\%$; p = 0.09), hand–foot syndrome (RR, 2.76; 95% CI, 0.50–15.16; $I^2 = 0\%$; p = 0.24), or vomiting (RR, 1.38; 95% CI, 0.72–2.66; $I^2 = 44\%$; p = 0.33) (Fig. 3).

Overall analysis of monotherapy regimens: PLD vs. single agent

PLD was similar in PFS (HR,1.02; 95% CI, 0.90–1.16; $I^2 = 0\%$; p = 0.72) and OS (HR, 0.88; 95% CI, 0.77–1.01; $I^2 = 0\%$; p = 0.07) to other single agents (Fig. 4).

With respect to grade 3–4 toxicities, PLD was associated with a significantly increased risk of mucositis/stomatitis (RR, 0.10; 95% CI, 0.04–0.23; $I^2 = 0\%$; p < 0.01) and hand–foot syndrome (RR, 0.03; 95% CI, 0.01–0.09; $I^2 = 0\%$; p < 0.01) compared with the other monotherapies. There were no differences in the risks of anemia (RR, 1.26; 95% CI, 0.86–1.83; $I^2 = 0\%$; p = 0.23), vomiting

(RR, 0.97; 95% CI, 0.57–1.66; $I^2 = 38\%$; p = 0.91), fatigue/ asthenia (RR, 1.09; 95% CI, 0.73–1.64; $I^2 = 19\%$; p = 0.66), thrombocytopenia (RR, 1.73; 95% CI, 0.93–3.24; $I^2 = 4\%$; p = 0.08), or neutropenia (RR, 1.32; 95% CI, 0.59–2.96; $I^2 = 86\%$; p = 0.50) (Fig. 5).

Subgroup analysis

We performed side-effect subgroup analysis with respect to neutropenia based upon the different drugs in the monotherapy regimens ($I^2 = 86\%$): one subgroup [18, 19] showed that canfosfamide and patupilone correlated with lower risk than PLD (RR, 0.39; 95% CI, 0.21-0.72; $I^2 = 33\%$; p < 0.01), while the other subgroup [16–18, 20] showed that gemcitabine, topotecan, Lifastuzumab vedotin (LIFA), and olaparib reflected higher risk than PLD (RR, 2.26; 95% CI, 1.61–3.17; $I^2 = 0\%$; p < 0.01). We then performed subgroup analysis for the differences in toxicity and side effects based on the different doses of PLD. In doublet regimens, we observed anemia at 30 mg/ m^2 vs. 45 mg/m² PLD (I² = 0%), and thrombocytopenia at $30 \text{ mg/m}^2 \text{ vs. } 45 \text{ mg/m}^2 \text{ PLD} (I^2 = 0\%)$. There was, however, no difference in the incidence of adverse reactions at the different doses of PLD. For monotherapy regimens, the incidence of mucositis/stomatitis was similar between 40 mg/m^2 and 50 mg/m^2 PLD (I² = 60.5%), and hand-foot syndrome was similar between 40 mg/m² and 50 mg/m² PLD ($I^2 = 30.2\%$).

Publication bias

To assess all studies with regard to PFS in potential publication bias, we used Egger's linear regression test (p = 0.635), as well as Begg's funnel plot (p = 0.592). The test results showed that this updated meta-analysis showed no significant publication bias (Supplementary Material 2).

Discussion

To the best of our knowledge, the present study is the most recently updated meta-analysis with respect to the curative effects and side effects of PLD in recurrent ovarian cancer chemotherapy. Our results suggest that PLD is as effective or better in the treatment of recurrent ovarian cancer compared to other therapies. The secondary indicators showed that most patients tolerated the therapy well and manifested no serious adverse reactions.

Doublet regimens

Our study results illustrated the superiority of platinum doublets of carbo plus PAC, carbo plus gemcitabine, and carbo plus PLD to single-agent platinum, and that carbo plus PLD was as effective as carbo plus PAC in women with highly sensitive and relapsed ovarian cancer [4, 22, 24, 25]. We therefore only selected and compared doublet regimens based on platinum in platinum-sensitive

Study	Intervention	No.of	Age, years	Type of trial	Patient characteristics	Pretreatment status	Main outcomes
		participatits	ivieulari (rariye)				
Pujade-Lauraine	carbo(AUC5) + PLD 30 mg/m2 q4wks	466	60.5 (24–82)	phase III randomized	PS ROC	After first-or second-line	PFS, OS,
2010 [13]	carbo(AUC5) + PAC 175 mg/m2 q3wks	509	61 (27–82)	multicenter, open-label trial		Platinum and taxane-based	Toxicity
Gladieff2012 [14]	carbo(AUC5) + PLD 30 mg/m2 q4wks	161	60 (24–82)	phase III randomized	PS ROC	After first- or second-line	PFS,
	carbo(AUC5) + PAC 175 mg/m2 q3wks	183	60 (30–80)	non-inferiority trial		platinum- and taxane-based	Toxicity
Mahner2014 [15]	carbo(AUC5) + PLD 30 mg/m2 q4wks	131	60 (30–80)	phase III randomized	PS ROC	Platinum and	PFS, OS,
	carbo(AUC5) + PAC 175 mg/m2 q3wks	128	63 (27–82)	multicenter trial		taxane-pretreated	Toxicity
Bafaloukos2010 [16]	carbo(AUC5) + PLD 45 mg/m2 q4wks	93	62 (38–89)	phase II randomized	PS ROC	One cycle or more	ORR, OS,
	carbo(AUC5) + PAC 175 mg/m2 q3wks	96	63 (37–81)	multicenter		Of platinum-based	loxicity
Mutch2007 [17]	PLD 50 mg/m2 IVI q4wks	96	62 (28–83)	phase III randomized	PS ROC	Prior platinum-based	PFS, OS,
	Gemcitabine 1000 mg/m2 D1,8 q3wks	66	59 (38–85)	multicenter open-label		S 2 prior regimens allowed	loxicity
Ferrandina2008 [18]	PLD 40 mg/m2 IVI q4wks	76	63 (28–80)	phase III randomized	Partial PS and	Failed first-line	OS,
	Gemcitabine 1000 mg/m2 D1,5,8,15 q4wks	77	63 (39–79)	multicenter	PR ROC	Platinum or paclitaxel	loxicity
Vergote2009I [19]	PLD 50 mg/m2 IVI q4wks	130	60 (30–82)	phase III randomized	platinum-refractory	Failed one second-Line	Toxicity
	Canfosfamide 1000 mg/m2 q3wks	231	60 (26–85)	multicenter	or PR ROC	therapy with either topotecan or PLD	
Vergote2009II [1 <mark>9</mark>]	PLD 50 mg/m2 IVI q4wks	130	60 (30–82)	phase III randomized	platinum-refractory	Failed one second-Line	Toxicity
	Topotecan 1.5 mg/m2 D1–5 q3wks	87	60 (30–82)	multicenter	or PR ROC	therapy with either topotecan or PLD	
Colombo2012 [20]	PLD 50 mg/m2 IVI q4wks	417	59 (23–84)	phase III randomized	PR ROC	Failed≥4 cycles of	PFS, OS,
	Patupilone 10 mg/m2 IVI q3wks	412	59 (25–87)	open-label		platinum-based or discontinued	loxicity
Banerjee2018 [21]	PLD 40 mg/m2 IVI q4wks	48	62 (52–86)	phase II randomized	PR ROC	Progressed or relapsed	PFS,
	LIFA 2.4 mg/kg q3wks	47	62 (43–83)	open-label		< 6 months with a platinum-based	Toxicity
Kaye2012l [<mark>22</mark>]	PLD 50 mg/m2 IVI q4wks	33	53 (43–81)	phase II open-label	Partial PS and	Recurred or progressed < 12	PFS, OS,
	Olaparib 200 mg bid continuously	32	58.5 (45–77)	randomized Multicenter	PR ROC	months with platinum-based	loxicity
Kaye2012II [<mark>22</mark>]	PLD 50 mg/m2 IVI q4wks	33	53 (43–81)	phase II open-label	Partial PS and	Recurred or progressed < 12	PFS,OS,
	Olaparib 400 mg bid continuously	32	53.5 (35–76)	randomized Multicenter	PK RUC	months with platinum-based	loxicity
Note: OS Overall sur	vival; PFS Progression-free survival; PS Platin	um-sensitive; P	R Platinum-resistan	t; ROC Recurrent ovarian	cancer		

Table 1 Characteristics of included studies

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	other bias
Pujade-Lauraine2010 [13]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Gladieff2012 [14]	Low risk	Unclear risk	High risk	Low risk	Low risk	Low risk	Low risk
Mahner2014 [15]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Bafaloukos2010 [16]	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Mutch2007 [17]	Low risk	Low risk	High risk	Unclear risk	Unclear risk	High risk	Low risk
Ferrandina2008 [18]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Vergote2009 [19]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Colombo2012 [20]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Banerjee2018 [21]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Kaye2012 [22]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk

Table 2 Risk of bias for included studies

recurrent ovarian cancer. PLD plus carbo was superior in PFS without a change in OS. We found that of four doublet regimen trials, only the studies by Pujade-Lauraine2010 and Gladieff (2012) showed that PFS was prolonged in the PLD-plus-carbo group. In the Pujade-Lauraine study, 90% of the women received postprogression treatment, and the proportion of women in the PAC-plus-carbo arm who received PLD as poststudy therapy (68%) was significantly higher than the proportion of women in the PLD-plus-carbo arm who received PAC (43%, P < 0.01), and this may have influenced the OS HR in the direction of the PAC-plus-carbo arm [11]. However, in the Gladieff study, OS was not assessed due to the fact that overall survival data were immature, such that there was no exact comparison between PFS and OS. Another perspective suggests the possibility that tumor cells that survive treatment with PLD plus carbo may be more aggressive or may be resistant to subsequent therapies. When the disease then recurs, it may progress more quickly or may be resistant to other therapies, thus negating any benefits on OS [10]. We also speculate that the study by Bafaloukos in 2010 (a phase-II study) did not have sufficient statistical power to assess OS, which may have affected the final results. The specific reasons for these disparate results remain unclear, and further research is therefore needed.

Study	PLD + carbo N	PAC + carbo N	Hazard Ratio IV,Random,95%CI	Weight	Hazard Ratio IV,Random,95%CI
PFS					
Gladieff2012	161	183	⊢ ∎→	23.9%	0.73 [0.58, 0,92]
Pujade-Lauraine2010	466	507	H H H	45.7%	0.82 [0.72, 0.94]
Bafaloukos2010	93	96	⊢ −	15.2%	0.98 [0.72, 1.33]
Mahner2015	131	128	⊢ ⊨ i	15.3%	1.03 [0.76, 1.40]
Subtotal (95%CI)	851	914	⊢♠⊣	100.0%	0.85 [0.74, 0.97]
Heterogeneity: $Tau^2 = 0.01$;	; $Chi^2 = 4.18$, $df = 3$ (1)	$P = 0.24$; $I^2 = 28\%$			
Test for overall effect: $Z = 2$	2.41 (P = 0.02)				
OS					
Pujade-Lauraine2010	466	507	⊢ <mark>≢</mark> 1	71.1%	0.99 [0.85, 1.15]
Bafaloukos2010	93	96	⊢	13.5%	0.88 [0.62, 1.25]
Mahner2015	131	128	I → → → →	15.4%	1.18 [0.85, 1.64]
Subtotal (95%CI)	690	731		100.0%	1.00 [0.88, 1.14]
Heterogeneity: $Tau^2 = 0.00$;	$chi^2 = 1.51, df = 2$ (1)	$P = 0.47$; $I^2 = 0\%$			
Test for overall effect: $Z = 0$	0.02 (P = 0.99)				
			0.4 0.6 0.8 1 1.2 1.4 1.6 1.8		
			Favours PLD + carbo Favours PAC + carbo		
Fig. 2 Forest plots of eff	icacy endpoints. D	oublet regimens			

Allergic reaction	PLD + carbo n/N	PAC + carbo n/N	Risk Ratio IV,Random,95%CI	Weight	Risk Ratio IV,Random,95%CI
Gladieff2012	5/161	17/180	=1	53.7%	0.33 [0.12, 0.87]
Bafaloukos2010	1/84	1/89		- 6.7%	1.06 [0.07, 16.67]
Mahner2015	4/131	10/128	-	39.6%	0.39 [0.13, 1.21]
Subtotal (95%Cl)	10/376	28/397	+	100.0%	0.38 [0.19, 0.78]
Heterogeneity: Tau ² = 0.0	00; Chi ² = 0.62, df =	= 2 (P = 0.73); I ² =0%			
Test for overall effect: Z =	= 2.65 (P < 0.01)				
Arthralgia/myalgia					
Gladieff2012	0/161	5/180	T	20.0%	0.10 [0.01, 1.82]
Pujade-Lauraine2010	1/466	6/501	P-+1	37.4%	0.18 [0.02, 1.48]
Bafaloukos2010	0/84	8/89	►	20.7%	0.06 [0.00, 1.06]
Mahner2015	1/131	1/128	H	- 21.9%	0.98 [0.06, 15.45]
	0/040	00/000	•	400.0%	0 40 50 05 0 001
SUDIOIAI (95%CI) Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	2/842 00; Chi ² = 2.23, df = = 2.55 (P = 0.01)	20/898 = 3 (P = 0.53); I ² =0%		100.0%	0.19 [0.05, 0.68]
Neutropenia					
Gladieff2012	62/161	91/180	-	25.3%	0.76 [0.60, 0.97]
Pujade-Lauraine2010	164/466	229/501	•	61.4%	0.77 [0.66, 0.90]
Bafaloukos2010	5/84	6/89	H	1.1%	0.88 [0 28. 2 79]
Mahner2015	36/131	51/128	-	12.2%	0.69 [0.49, 0.98]
	50/151	51,120			[0.10, 0.00]
Subtotal (95%Cl) Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =	267/842 00; Chi ² = 0.39, df = = 4.43 (P < 0.01)	377/898 = 3 (P = 0.94); I ² =0%	•	100.0%	0.76 [0.67, 0.86]
Mucositis/stomatitis					
Gladieff2012	3/161	3/180	H H	26.9%	1.12 [0.23, 5.46]
Puiade-Lauraine2010	9/466	5/501	H B	57.5%	1.94 [0.65, 5.73]
Bafaloukos2010	3/84	0/89	· •	- 7.8%	7,41 [0.39, 141 37]
Mahner2015	3/131	0/128	-	- 7.8%	6.84 [0.36, 131.13]
Subtotal (95%CI)	18/842	8/898	 ←'	100.0%	2.04 [0.90, 4.66]
Heterogeneity: Tau ^z = 0.0 Test for overall effect: Z =	00; Chi ^c = 2.00, df = = 1.70 (P = 0.09)	: 3 (P = 0.57); I ^z =0%			
Fatigue/asthenia					
Gladieff2012	15/161	15/180	+	25.3%	1.12 [0.56, 2.21]
Pujade-Lauraine2010	31/466	33/501	+ +	52.6%	1.01 [0.63, 1.62]
Bafaloukos2010	6/84	6/89	H	9.9%	1.06 [0.36. 3.16]
Mahner2015	10/131	6/128	H=	12.2%	1.63 [0.61, 4.35]
man11012010	10/151	0/120		12.270	1.00 [0.01, 4.00]
Subtotal (95%Cl)	62/842	60/898	+ '	100.0%	1.10 [0.78, 1.56]
Hand-foot syndrome					
Gladieff2012	1/161	1/180		38.1%	1.12 [0.07, 17.73]
Pujade-Lauraine2010	0/466	0/501			Not estimable
Bafaloukos2010	1/84	0/89		- 28.6%	3.18 [0.13, 76.91]
Mahner2015	3/131	0/128	-	- 33.3%	6.84 [0.36,131.13]
Subtotal (95%Cl) Heterogeneity: Tau ² = 0.0	5/842 00; Chi ² = 1.51, df =	1/898 = 2 (P = 0.47); I ² =0%	⊢ _	100.0%	2.76 [0.50, 15.16]
Test for overall effect: Z =	= 0.02 (P = 0.99)				
Test for overall effect: Z = Vomiting	= 0.02 (P = 0.99)				
Test for overall effect: Z = Vomiting Gladieff2012	= 0.02 (P = 0.99) 16/161	7/180		29.3%	2.56 [1.08, 6.05]
Test for overall effect: Z = Vomiting Gladieff2012 Pujade-Lauraine2010	16/161 22/466	7/180 23/501	1	29.3% 41.0%	2.56 [1.08, 6.05] 1.03 [0.58, 1.82]
Test for overall effect: Z = Vomiting Gladieff2012 Pujade-Lauraine2010 Bafaloukos2010	16/161 22/466 4/84	7/180 23/501 1/89	10-1 1-	29.3% 41.0% — 7.9%	2.56 [1.08, 6.05] 1.03 [0.58, 1.82] 4.24 [0.48, 37.15]
Test for overall effect: Z = Vomiting Gladieff2012 Pujade-Lauraine2010 Bafaloukos2010 Mahner2015	16/161 22/466 4/84 5/131	7/180 23/501 1/89 7/128		29.3% 41.0% 	2.56 [1.08, 6.05] 1.03 [0.58, 1.82] 4.24 [0.48, 37.15] 0.70 [0.23, 2.14]
Test for overall effect: Z = Vomiting Gladieff2012 Pujade-Lauraine2010 Bafaloukos2010 Mahner2015 Subtotal (95%CI) Heterogeneity: Tau ² = 0. Test for overall effect: Z =	16/161 22/466 4/84 5/131 47/842 19; Chi ² = 5.34, df = = 0.96 (P = 0.33)	7/180 23/501 1/89 7/128 38/898 : 3 (P = 0.15); I ² =44%		29.3% 41.0% 7.9% 21.7% 100.0%	2.56 [1.08, 6.05] 1.03 [0.58, 182] 4.24 [0.48, 37.15] 0.70 [0.23, 2.14] 1.38 [0.72, 2.66]
Test for overall effect: Z = Vomiting Gladieff2012 Pujade-Lauraine2010 Bafaloukos2010 Mahner2015 Subtotal (95%CI) Heterogeneity: Tau ² = 0.: Test for overall effect: Z = Anemia	16/161 22/466 4/84 5/131 47/842 19: Chi ² = 5.34, df = 0.96 (P = 0.33)	7/180 23/501 1/89 7/128 38/898 = 3 (P = 0.15); I ² =44%		29.3% 41.0% 7.9% 21.7% 100.0%	2.56 [1.08, 6.05] 1.03 [0.58, 1.82] 4.24 [0.48, 37.15] 0.70 [0.23, 2.14] 1.38 [0.72, 2.66]
Test for overall effect: Z = Vomiting Gladieff2012 Pujade-Lauraine2010 Mahner2015 Subtotal (95%CI) Heterogeneity: Tau ² = 0. Test for overall effect: Z = Anemia Giariuff2012	16/161 22/466 4/84 5/131 47/842 19: Ch ² = 5.34, df = 0.96 (P = 0.33)	7/180 23/501 1/89 7/128 38/898 = 3 (P = 0.15); I ² =44%		29.3% 41.0% 7.9% 21.7% 100.0%	2.56 (1.08, 6.05) 1.03 (0.58, 1.82) 4.24 (0.48, 37.15) 0.70 (0.23, 2.14) 1.38 (0.72, 2.66)
Test for overall effect: Z = Vomiting Gladieff2012 Pujade-Lauraine2010 Bafaloukos2010 Mahner2015 Subtotal (95%CI) Heterogeneity: Tau ² = 0.: Test for overall effect: Z = Anemia Gladieff2012 PujadeJ arguine2010	16/161 22/466 4/84 5/131 47/842 9; Ch ² = 5.34, df = 0.96 (P = 0.33) 17/161 37/466	7/180 23/501 1/89 7/128 38/898 = 3 (P = 0.15); I ² =44% <u>8/180</u> 27/501		29.3% 41.0% 21.7% 100.0% 21.0% 60.3%	2.56 [1.08, 6.05] 1.03 [0.58, 1.82] 4.24 [0.48, 37.15] 0.70 [0.23, 2.14] 1.38 [0.72, 2.66] 2.54 [1.06, 6.05] 1.51 [0.91, 2.53]
Test for overall effect: Z = Vomiting Gladieff2012 Pujade-Lauraine2010 Bafaloukos2010 Mahner2015 SUbtotal (95%CI) Heterogeneity: Tau ² = 0.: Testos (95%CI) Heterogeneity: Tau ² = 0.: Anemia Gladieff2012 Pujade-Lauraine2010 Bafaloukos2010	16/161 22/466 4/84 5/131 47/842 19; Ch ² = 5.34, df = 0.96 (P = 0.33) 17/161 37/466 8/8/4	7/180 23/501 1/89 7/128 38/898 = 3 (P = 0.15); I ² =44% 8/180 27/501 3/89		29.3% 41.0% 7.9% 21.7% 100.0% 21.0% 60.3% – 8.6%	2.56 [108, 6.05] 1.03 [0.58, 1.82] 4.24 [0.48, 37.15] 0.70 [0.23, 2.14] 1.38 [0.72, 2.66] 2.54 [1.06, 6.05] 1.51 [0.91, 2.53] 3.02 [077 1178]
Test for overall effect: Z = Vomiting Gladieff2012 Pujade-Lauraine2010 Bafaloukos2010 Mahner2015 Subtotal (95%CI) Heterogeneity: Tau ² = 0.: Test for overall effect: Z = Anemia Gladieff2012 Pujade-Lauraine2010 Bafaloukos2010 Mahner2015	16/161 22/466 4/84 5/131 47/842 19: Ch ² = 5.34, df = 0.96 (P = 0.33) 17/161 37/466 8/84 7/131	7/180 23/501 1/89 7/128 38/898 * 3 (P = 0.15); I ² =44% 8/180 27/501 3/89 4/128		29.3% 41.0% 7.9% 21.7% 100.0% 21.0% 60.3% - 8.6% 10.1%	2.56 [1.08, 6.05] 1.03 [0.58, 1.82] 4.24 [0.48, 37.15] 0.70 [0.23, 2.14] 1.38 [0.72, 2.66] 2.54 [1.06, 6.05] 1.51 [0.31, 2.53] 3.02 [0.77, 11.78] 1.75 [0.50, 6.13]
Test for overall effect: Z = Vomiting Gladieff2012 Pujade-Lauraine2010 Bafaloukos2010 Mahner2015 Subtotal (95%CI) Heterogeneity: Tau ² = 0. Test for overall effect: Z = Anemia Gladieff2012 Pujade-Lauraine2010 Bafaloukos2010 Mahner2015 Subtotal (95%CI) Heterogeneity: Tau ² = 0.1 Fest for overall effect: Z =	16/161 22/466 4/84 5/131 47/842 19: Ch ² = 5.34, df 1 37/161 37/166 8/84 7/131 69/842 00: Chi ² = 1.59, df 1 2.2.94 (P < 0.01)	7/180 23/501 1/89 7/128 38/898 = 3 (P = 0.15); l ² =44% 8/180 27/501 3/89 4/128 42/898 : 3 (P = 0.66); l ² =0%		29.3% 41.0% 7.9% 21.7% 100.0% - 21.0% 60.3% 8.6% 10.1% 100.0%	2.56 [1.08, 6.05] 1.03 [0.58, 1.82] 4.24 [0.48, 37.15] 0.70 [0.23, 2.14] 1.38 [0.72, 2.66] 2.54 [1.06, 6.05] 1.51 [0.91, 2.53] 3.02 [0.77, 11.78] 1.75 [0.50, 6.13] 1.82 [1.22, 2.71]
Test for overall effect: Z = Vomiting Gladieff2012 Pujade-Lauraine2010 Bafaloukos2010 Mahner2015 Subtotal (95%CI) Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Anemia Gladieff2012 Pujade-Lauraine2010 Bafaloukos2010 Mahner2015 Subtotal (95%CI) Heterogeneity: Tau ² = 0.0 Fest for overall effect: Z = Thrombocytopenia	16/161 22/466 4/84 5/131 47/842 19: Ch ² = 5.34, df + 0.96 (P = 0.33) 17/161 37/466 8/84 7/131 69/842 00: Chi ² = 1.59, df + 2.94 (P < 0.01)	7/180 23/501 1/89 7/128 38/898 = 3 (P = 0.15); I ² =44% 8/180 27/501 3/89 4/128 42/998 : 3 (P = 0.66); I ² =0%		29.3% 41.0% 7.9% 21.7% 100.0% - 21.0% 60.3% 8.6% 10.1% 100.0%	2.56 [1.08, 6.05] 1.03 [0.58, 1.82] 4.24 [048, 37.15] 0.70 [0.23, 2.14] 1.38 [0.72, 2.66] 2.54 [1.06, 6.05] 1.51 [0.91, 2.53] 3.02 [0.77, 11.78] 1.75 [0.50, 6.13] 1.82 [1.22, 2.71]
Test for overall effect: Z = Vomiting Gladieff2012 Pujade-Lauraine2010 Bafaloukos2010 Mahner2015 Subtotal (95%CI) Heterogeneity: Tau ² = 0.: Test for overall effect: Z = Amemia Gladieff2012 Pujade-Lauraine2010 Bafaloukos2010 Mahner2015 Subtotal (95%CI) Heterogeneity: Tau ² = 0.(Test for overall effect: Z = Thrombocytopenia CirclestP013	16/161 22/466 4/84 5/131 47/842 19: Chi ² = 5.34, df ≠ 0.96 (P = 0.33) 17/161 37/466 8/84 7/131 69/842 00: Chi ² = 1.59, df ≠ 2.94 (P < 0.01)	7/180 23/501 1/89 7/128 33/898 • 3 (P = 0.15); I ² =44% 8/180 27/501 3/89 4/128 42/898 • 3 (P = 0.66); I ² =0%		29.3% 41.0% 7.9% 21.7% 100.0% 21.0% 60.3% 8.6% 10.1% 100.0%	2.56 [1.08, 6.05] 1.03 [0.58, 1.82] 4.24 [0.48, 37.15] 0.70 [0.23, 2.14] 1.38 [0.72, 2.66] 2.54 [1.06, 6.05] 1.51 [0.31, 2.53] 3.02 [0.77, 11.78] 1.75 [0.50, 6.13] 1.82 [1.22, 2.71]
Test for overall effect: Z = Voniting Gladieff2012 Pujade-Lauraine2010 Mahner2015 Subtotal (95%CI) Heterogeneiky: Tau ² = 0. Test for overall effect: Z = Anemia Gladieff2012 Pujade-Lauraine2010 Bafaloukos2010 Mahner2015 Subtotal (95%CI) Heterogeneiky: Tau ² = 0.1 Test for overall effect: Z = Thrombocytopenia Gladieff2012	16/161 22/466 4/84 5/131 47/842 19: Ch ² = 5.34, ef 4 ≈ 0.96 (P = 0.33) 17/161 37/466 8/84 7/131 69/842 00: Ch ² = 1.59, ef 4 = 1.59, ef 4 ≥ 2.94 (P < 0.01)	7/180 23/501 1/89 7/128 38/898 = 3 (P = 0.15); I ² =44% 8/180 27/501 3/89 4/128 • 42/898 • 3 (P = 0.66); I ² =0%		29.3% 41.0% 7.9% 21.7% 100.0% - 21.0% 60.3% 8.6% 10.1% 100.0% 23.3%	2.56 [1.08, 6.05] 1.03 [0.58, 1.82] 4.24 [0.48, 37.15] 0.70 [0.23, 2.14] 1.38 [0.72, 2.66] 2.54 [1.06, 6.05] 1.51 [0.91, 2.53] 3.02 [0.77, 11.78] 1.75 [0.50, 6.13] 1.82 [1.22, 2.71]
Test for overall effect: Z = Vomiting Gladieff2012 Pujade-Lauraine2010 Bafaloukos2010 Mahner2015 Subtotal (95%CI) Heterogeneity: Tau ² = 0.: Test for overall effect: Z = Anemia Gladieff2012 Pujade-Lauraine2010 Mahner2015 Subtotal (95%CI) Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Thrombocytopenia Gladieff2012 Pujade-Lauraine2010	16/161 22/466 4/84 5/131 47/842 9.9; Ch ² = 5.34, df ≠ 9.9; Ch ² = 5.34, df ≠ 9.9; Ch ² = 5.34, df ≠ 9.9; Ch ² = 1.59, df ≠ 8/84 7/131 69/842 20; Ch ² = 1.59, df ≠ 2.94 (P < 0.01) 24/161 7/4/466	7/180 23/501 1/89 7/128 38/898 = 3 (P = 0.15); I ² =44% 8/180 27/501 3/89 4/128 42/898 • 3 (P = 0.66); I ² =0%		29.3% 41.0% 21.7% 100.0% 21.0% 60.3% 8.6% 10.1% 100.0% 23.3% 63.3%	2.56 [108, 6.05] 1.03 [0.58, 1.82] 4.24 [0.48, 37.15] 0.70 [0.23, 2.14] 1.38 [0.72, 2.66] 2.54 [1.06, 6.05] 1.51 [0.91, 2.53] 3.02 [0.77, 11.78] 1.75 [0.50, 6.13] 1.82 [1.22, 2.71] 2.24 [1.16, 4.32] 2.57 [1.72, 3.83] 2.80 [1.72, 3.83] 2.81 [1.72, 3.83] 2.81 [1.72, 3.83]
Test for overall effect: Z = Voniting Gladieff2012 Pujade-Lauraine2010 Bafaloukos2010 Mahner2015 Subtotal (95%CI) Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Anemia Gladieff2012 Pujade-Lauraine2010 Bafaloukos2010 Mahner2015 Subtotal (95%CI) Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Thrombocytopenia Gladieff2012 Pujade-Lauraine2010 Bafaloukos2010	16/161 22/466 4/84 5/131 47/842 19: Chi ² = 5.34, df = 19: Chi ² = 5.34, df = 19: Chi ² = 5.34, df = 17/161 37/466 8/84 7/131 69/842 200: Chi ² = 1.59, df = 2.94 (P < 0.01) 24/161 74/466 10/84	7/180 23/501 1/89 7/128 38/898 * 3 (P = 0.15); I ² =44% 8/180 27/501 3/89 4/128 42/898 * 3 (P = 0.66); I ² =0%		29.3% 41.0% 7.9% 21.7% 100.0% 21.0% 60.3% 10.1% 100.0% 23.3% 63.3% 4.6%	2.56 [1.08, 6.05] 1.03 [0.58, 1.82] 4.24 [0.48, 37.15] 0.70 [0.23, 2.14] 1.38 [0.72, 2.66] 2.54 [1.06, 6.05] 1.51 [0.31, 2.53] 3.02 [0.77, 11.78] 1.75 [0.50, 6.13] 1.82 [1.22, 2.71] 2.24 [1.16, 4.32] 2.57 [1.72, 3.83] 5.30 [1.20, 23.47] 2.61 [1.21, 21.21] 2.61 [1.21, 21.21] 2.65 [1.16, 4.32] 2.57 [1.72, 3.83] 5.30 [1.20, 23.47]
Test for overall effect: Z = Vomiting Gladieff2012 Pujade-Lauraine2010 Mahner2015 Subtotal (95%CI) Heterogeneity: Tau ² = 0. Test for overall effect: Z = Anemia Gladieff2012 Pujade-Lauraine2010 Bataloukos2010 Mahner2015 Subtotal (95%CI) Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Thrombocytopenia Gladieff2012 Pujade-Lauraine2010 Bataloukos2010 Mahner2015	16/161 22/466 4/84 5/131 47/842 19: Ch ² = 5.34, ef 4 = 0.96 (P = 0.33) 17/161 37/466 8/84 7/131 69/842 00: Ch ² = 1.59, ef 4 = 2.94 (P < 0.01) 24/161 74/466 10/84 16/131	7/180 23/501 1/89 7/128 38/898 = 3 (P = 0.15); I ² =44% 8/180 27/501 3/89 4/128 42/898 = 3 (P = 0.66); I ² =0%		29.3% 41.0% 21.7% 100.0% 21.0% 60.3% 8.6% 10.1% 100.0% 23.3% 63.3% 4.6% 8.8%	2.56 [1.08, 6.05] 1.03 [0.58, 1.82] 4.24 [0.48, 37.15] 0.70 [0.23, 2.14] 1.38 [0.72, 2.66] 2.54 [1.06, 6.05] 1.51 [0.91, 2.53] 3.02 [0.77, 11.78] 1.75 [0.50, 6.13] 1.82 [1.22, 2.71] 2.24 [1.16, 4.32] 2.57 [1.72, 3.83] 5.30 [1.20, 23.47] 3.91 [1.34, 11.37]
Test for overall effect: Z = Vomiting Gladieff2012 Pujade-Lauraine2010 Bafaloukos2010 Mahner2015 Subtotal (95%CI) Heterogeneity: Tau ² = 0: Fest for overall effect: Z = Anemia Gladieff2012 Pujade-Lauraine2010 Mahner2015 Subtotal (95%CI) Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = Thrombocytopenia Gladieff2012 Pujade-Lauraine2010 Bafaloukos2010 Mahner2015 Subtotal (95%CI)	16/161 22/466 4/84 5/131 47/842 19: Ch ² = 5.34, df = 0.96 (P = 0.33) 17/161 37/466 8/84 7/131 69/842 00: Ch ² = 1.59, df = 2.94 (P < 0.01) 24/161 7.4/466 10/84 16/131 124/842	7/180 23/501 1/89 7/128 38/898 = 3 (P = 0.15); I ² =44% 8/180 27/501 3/89 4/128 42/898 = 3 (P = 0.66); I ² =0% 12/180 31/501 2/89 4/128 49/898		29.3% 41.0% 7.9% 21.7% 100.0% 21.0% 60.3% 8.6% 10.1% 100.0% 23.3% 63.3% 63.3% 63.3% 8.8% 100.0%	2.56 [1.08, 6.05] 1.03 [0.58, 1.82] 4.24 [0.48, 37.15] 0.70 [0.23, 2.14] 1.38 [0.72, 2.66] 2.54 [1.06, 6.05] 1.51 [0.91, 2.53] 3.02 [0.77, 11.78] 1.75 [0.50, 6.13] 1.82 [1.22, 2.71] 2.24 [1.16, 4.32] 2.57 [1.72, 3.83] 5.30 [1.0, 2.347] 3.91 [1.34, 11.37] 2.67 [1.94, 3.67]
Test for overall effect: Z = Vomiting Gladieff2012 Pujade-Lauraine2010 Bafaloukos2010 Mahner2015 Subtotal (95%CI) Heterogeneity: Tau ² = 0.: Test for overall effect: Z = Anemia Gladieff2012 Pujade-Lauraine2010 Mahner2015 Subtotal (95%CI) Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Thrombocytopenia Gladieff2012 Pujade-Lauraine2010 Bafaloukos2010 Mahner2015 Subtotal (95%CI) Heterogeneity: Tau ² = 0.1 Heterogeneity: Tau ² = 0.1	16/161 22/466 4/84 5/131 47/842 9: Ch ² = 5.34, df + 0.96 (P = 0.33) 17/161 37/466 8/84 7/131 69/842 00; Ch ² = 1.59, df + 2.94 (P < 0.01) 24/161 74/466 10/84 16/131 124/842 00; Ch ² = 1.63, df +	7/180 23/501 1/89 7/128 33/898 = 3 (P = 0.15); I ² =44% 8/180 27/501 3/89 4/128 42/898 = 3 (P = 0.66); I ² =0% 12/180 31/501 2/89 4/128 49/898 : 3 (P = 0.65); I ² =0%		29.3% 41.0% 7.9% 21.7% 100.0% 21.0% 60.3% 60.3% 60.3% 101.1% 100.0%	2.56 [1.08, 6.05] 1.03 [0.58, 1.82] 4.24 [0.48, 37.15] 0.70 [0.23, 2.14] 1.38 [0.72, 2.66] 1.51 [0.91, 2.53] 3.02 [0.77, 11.78] 1.75 [0.50, 6.13] 1.82 [1.22, 2.71] 2.24 [1.16, 4.32] 2.57 [1.72, 3.83] 5.30 [1.20, 23.47] 3.91 [1.34, 11.37] 2.67 [1.94, 3.67]

Fig. 3 Forest plots of toxicity endpoints for the doublet regimens

Study	Non-PLD arm N	PLD arm N	Hazard Ratio IV,Random,95%Cl	Weight	Hazard Ratio IV,Random,95%CI
PFS					
Banerjee2018	47	46	⊢ ∎	5.4%	0.78 [0.46, 1.32]
Kaye2012II	32	33		3.6%	0.86 [0.45, 1.64]
Kaye2012 I	32	33		3.7%	0.91 [0.48, 1.73]
Mutch2007	99	96	⊢ _	15.9%	0.98 [0.72, 1.33]
Colombo2012	412	417	H a H	55.2%	1.05 [0.89, 1.24]
Ferrandina2008	77	76	┝┿╋╼╌┥	16.2%	1.14 [0.84, 1.55]
Subtotal (95%CI)	699	701	H A -I	100.0%	1.02 [0.90, 1.16]
Heterogeneity: Tau ² =	0.00; Chi ² = 2.07, df = 5	5 (P = 0.84); I ² =0%			
Test for overall effect: 2	Z = 0.36 (P = 0.72)				
os					
Kaye2012 I	32	33		2.4%	0.66 [0.27, 1.61]
Ferrandina2008	77	76	⊢∎ I	11.2%	0.74 [0.49, 1.12]
Mutch2007	99	96	1- 8 - 1 -1	12.3%	0.77 [0.52, 1.14]
Colombo2012	412	417	H <mark>a</mark> H	71.4%	0.93 [0.79, 1.09]
Kaye2012∏	32	33	⊢	2.7%	1.01 [0.44, 2.32]
Subtotal (95%CI)	652	655		100.0%	0.88 [0.77, 1.01]
Heterogeneity: Tau ² =	0.00; Chi ² = 2.07, df = 4	4 (P = 0.72); I ² =0%			
Test for overall effect: 2	Z = 1.81 (P = 0.07)				
			1 I I I I		
			0 0.5 1 1.5 2 2.5		
		F	Favours Non-PLD arm Favours PLD arm		
Fig. 4 Forest plots of e	efficacy endpoints. Mo	notherapy regime	ns		

We compared PFS and OS based on different PLD doses, and did not observe any statistical significance between PLD at 30 mg/m^2 every 4 weeks compared with PLD at 45 mg/m^2 every 4 weeks. Therefore, we recommend that PLD at 30 mg/m^2 every 4 weeks be used as the initial dosage in PLD-plus-carbo doublet regimens.

When we evaluated grade 2 or higher toxicities, we noted that PLD plus carbo was associated with a decreased risk of alopecia (RR, 0.09; 95% CI, 0.07–0.12; $I^2 = 0\%$; p < 0.01) and neuropathy (RR, 0.19; 95% CI, 0.14–0.27; $I^2 = 19\%$; p < 0.01) compared with PAC plus carbo. PLD plus carbo, however, was associated with an increased risk of mucositis/stomatitis (RR, 2.12; 95% CI, 1.54–2.93; $I^2 = 0\%$; p < 0.01) and hand–foot syndrome (RR, 6.12; 95% CI, 3.84–9.76; $I^2 = 0\%$; p < 0.01).

Compared with grade 3–4 severe toxicities, both handfoot syndrome and mucositis/stomatitis primarily arose with low-grade toxicities, and the patients' adverse symptoms were mild. Both anemia and thrombocytopenia were principally associated with severe toxicities. Fortunately, the adverse incidence was not high (8.2 and 14.7%, respectively). We then laterally compared the incidence of side effects at two different PLD doses (grade 3–4 toxicity): for anemia, 30 mg/m² vs. 45 mg/m² PLD (8.0% vs. 9.5%, respectively), and for thrombocytopenia, 30 mg/m² vs. 45 mg/m² PLD (15.0% vs. 12.0%, respectively). These two adverse reactions did not show a significant dosedependency for PLD, which may be because the combination with carbo reduced the toxic side effects of PLD.

Our updated meta-analysis results showed that PLD plus carbo provided a non-inferior survival rate and was well tolerated. Hence, PLD plus carbo emerged as a favorable option for platinum-sensitive patients in the recurrent setting.

Single regimens

In platinum-resistant or -refractory recurrent ovarian cancer, PLD shows survival results similar to those of other single agents, and, thus, platinum-resistant women have been challenged with non-platinum drugs. One study showed that gemcitabine plus PLD was a very attractive combination given that it possessed different mechanisms of action and different toxicity profiles [26]; this combination did not reduce the individual effect of either agent, but rather increased the activity of the drugs in an additive fashion. This therapy was well tolerated by most platinum-resistant ovarian cancer patients, and patients with higher levels of baseline deoxycytidine kinase exhibited longer PFS. The usage recommended was 35 mg/m^2 of PLD on day 1, and 1000 mg/m^2 of gemcitabine on days 1 and 15 q4 weeks. However, as this was a phase-Ib study, it requires further exploration. Other investigators demonstrated that olaparib combined with PLD was well tolerated, but the combination

Anemia	n/N	PLD arm n/N	Risk Ratio IV,Random,95%Cl	Weight	Risk Ratio IV,Random,95%CI
Banerjee2018	3/46	0/47		1.6%	7.15 [0.38, 134.66]
Kaye2012II	4/32	0/32	-	1.7%	9.00 [0.50, 160.59]
Kaye2012 I	2/32	0/32		1.6%	5.00 [0.25, 100.20]
Mutch2007	3/99	2/96	· · · · · · · · · · · · · · · · · · ·	4.5%	1.45 [0.25, 8.51]
Colombo2012	18/402	15/409	H <mark>a</mark> i	31.3%	1.22 [0.62, 2.39]
Ferrandina2008	5/71	4/72	H B I	8.7%	1.27 [0.35, 4.53]
Vergote2009 T	12/130	10/87	Here - 1	22.4%	0.80 [0.36, 1.78]
Vergole2009 I	12/130	10/87		22.4 %	0.00 [0.00, 1.70]
vergote200911	20/130	10/8/		20.1%	1.34 [0.66, 2.72]
Subtotal (95%Cl)	67/942	41/862	• -	100.0%	1 26 [0 86 1 83]
Heterogeneity: Tau ² = 1 Fest for overall effect: 7	0.00; Chi ² = 5.37, df = 7 Z = 1.19 (P = 0.23)	(P = 0.61); I ² =0%		100.078	1.20 [0.00, 1.00]
Vomiting					
Panariaa2018	2/46	3/47	H.	7.6%	0.68 [0.12, 3.89]
Kaue2012 TT	2/40	3/47		2.5%	1 00 [0.12, 0.03]
Kayezo 12 II	1/32	1/32		3.3%	1.00 [0.07, 13.30]
Kaye2012 I	0/32	1/32		2.7%	0.33 [0.01, 7.89]
Mutch2007	12/99	4/96		14.7%	2.91 [0.97, 8.71]
Colombo2012	32/402	24/409		28.4%	1.36 [0.81, 2.26]
Ferrandina2008	1/71	4/72	T	5.3%	0.25 [0.03, 2.21]
Vergote2009 I	17/130	10/87	1 1 -1	22.3%	1.14 [0.55, 2.37]
Vergote2009II	5/130	10/87	•1	15.7%	0.33 [0.12, 0.95]
Subtotal (95%Cl)	70/942	57/862		100.0%	0.97 [0.57, 1.66]
Heterogeneity: Tau ² = 1	0.19; Chi ² = 11.33, df =	3 (P = 0.12); I ² =38%			
- osciol overall effect: 2	E = 0.11 (F = 0.91)				
Fatigue/asthenia	2/46	3/47	1 -	5.0%	0.68 [0 12 3 89]
Kave2012T	2/40	4/20	1 -	7 3%	0.75 [0.18 3.00]
Kaya2012 T	3/32	4/22		F 70/	0.10 [0.10, 0.08]
aye2012 1	2/32	4/32		5.7%	0.50 [0.10, 2.54]
Mutch2007	11/99	1/96		3.8%	10.67 [1.40, 81.04]
Colombo2012	42/402	34/409	P 1	37.5%	1.26 [0.82, 1.93]
Ferrandina2008	6/71	4/72	· += ·	9.4%	1.52 [0.45, 5.16]
/ergote2009 I	14/130	8/87	H - 1	17.6%	1.17 [0.51, 2.67]
√ergote2009Ⅱ	7/130	8/87	10 -1	13.6%	0.59 [0.22, 1.56]
Published (OPA) OF	07/010	66/000	L.	400 001	1 00 10 70 1 0 1
leterogeneity: Tau ² =	87/942 0.07; Chi ² = 8.70. df = 7	66/862 (P = 0.28): I ² =19%	Γ	100.0%	1.09 [0.73, 1.64]
est for overall effect: 2	Z = 0.43 (P = 0.66)	(,			
hrombocytopenia					
	0/46	0/47			Not optimoble
Saneijee2010	0/40	0/47		2.00/	0.00.00.00.7.003
Caye201211	0/32	1/32		3.9%	0.33 [0.01, 7.89]
Kaye2012 I	0/32	1/32		3.9%	0.33 [0.01, 7.89]
Mutch2007	6/99	5/96		27.3%	1.16 [0.37, 3.69]
errandina2008	4/71	0/72	·	4.6%	9.13 [0.50, 166.43]
/ergote2009 I	9/130	4/87	H B	27.6%	1.51 [0.48, 4.74]
/ergote2009Ⅱ	19/130	4/87		32.8%	3.18 [1.12, 9.02]
		15/406	•	100.0%	1.73 [0.93, 3.24]
Subtotal (95%CI)	38/494	13/400			
Subtotal (95%Cl) Heterogeneity: Tau ² =	38/494 0.03; Chi ² = 5.21, df = 5	(P = 0.39); I ² =4%			
Subtotal (95%CI) Heterogeneity: Tau ² = 1 Test for overall effect: 2	38/494 0.03; Chi ² = 5.21, df = 5 Z = 1.73 (P = 0.08)	(P = 0.39); l ² =4%			
Subtotal (95%Cl) Heterogeneity: Tau ² = 1 Fest for overall effect: 2 Neutropenia	38/494 0.03; Chi ² = 5.21, df = 5 Z = 1.73 (P = 0.08)	(P = 0.39); l ² =4%			
Subtotal (95%Cl) Heterogeneity: Tau ² = 1 Fest for overall effect: 2 Neutropenia Banerjee2018	38/494 0.03; Chi ² = 5.21, df = 5 Z = 1.73 (P = 0.08) 6/46	2/47		i 11.7%	3.07 [0.65, 14.41]
Subtotal (95%CI) Heterogeneity: Tau ² = 1 Fest for overall effect: 2 Neutropenia Banerjee2018 Mutch2007	38/494 0.03; Chi ² = 5.21, df = 5 Z = 1.73 (P = 0.08) 6/46 38/99	2/47 18/96	H		3.07 [0.65, 14.41] 2.05 [1.26, 8.38]
Subtotal (95%Cl) Heterogeneity: Tau ² = Test for overall effect: 2 Neutropenia Banerjee2018 Mutch2007 Colombo2012	38/494 0.03; Chi ² = 5.21, df = 5 Z = 1.73 (P = 0.08) 6/46 38/99 12/402	2/47 18/96 41/409	⊧ ⊧=i		3.07 [0.65, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56]
Subtotal (95%Cl) Heterogeneity: Tau ² = Test for overall effect: 2 Neutropenia Banerjee2018 Mutch2007 Colombo2012 Ferrandina2008	38/494 0.03; Ch ² = 5.21, df = 5 Z = 1.73 (P = 0.08) 6/46 38/99 12/402 16/71	2/47 18/96 41/409 5/72	↓		3.07 [0.65, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56] 3.25 [1.26, 8.38]
Subtotal (95%CI) Heterogeneity: Tau ² = Fest for overall effect: 2 Neutropenia Banerjee2018 Mutch2007 Colombo2012 Ferrandina2008 Fergote2009 I	38/494 0.03; Chi ² = 5.21, df = 5 Z = 1.73 (P = 0.08) 6/46 38/99 12/402 16/71 10/130	(P = 0.39); I ² =4% 2/47 18/96 41/409 5/72 12/87			3.07 [0.65, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56] 3.25 [1.26, 8.38] 0.56 [0.25, 1.23]
Subtotal (95%CI) Heterogeneity: Tau ² = Test for overall effect: 2 Neutropenia Banerjee2018 Mutch2007 Colombo2012 Ferrandina2008 Vergote2009 I Vergote2009 I	38/494 0.03; Chi ² = 5.21, df = 5 Z = 1.73 (P = 0.08) 6/46 38/99 12/402 16/71 10/130 39/130	(P = 0.39); f ² = 4% 2/47 18/96 41/409 5/72 12/87 12/87	⊨ _ =	11.7% 19.0% 18.1% 15.9% 17.0% 18.4%	3.07 [0.65, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56] 3.25 [1.26, 8.38] 0.56 [0.25, 1.23] 2.17 [1.21, 3.91]
Subtotal (95%CI) Heterogeneity: Tau ² = Fest for overall effect: ; Neutropenia Banerjee2018 Mutch2007 Colombo2012 Ferrandina2008 Vergote2009 I Vergote2009 I Vergote2009 I	38/494 0.03; Chi ² = 5.21, df = 5 2 = 1.73 (P = 0.08) 6/46 38/99 12/402 16/71 10/130 39/130 121/878	(P = 0.39); f ² =4% 2/47 18/96 41/409 5/72 12/87 12/87 90/798		11.7% 19.0% 18.1% 15.9% 17.0% 18.4%	3.07 [0.65, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56] 3.25 [1.26, 8.38] 0.56 [0.25, 1.23] 2.17 [1.21, 3.91] 1.32 [0.59 2.96]
Subtotal (95%CI) Heterogeneity. Tau ² = Test for overall effect: ; Neutropenia Banerjee2018 Mutch2007 Colombo2010 Ferrandina2008 Vergote2009 II Vergote2009 II Subtotal (95%CI) Heterogeneity. Tau ² = Test for overall effect: ;	38/494 0.03, Ch ² = 5.21, df = 6 Z = 1.73 (P = 0.08) 6/46 38/99 12/402 16/71 10/130 39/130 121/878 121/878 0.84; Ch ² = 38.85, df = 1.81 (P = 0.07)	2/47 18/96 41/409 5/72 12/87 90/798 5 (P < 0.00001); i ² =t	P = P = _	11.7% 19.0% 18.1% 15.9% 17.0% 18.4% 100.0%	3.07 [0.65, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56] 3.25 [1.26, 8.38] 0.56 [0.25, 1.23] 2.17 [1.21, 3.91] 1.32 [0.59, 2.96]
Subtotal (95%CI) Heterogeneity: Tau ² = Test for overall effect ; Veutropenia Jamerjee2018 Autch2007 Zolombo2012 errandina2008 errandina2008 Vergote2009 I Vergote2009 I Subtotal (95%CI) Heterogeneity: Tau ² = 'est for overall effect: 2	33/494 33/494 22 = 1.73 (P = 0.08) 6/46 38/99 12/402 16/71 10/130 39/130 121/878 2 = 1.81 (P = 0.07) 2 = 1.81 (P = 0.07)	(P = 0.39); i ² =4% 2/47 18/96 41/409 5/72 12/87 12/87 90/798 5 (P < 0.00001); i ² =4	P → → → → → → → → → → → → → → → → → → →	11.7% 19.0% 18.1% 15.5% 17.0% 18.4% 18.4%	3.07 [0.65, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56] 3.25 [1.26, 8.38] 0.56 [0.25, 1.23] 2.17 [1.21, 3.91] 1.32 [0.59, 2.96]
Subtotal (95%CI) Heterogeneity: Tau ² = Test for overall effect: ; Neutropenia Jameriee2018 Vutch2007 Joiombc2012 Ferandina2008 (vergote2009 II Subtotal (95%CI) Heterogeneity: Tau ² = Fest for overall effect: ; Mucositi/stomattis Jameriee2018	33/494 33/494 Z = 1.73 (P = 0.08) 6/46 38/99 12/402 16/71 10/130 39/130 121/878 0.84; Ch ² = 3.88, df = z = 1.81 (P = 0.07) 0/46	(P = 0.39); i ² =4% 2/47 18/96 41/409 5/72 12/87 12/87 5 (P < 0.0001); i ² =4 3/47	38%	→ 11.7% 19.0% 18.1% 15.9% 17.0% 18.4% 100.0%	3.07 [0.65, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56] 3.25 [1.26, 8.38] 0.56 [0.25, 1.23] 2.17 [1.21, 3.91] 1.32 [0.59, 2.96]
Subtotal (95%CI) Heterogeneity: Tau ² = Fest for overal effect: ' Neutropenia Banerjee2018 Much:2007 Colombo2012 Ferrandina2008 (Pergole2000 I Heterogeneity: Tau ² = Fest for overal effect: 2 Mucositis/stomatitis Banerjee2018 Gwe2012 II	33/494 30; Chr ² = 5, 21, df = 5 Z = 1.73 (P = 0.08) 6/46 3.8/99 1.2/402 16/71 10/130 39/130 12/4878 0.84; Chr ² = 88, df = Z = 1.81 (P = 0.07) 0/46 0/32	(P = 0.39); f ² =4% 2/47 18/96 41/409 5/72 12/87 12/87 90/798 5 (P < 0.00001); f ² =6 3/47 2/32	38%	 11.7% 19.0% 18.1% 15.9% 17.0% 18.4% 100.0% 7.9% 7.9% 7.9% 7.9% 	3.07 [0.85, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56] 3.25 [1.28, 8.38] 0.56 [0.25, 1.23] 2.17 [1.21, 3.91] 1.32 [0.59, 2.96] 0.15 [0.01, 2.76] 0.20 [0.01, 4.01]
Subtotal (95%CI) Heterogeneity: Tau ² = Test for overall effect: ; Veutropenia Jamerjee2018 Wutch2007 Joombo2012 Ferrandina2008 (vergote2009 I Vergote2009 I Heterogeneity: Tau ² = Test for overall effect: 2 Mucositia/stomatits Jamerjee2018 Kaye2012 I Kaye2012 I	38/494 303 Chr ² = 5.21, df = 5 Z = 1.73 (P = 0.08) 6/46 38/99 12/402 16/71 10/130 39/130 121/878 0.84; Chr ² = 36.85, df = Z = 1.81 (P = 0.07) 0/46 0/32 0/32	(P = 0.39); f ² = 4% 2/47 18/96 41/409 5/72 12/87 90/798 5 (P < 0.00001); f ² = 1 3/47 2/32 2/32	38%	→ 11.7%, 19.0% 18.1% 15.9% 17.0% 18.4% 100.0% 7.9% 7.9% 7.6%	3.07 [0.65, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56] 3.25 [1.26, 8.38] 0.56 [0.25, 1.23] 2.17 [1.21, 3.91] 1.32 [0.59, 2.96] 0.15 [0.01, 2.75] 0.20 [0.01, 4.01]
Subtotal (95%CI) teterogeneity: Tau ² = test for overall effect: test for overall effect: test for overall effect: terrandina2008 tergole2000 I tergole2000 I Subtotal (95%CI) teterogeneity: Tau ² = fest for overall effect: teterogeneity: Tau ² = fest for overall effect: teterogeneity: Tau ² = tetorositis/stomatitis gamejec2018 daye2012 II daye2012 I	33/494 33/494 25.1 df 5 2 = 1.73 (P = 0.08) 6/46 38/99 12/402 16/71 10/130 39/130 121/878 0.84; Chi ² = 36.8, df = Z = 1.81 (P = 0.07) 0/46 0/32 0/32 1200	(P = 0.39); f ² =4% 2/47 18/96 41/409 5/72 12/87 12/87 90/798 5 (P < 0.00001); f ² =1 3/47 2/32 2/32 2/32	36%	→ 11.7% 19.0% 18.1% 15.9% 17.0% 18.4% 100.0%	3.07 [0.65, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56] 3.25 [1.28, 8.38] 0.56 [0.25, 1.23] 2.17 [1.21, 3.91] 1.32 [0.59, 2.96] 0.15 [0.01, 2.75] 0.20 [0.01, 4.01] 0.20 [0.01, 4.01]
Subtotal (95%CI) Heterogeneity: Tau ² = Test for overall effect ; Veutropenia Jamerjee2018 Wuch2007 Colombo2012 Ferrandina2008 (vergote2009 II Subtotal (95%CI) Heterogeneity: Tau ² = I Test for overall effect ; Wucositis/stomatitis Amerjee2018 (avge2012 I Auge2012 I Wuch2007	33/494 33/494 22 = 1.73 (P = 0.08) 6/46 38/99 12/402 16/71 10/130 39/130 121/878 121/878 0.84; Ch ² = 36.85, df = 2 = 1.81 (P = 0.07) 0/46 0/32 0/32 0/32 0/32 0/32	(P = 0.39); P = 4% 2/47 18/96 41/409 5/72 12/87 90/798 5 (P < 0.00001); P = 4 3/47 2/32 3/96 1 / 409	38%		3.07 [0.65, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56] 3.25 [1.26, 8.38] 0.56 [0.25, 1.23] 2.17 [1.21, 3.91] 1.32 [0.59, 2.96] 0.15 [0.01, 2.75] 0.20 [0.01, 4.01] 0.20 [0.01, 4.01] 0.32 [0.03, 3.05]
Subtotal (95%CI) Heterogeneity: Tau ² = Fest for overall effect: 3 Weutropenia Jamerjee2018 Muchc2007 Dolombo2012 Ferrandina2008 Jergode2009 II Subtotal (95%CI) Heterogeneity: Tau ² = Fest for overall effect: 2 Mucositis/stomatils Jamerjee2018 Gaye2012 II Kolyc2012 I Muchc2007 Dolombo2012 -	33/494 33/494 25.1, dF 5 2 = 1.73 (P = 0.08) 6/46 38/99 12/402 16/71 10/130 39/130 121/878 8.8, dF = 2 = 1.81 (P = 0.07) 0/46 0/32 0/32 1/99 2/402 1/99 2/402	(P = 0.39); f ² =4% 2/47 18/96 41/409 5/72 12/87 90/798 5 (P < 0.0001); f ² =1 3/47 2/32 2/32 3/96 41/409	38%	→ 11.7% 19.0% 18.1% 15.9% 17.0% 18.4% 100.0% 7.9% 7.6% 7.6% 7.6% 13.5% 13.5% 3.4.1%	3.07 [0.65, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56] 3.25 [1.26, 8.38] 0.56 [0.25, 1.23] 2.17 [1.21, 3.91] 1.32 [0.59, 2.96] 0.15 [0.01, 2.75] 0.20 [0.01, 4.01] 0.32 [0.03, 3.05] 0.05 [0.01, 0.20]
Subtotal (95%CI) teterogeneity: Tau ² = test for overall effect: 2 teutropenia Samerjee2018 duch2007 Dolombo2012 terrandina2008 (regole2009 II Subtotal (95%CI) teterogeneity: Tau ² = (test for overall effect: 2 duccositis/stomattis Banerjee2018 dange/e2012 II duch2007 Joiombo2012 I formational subtomation ducational subtomational subtomation ducational subtomation ducational subtomation	33/494 303 Chr ² = 5.21, df = 5 Z = 1.73 (P = 0.08) 6/46 38/99 12/402 16/71 10/130 39/130 12/1878 0.84; Ch ² = 36.85, df = Z = 1.81 (P = 0.07) 0/46 0/32 0/32 0/32 1/99 2/402 1/71	(P = 0.39); P = 4% 2/47 1.8/96 41/409 5/72 12/87 90/798 90/798 5 (P < 0.00001); P = 4 3/47 2/32 2/32 3/96 41/409 2/72			3.07 [0.65, 14.41] 2.05 [1.26, 6.38] 0.30 [0.16, 0.56] 3.25 [1.26, 8.38] 0.56 [0.25, 1.23] 2.17 [1.21, 3.91] 1.32 [0.59, 2.96] 0.15 [0.01, 2.75] 0.20 [0.01, 4.01] 0.20 [0.01, 4.01] 0.32 [0.03, 3.06] 0.05 [0.01, 0.20] 0.51 [0.05, 5.47]
Subtotal (95%CI) teterogeneity: Tau ² = teterogeneity: Tau ² = teterogeneity: Tau ² = teterogeneity: teterogeneity: teterogeneity: teterogeneity: teterogeneity: teterogeneity: Tau ² = teterogen	33/494 33/494 25.1 d+ 5 2 = 1.73 (P = 0.08) 6/46 38/99 12/402 16/71 10/130 12/402 16/71 10/130 12/402 16/71 10/130 12/402 1.71 10/130 12/402 1.71 10/130 12/402 1.71 10/130 12/402 1.71	(P = 0.39); f ² =4% 2/47 18/96 41/409 5/72 12/87 90/798 5 (P < 0.0001); f ² =1 3/47 2/32 2/32 3/96 41/409 2/72 14/87	36%	— 11.7% 19.0% 18.1% 15.9% 17.0% 18.4% 100.0% 7.9% 7.8% 7.8% 13.5% 34.1% 12.0% 8.8%	3.07 [0.65, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56] 3.25 [1.26, 8.38] 0.56 [0.25, 1.23] 2.17 [1.21, 3.91] 1.32 [0.59, 2.96] 0.15 [0.01, 2.75] 0.20 [0.01, 4.01] 0.32 [0.03, 3.05] 0.05 [0.01, 0.20] 0.51 [0.05, 5.47] 0.02 [0.00, 0.38]
Subtotal (95%CI) Heterogeneily: Tau ² = Test for overal effect: 3 Neutropenia Banerjee2018 Muchc2007 Colombo2012 Ferrandina2008 dergote2009 I Heterogeneily: Tau ² = 1 Fest for overal effect: 2 Nucositis/stomatitis Banerjee2018 Gwg2012 I Heterogeneily: Cau ² = Test for overal effect: 2 Jointhe2018 Gwg2012 I Jointhe2012 Ferrandina2008 Fergote2009 I /ergote2009 I	33/494 30; Chr ² = 5, 21, df = 5 Z = 1.73 (P = 0.08) 6/46 3.8/99 12/402 16/71 10/130 12/1878 0.84; Chr ² = 36.8, df = Z = 1.81 (P = 0.07) 0/46 0/32 0/32 1/99 2/402 1/71 0/130 0/130	(P = 0.39), $P = 4%2/4718/9641/4095/7212/8712/8790/7985 (P < 0.00001); P = 13/472/322/322/323/9641/4092/7214/87$		 11.7% 19.0% 18.1% 15.9% 17.0% 18.4% 100.0% 7.9% 7.6% 7.6% 3.5% 3.4.1% 3.6% 8.6% 	3.07 [0.65, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56] 3.25 [1.28, 8.38] 0.56 [0.25, 1.23] 2.17 [1.21, 3.91] 1.32 [0.59, 2.96] 0.15 [0.01, 2.75] 0.20 [0.01, 4.01] 0.20 [0.01, 4.01] 0.32 [0.03, 3.05] 0.05 [0.01, 0.20] 0.51 [0.05, 5.47] 0.02 [0.00, 0.38]
Subtotal (95%C) Heterogeneity: Tau" = Fest for overall effect: ' Yeutropenia Banerjee2018 Wutch2007 Joiombo2012 Fergole2009 II Subtotal (95%CI) Heterogeneity: Tau" = Fest for overall effect: ' Rucositis/stomatitis Banerjee2018 Gaye2012 I Mutch2007 Joiombo2012 Fergole2009 I Fergole2009 I Fergole2009 I Fergole2009 I Subtotal (95%CN)	33/494 33/494 30; Chr ² = 5, 21, df = 5 Z = 1.73 (P = 0.08) 6/46 3.8099 1.2/402 16/71 10/130 39/130 39/130 10/130 0.32 0.32 1.99 2/402 1/71 0/130 0/130 4/942	(P = 0.39); P = 4% 2/47 1.8/96 41/409 5/72 12/87 90/798 90/798 5 (P < 0.00001); P = 4 3/47 2/32 2/32 3/96 41/409 2/72 1.4/87 81/862	36%	 11.7% 19.0% 18.1% 15.9% 17.0% 18.4% 100.0% 7.9% 7.6% 7.6% 7.6% 3.4% 8.6% 8.6% 100.0% 	3.07 [0.85, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56] 3.25 [1.28, 8.38] 0.56 [0.25, 1.23] 2.17 [1.21, 3.91] 1.32 [0.59, 2.96] 0.15 [0.01, 2.76] 0.20 [0.01, 4.01] 0.20 [0.01, 4.01] 0.32 [0.33, 3.05] 0.55 [0.01, 0.20] 0.51 [0.05, 5.47] 0.02 [0.00, 0.38] 0.20 [0.00, 0.38]
Subtotal (95%CI) Heterogeneity: Tau ² = Test for overall effect: 3 Neutropenia Banerjee2018 Much2007 Colombo2012 Ferrandina2008 (vergote2009 II Subtotal (95%CI) Heterogeneity: Tau ² = I Eest for overall effect: 3 Mucositis/stomatis Banerjee2018 Gave2012 I Much2007 Colombo2012 Ferrandina2008 (regote2009 II Subtotal (95%CI) Heterogeneity: Tau ² = Fer tor overall effect: 3	33/494 33/494 30; Chr ² = 5.21, df = 5 Z = 1.73 (P = 0.08) 6/46 3.8/99 1.2/402 16/71 10/130 39/130 39/130 39/130 39/130 39/130 04/66 0/32 0/32 1/99 2/402 1/71 0/130 0/130 0/130 4/942 0.00; Chr ² = 6.99, df = 7 Z = 5.48 (P < 0.01)	(P = 0.39); P = 4% $2/47$ $18,96$ $41/409$ $5/72$ $12/87$ $90/798$ $5 (P < 0.00001); P = 4$ $3/47$ $2/32$ $2/32$ $3/96$ $41/409$ $2/72$ $14/87$ $14/87$ $81/862$ $(P = 0.43); P = 0%$	36%		3.07 [0.65, 14.41] 2.05 [1.26, 6.38] 0.30 [0.16, 0.56] 3.25 [1.26, 8.38] 0.56 [0.25, 1.23] 2.17 [1.21, 3.91] 1.32 [0.59, 2.96] 0.15 [0.01, 2.75] 0.20 [0.01, 4.01] 0.20 [0.01, 4.01] 0.32 [0.33, 3.05] 0.55 [0.01, 0.20] 0.55 [10.05, 5.47] 0.02 [0.00, 0.38] 0.20 [0.00, 0.38] 0.10 [0.04, 0.23]
Subtotal (95%CI) Heterogeneity: Tau ² = Test for overall effect: ; Veutropenia Jamerjee2018 Wutch2007 Colombo2012 Ferrandina2008 (vergote2009 I Subtotal (95%CI) Heterogeneity: Tau ² = 1 Test for overall effect: ; Wutch2007 Jamerjee2018 Aqw22012 I Wutch2007 Jamerjee2018 Aqw22012 I Wutch2007 Jamerjee2018 Aqw22012 I Wutch2007 Jamerjee2018 Subtotal (95%CI) Heterogeneity: Tau ² = 1 Test for overall effect: ; Wutch2007 Jamerjee2019 I Subtotal (95%CI) Heterogeneity: Tau ² = 1 Test for overall effect: ;	33/494 0.03; Chr ² = 5.21, df = 5 Z = 1.73 (P = 0.08) 6/46 38/99 12/402 16/71 10/130 39/130 121/878 0.84; Chr ² = 3.88, df = Z = 1.81 (P = 0.07) 0/46 0/32 1/99 2/402 1/71 0/130 0/130 0/130 4/942 Z = 5.48 (P < 0.01)	(P = 0.39); P = 4% 2/47 18/96 41/409 5/72 12/87 90/798 5 (P < 0.00001); P = 4 3/47 2/32 2/32 3/96 41/409 2/72 14/87 81/862 (P = 0.43); P = 0%	36%		3.07 [0.65, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56] 3.25 [1.26, 8.38] 0.56 [0.25, 1.23] 2.17 [1.21, 3.91] 1.32 [0.59, 2.96] 0.15 [0.01, 2.75] 0.20 [0.01, 4.01] 0.20 [0.01, 4.01] 0.20 [0.03, 3.05] 0.05 [0.01, 0.20] 0.51 [0.05, 5.47] 0.02 [0.00, 0.38] 0.02 [0.00, 0.38] 0.02 [0.00, 0.38]
Subtotal (95%CI) Heterogeneily: Tau ² = Test for overal effect: 3 Neutropenia Banerjee2018 Much2007 Colombo2012 Ferrandina2008 Vergote2009 I Subtotal (95%CI) Heterogeneity: Tau ² = Test for overal effect: 2 Muccisitis/stomatitis Banerjee2018 Kaye2012 I Much2007 Colombo2012 Ferrandina2008 Vergote2009 I Subtotal (95%CI) Heterogeneity: Tau ² = Test for overal effect: 2 Hand-foot syndrome Banerjee2018	33/494 33/494 2 = 1.73 (P = 0.08) 6/46 38:99 12/402 16/71 10/130 39/130 12/1878 0.84; Ch2 = 3.85, df = 7 2 = 1.81 (P = 0.07) 0/46 0.32 0.732 1/71 0/130 0/130 0/130 4/942 0.00; Ch2 = 6.99, df = 7 2 = 5.48 (P < 0.01)	(P = 0.39); f ² = 4% 2/47 1.8/96 41/409 5/72 12/87 12/87 90/798 90/798 90/798 3/47 2/32 2/32 3/96 41/409 2/72 14/87 81/862 (P = 0.43); f ² = 0%	36%	 11.7% 19.0% 18.1% 15.9% 17.0% 18.4% 100.0% 7.9% 13.5% 34.1% 34.1% 3.5% 8.6% 100.0% 	3.07 [0.65, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56] 3.25 [1.28, 8.38] 0.66 [0.25, 1.23] 2.17 [1.21, 3.91] 1.32 [0.59, 2.96] 0.15 [0.01, 2.75] 0.20 [0.01, 4.01] 0.20 [0.01, 4.01] 0.20 [0.01, 4.01] 0.35 [0.05, 5.47] 0.20 [0.00, 0.38] 0.20 [0.00, 0.38] 0.20 [0.00, 0.38]
Subtotal (95%CI) Heterogeneity: Tau ² = Test for overall effect: ; Neutropenia Banerige2018 Mutch2007 Colombo2012 Ererrandina2008 (vergote2009 II Subtotal (95%CI) Heterogeneity: Tau ² = 1 Test for overall effect: ; Mucositis/stomatits Banerige2018 Kaye2012 I Mutch2007 Colombo2012 Errandina2008 (vergote2009 II Subtotal (95%CI) Subtotal (95%CI) Subtotal (95%CI) Subtotal (95%CI) Subtotal (95%CI) Exet or overall effect: ; Mand-foot syndrome Banerige2018 Kaye2012 I	33/494 33/494 2 = 1.73 (P = 0.98) 6/46 38/99 12/402 16/71 10/130 39/130 121/878 0.84; Chr ² = 3.88, df = z = 1.81 (P = 0.07) 0/46 0/32 1/71 0/130 0/130 0/130 0/130 0/130 0/2 = 5.48 (P < 0.01) 0/46 0/32	(P = 0.39); P = 4% 2/47 18/96 41/409 5/72 12/87 90/798 5 (P < 0.00001); P = 4 3/47 2/32 2/32 3/96 41/409 2/72 14/87 81/862 (P = 0.43); P = 0% 0/47 12/32	36%		3.07 [0.65, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56] 3.25 [1.26, 8.38] 0.56 [0.25, 1.23] 2.17 [1.21, 3.91] 1.32 [0.59, 2.96] 0.15 [0.01, 2.75] 0.20 [0.01, 4.01] 0.20 [0.01, 4.01] 0.20 [0.03, 3.05] 0.05 [0.01, 0.20] 0.51 [0.05, 5.47] 0.02 [0.00, 0.38] 0.02 [0.00, 0.38] 0.02 [0.00, 0.38] 0.10 [0.04, 0.23]
Subtotal (95%CI) Heterogeneily: Tau ² = Test for overal effect: 3 Neutropenia Banerjee2018 Much2007 Colombo2012 Ferrandina2008 Vergote2009 I Subtotal (95%CI) Heterogeneily: Tau ² = Test for overal effect: 2 Muccositis/stomatitis Banerjee2018 Kaye2012 I Kaye2012 I Kaye2012 I Vergote2009 I Vergote2009 I Vergote2009 I Vergote2009 I Subtotal (95%CI) Heterogeneily: Tau ² = Test for overal effect: 2 Hand-foot syndrome Banerjee2018 Kaye2012 I	$\begin{array}{c} 33/494\\ 33/494\\ 32/501 \\ z=1,73 \ (P=0.08) \\ \hline \\ 6/46\\ 38/99\\ 12/402\\ 16/71\\ 10/130\\ 39/130\\ \hline \\ 12/1678\\ 0.84; Ch^2=3.88, df=7\\ Z=1.81 \ (P=0.07) \\ \hline \\ 0/46\\ 0/32\\ 0.032\\ 0.00; Ch^2=6.99, df=7\\ Z=5.48 \ (P<0.01) \\ \hline \\ 0/46\\ 0/32\\ 0.032\\ 0.032\\ 0.032\\ \end{array}$	(P = 0.39), $P = 4%2/4718/9641/4095/7212/8790/7985 (P < 0.0001)$, $P = 13/472/322/323/9641/4092/7214/8714/8781/862(P = 0.43)$, $P = 0%0/4712/3212/32$		 11.7% 19.0% 18.1% 15.9% 17.9% 18.4% 100.0% 7.9% 13.5% 34.1% 12.0% 8.6% 8.6% 100.0% 	3.07 [0.65, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56] 3.25 [1.28, 8.38] 0.56 [0.25, 1.23] 2.17 [1.21, 3.91] 1.32 [0.59, 2.96] 0.15 [0.01, 2.75] 0.20 [0.01, 4.01] 0.20 [0.01, 4.01] 0.20 [0.01, 4.01] 0.20 [0.01, 4.01] 0.25 [0.00, 0.38] 0.05 [0.00, 0.38] 0.02 [0.00, 0.38] 0.10 [0.04, 0.23] Not estimable 0.04 [0.00, 0.65]
Subtotal (95%CI) Heterogeneity: Tau ² = Test for overall effect: ² Neutropenia Baneriee2019 Mutch2007 Colombo2012 Ferrandina2008 (vergote2009 II Subtotal (95%CI) Heterogeneity: Tau ² = I Test for overall effect: ² Mutch2007 Colombo2012 Ferrandina2008 Vergote2009 II Wutch2007 Colombo2012 Ferrandina2008 Vergote2009 II Subtotal (95%CI) Stetterogeneity: Tau ² = I Test for overall effect: ² Hand-foot syndrome Banerjee2018 Kaye/2012 II Kaye/2012 II Kaye/2012 I	$\begin{array}{c} 33/494\\ 0.35(Ch^2=5.21, d=5\\ Z=1.73(P=0.08)\\ \hline\\ & 6/46\\ 38/99\\ 12/402\\ 16/71\\ 10/130\\ 39/130\\ \hline\\ & 121/878\\ 0.84; Ch^2=3.88, df=\\ & 0.732\\ 0.732\\ 0.732\\ 0.732\\ 0.732\\ 0.732\\ 0.732\\ 0.732\\ 0.748\\ 0.748\\ 0.732\\ 0.758\\ 0.7$	(P = 0.39), $P = 4%2/4718/9641/4095/7212/8790/7985 (P < 0.00001)$, $P = 13/472/323/3641/4092/7214/8781/862(P = 0.43)$, $P = 0%0/4712/32$			3.07 [0.65, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56] 3.25 [1.26, 8.38] 0.56 [0.25, 1.23] 2.17 [1.21, 3.91] 1.32 [0.59, 2.96] 0.15 [0.01, 2.75] 0.20 [0.01, 4.01] 0.20 [0.03, 3.05] 0.05 [0.01, 2.00] 0.51 [0.05, 5.47] 0.02 [0.00, 0.38] 0.02 [0.00, 0.38] 0.02 [0.00, 0.38] 0.02 [0.00, 0.38] 0.04 [0.00, 0.65] 0.04 [0.00, 0.65] 0.05 [0.00, 0.78]
Subtotal (95%C)) teterogeneity: Tau ² = test for overal effect: 2 Veutropenia Banerjee2018 Much2007 200mb02012 Ferrandina2008 (regole2000 I Subtotal (95%C)) teterogeneity: Tau ² = test for overal effect: 2 Muccositis/stomatitis Banerjee2018 Gaye2012 I Much2007 200mb02012 Test for overal effect: 2 Handsoto syndrome Banerjee2018 Gaye2012 I test for overal effect: 2 Handsoto syndrome Banerjee2018 Gaye2012 I Subtotal (95%C)) teterogeneity: Tau ² = Test for overal effect: 2 Handsoto syndrome Banerjee2018 Gaye2012 I Much2007 200mb02012 I Much2007 200mb02012 I	33/494 33/494 23/51, CH ² = 5.21, df = 5 Z = 1.73 (P = 0.08) 6/46 38/99 12/402 16/71 10/130 39/130 121/878 0.84; CH ² = 3.85, df = 7 Z = 1.81 (P = 0.07) 0/46 0/32 0/32 0/32 0.00; CH ² = 6.99, df = 7 Z = 5.48 (P < 0.01) 0/42 0/32 0/	(P = 0.39); f ² = 4% 2/47 18/96 41/409 5/72 12/87 90/798 5 (P < 0.0001); f ² = 1 3/47 2/32 2/32 3/96 41/409 2/72 14/87 14/87 81/862 (P = 0.43); f ² = 0% 0/47 12/32 12/32 10/96 55/400		 11.7% 19.0% 18.1% 15.9% 17.0% 18.4% 100.0% 7.9% 7.6% 7.6% 7.6% 34.1% 12.0% 8.6% 8.6% 100.0% 	3.07 [0.65, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56] 3.25 [1.26, 8.38] 0.56 [0.25, 1.23] 2.17 [1.21, 3.91] 1.32 [0.59, 2.96] 0.15 [0.01, 2.75] 0.20 [0.01, 4.01] 0.22 [0.01, 4.01] 0.22 [0.01, 4.01] 0.22 [0.01, 4.01] 0.25 [0.03, 3.05] 0.05 [0.01, 0.20] 0.51 [0.05, 5.47] 0.22 [0.00, 0.38] 0.02 [0.00, 0.38] 0.02 [0.00, 0.38] 0.02 [0.00, 0.38] 0.04 [0.00, 0.65] 0.04 [0.00, 0.65] 0.05 [0.00, 0.76]
Subtotal (95%CI) Heterogeneity: Tau ² = Test for overall effect; 2 Neutropenia Banerjee2018 Much2007 Colombo2012 Ferrandina2008 Vergote2009 II Subtotal (95%CI) Heterogeneity: Tau ² = 1 Test for overall effect; 2 Mucositis/stotnattis Banerjee2018 Banerjee2018 Banerjee2018 Banerjee2019 I Subtotal (95%CI) Heterogeneity: Tau ² = Test for overall effect; 2 Hand-foot syndrome Banerjee2018 Caye2012 I Heterogeneity: Tau ² = Test for overall effect; 2 Hand-foot syndrome Banerjee2018 Caye2012 I Hand-foot syndrome Banerjee2018 Caye2012 I Much2007 Colombo2012 Ferrandina2008	$\begin{array}{c} 33/494\\ 0.35(Ch^2=5.21, d=5\\ Z=1.73(P=0.08)\\ \hline\\ & 6/46\\ 3.8/99\\ 1.2/402\\ 16/71\\ 10/130\\ 39/130\\ \hline\\ & 121678\\ 0.84; Ch^2=3.68, df=2\\ 0.732\\ 0.732\\ 0.732\\ 0.732\\ 0.732\\ 0.71\\ 0/130\\ \hline\\ & 0/46\\ 0.732\\ 0.71\\ 0/130\\ \hline\\ & 0/46\\ 0.732\\ 0.99\\ 0.46\\ 0.72\\ 0.99\\ 0.46\\ 0.72\\ 0.99\\ 0.46\\ 0.71\\ 0.99\\ 0.46\\ 0.72\\ 0.99\\ 0.46\\ 0.72\\ 0.99\\ 0.46\\ 0.71\\ 0.99\\ 0.46\\ 0.71\\ 0.99\\ 0.46\\ 0.72\\ 0.99\\ 0.46\\ 0.71\\ 0.99\\ 0.46\\ 0.72\\ 0.99\\ 0.46\\ 0.71\\ 0.99\\ 0.46\\ 0.99\\ 0.46$	(P = 0.39), $P = 4%2/4718/9641/4095/7212/8790/7985 (P < 0.00001)$, $P = 103/472/323/9641/4092/7214/8781/862(P = 0.43)$, $P = 0%0/4712/3212/3212/3210/9655/4094/72$		 11.7% 19.0% 18.1% 15.9% 17.0% 18.4% 100.0% 7.9% 7.6% 13.5% 34.1% 12.0% 8.6% 8.6% 8.6% 100.0% 14.6% 14.6% 14.6% 14.2% 14.2% 14.2% 14.2% 14.2% 14.2% 14.2% 14.2% 14.3% 	3.07 [0.65, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56] 3.25 [1.26, 8.38] 0.56 [0.25, 1.23] 2.17 [1.21, 3.91] 1.32 [0.59, 2.96] 0.15 [0.01, 2.75] 0.20 [0.01, 4.01] 0.20 [0.03, 3.05] 0.05 [0.01, 2.02] 0.51 [0.05, 5.47] 0.02 [0.00, 0.38] 0.02 [0.00, 0.38] 0.02 [0.00, 0.38] 0.02 [0.00, 0.38] 0.02 [0.00, 0.38] 0.04 [0.00, 0.65] 0.04 [0.00, 0.65] 0.04 [0.00, 0.65] 0.04 [0.00, 0.78] 0.05 [0.00, 0.78] 0.05 [0.00, 0.78]
Subtotal (95%CI) Heterogeneity: Tau ² = Test for overall effect: 2 Neutropenia Banerjee2018 Muchc2007 Colombo2012 Ferrandina2008 (vergole22008 II Subtotal (95%CI) Heterogeneity: Tau ² = Fest for overall effect: 2 Wucositis/stomatilis Banerjee2018 Gwye2012 I Hutch2007 Joidmbc2012 Gergote2008 II Subtotal (95%CI) Heterogeneity: Tau ² = Fest for overall effect: 2 Hand-foot syndrome Banerjee2018 Gwye2012 I Hand-foot syndrome Banerjee2018 Gwye2012 I Hand-foot syndrome Banerjee2018 Gwye2012 I Jand-foot Syndrome Banerjee2018 Gwye2012 I Jand-foot Syndrome Banerjee2018 Gwye2012 I Jand-foot Syndrome Banerjee2018 Gwye2012 I Jand-foot Syndrome Banerjee2018 Gwye2012 I Jointbo2012 Ferrandina2008	33/494 33/494 23/27 2 = 1.73 (P = 0.08) 6/46 38/99 12/402 16/71 10/130 39/130 12/1878 0.84; Chr ² = 3.85, df = 7 = 1.81 (P = 0.07) 0/46 0/32 0/32 0/32 0/32 0/130 0/130 0/130 0/130 0/130 0/130 0/130 0/130 0/130 0/132 0/32	$(P = 0.39)$; $r^2 = 4\%$ 2/47 18/96 41/409 5/72 12/87 90/798 $5 (P < 0.0001)$; $r^2 = 10^{-1}$ 3/47 2/32 2/32 3/96 41/409 2/32 12/87 3/47 2/32 2/32 3/96 41/409 2/72 14/87 14/87 14/87 14/87 14/87 14/87 14/87 14/87 14/87 14/87 14/87 12/32 12/32 12/32 10/96 55/409 4/72 13/87		 11.7% 19.0% 18.1% 15.9% 17.0% 18.4% 100.0% 7.9% 7.9% 7.9% 7.9% 7.9% 8.6% 8.6% 100.0% 14.6% 14.6% 14.8% 14.8% 13.4% 	3.07 [0.65, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56] 3.25 [1.26, 8.38] 0.56 [0.25, 1.23] 2.17 [1.21, 3.91] 1.32 [0.59, 2.96] 0.15 [0.01, 2.75] 0.20 [0.01, 4.01] 0.22 [0.01, 4.01] 0.22 [0.03, 3.05] 0.05 [0.01, 0.20] 0.51 [0.05, 5.47] 0.20 [0.00, 0.38] 0.02 [0.00, 0.38] 0.02 [0.00, 0.38] 0.02 [0.00, 0.38] 0.02 [0.00, 0.38] 0.04 [0.00, 0.55] 0.04 [0.00, 0.65] 0.04 [0.00, 0.15] 0.05 [0.00, 0.15] 0.11 [0.01, 12.05]
Subtotal (95%CI) Heterogeneily: Tau ² = Test for overal effect: 3 Keutropenia Banerjee2018 Much2007 Colombo2012 Ferrandina2008 Vergote2009 I Subtotal (95%CI) Heterogeneily: Tau ² = Test for overal effect: 2 Mucositis/stomatitis Banerjee2018 Kaye2012 I Much2007 Subtotal (95%CI) Heterogeneily: Tau ² = Ferst for overal effect: 2 Hand-foot syndrome Subtotal (95%CI) Heterogeneily: Tau ² = Fest for overal effect: 2 Hand-foot syndrome Samerjee2018 Kaye2012 I Much2007 Subtotal (95%CI) Heterogeneily: Tau ² = Fest for overal effect: 2 Hand-foot syndrome Gaye2012 I Much2007 Subtotal (95%CI) Heterogeneily: Tau ² = Fest for overal effect: 2 Hand-foot syndrome Ferrandina2008	$\begin{array}{c} 33/494\\ 33/494\\ 38/99\\ 12/402\\ 16/71\\ 10/130\\ 38/99\\ 12/402\\ 16/71\\ 10/130\\ 39/130\\ 12/1678\\ 0.84; Chr^2 = 3.88, df = 7\\ Z = 1.81 (P = 0.07)\\ 0/46\\ 0/32\\ 0/32\\ 1/99\\ 2/402\\ 1/71\\ 0/130\\ 0/130\\ 0\\ 4/942\\ Z = 5.48 (P < 0.01)\\ 0/32\\ 0/3$	(P = 0.39); $P = 4%2/4718/9641/4095/7212/8712/8790/7985 (P < 0.00001)$; $P = 13/472/322/323/9641/4092/7214/8781/862(P = 0.43)$; $P = 0%0/4712/3210/9655/40947/213/87$		11.7% 19.0% 18.1% 15.9% 17.0% 18.4% 100.0% 7.8% 7.8% 7.8% 7.8% 13.5% 34.1% 34.5% 13.6% 13.6% 14.6% 14.6% 14.2% 14.8% 14.3%	3.07 [0.65, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56] 3.25 [1.28, 8.38] 0.56 [0.25, 1.23] 2.17 [1.21, 3.91] 1.32 [0.59, 2.96] 0.15 [0.01, 2.75] 0.20 [0.01, 4.01] 0.20 [0.01, 4.01] 0.20 [0.01, 4.01] 0.20 [0.01, 4.01] 0.25 [0.00, 0.38] 0.05 [0.00, 0.38] 0.10 [0.04, 0.23] 0.10 [0.04, 0.23] 0.10 [0.04, 0.23] 0.10 [0.00, 0.65] 0.05 [0.00, 0.65] 0.05 [0.00, 0.75] 0.01 [0.00, 0.15] 0.11 [0.01, 2.05] 0.02 [0.00, 0.41]
Subtotal (95%Cl) Heterogeneily: Tau ² = Test for overall effect: 3 Neutropenia Banerjee2018 Much2007 Colombo2012 Ferrandina2008 Vergote2009 I Subtotal (95%Cl) Heterogeneily: Tau ² = Test for overall effect: 3 Mucositis/stomatitis Banerjee2018 Kaye2012 I Much2007 Jolombo2012 Ferrandina2008 Jergote2009 I Vergote2009 I Heterogeneily: Tau ² = Test for overall effect: 3 andrejee2018 Kaye2012 I Much2007 Jolombo2012 Ferrandina2008 Jergote2009 I Agey2012 I Much2007 Jolombo2012 Ferrandina2008 Vergote2009 I Subtotal (95%Cl) - Heterogeneily: Tau ² = Test for overall effect: 2 and-foot syndrome Ferrandina2008 Vergote2009 I Jerrandina2008 Vergote2009 I	$\begin{array}{c} 33/494\\ 33/494\\ 35/10^2 = 5.1, d= 5\\ Z= 1.73 (P=0.08)\\ \hline \\ 6/46\\ 38/99\\ 12/402\\ 16/71\\ 10/130\\ 39/130\\ \hline \\ 121/878\\ 0.84; Ch^2 = 38.85, df = \\ Z= 1.81 (P=0.07)\\ \hline \\ 0/46\\ 0/32\\ 0/32\\ 1/99\\ 2/402\\ 1/71\\ 0/130\\ 0/130\\ \hline \\ 0/46\\ 0/32\\ 0.99\\ 0/402\\ 0.71\\ 0/130\\ 0/130\\ 0/130\\ \hline \end{array}$			 11.7% 10.0% 18.4% 100.0% 7.9% 7.8% 7.6% 13.5% 34.1% 8.6% 100.0% 14.6% 14.6% 14.3% 14.3% 	3.07 [0.65, 14.41] 2.05 [1.26, 8.38] 0.30 [0.16, 0.56] 3.25 [1.28, 8.38] 0.56 [0.25, 1.23] 2.17 [1.21, 3.91] 1.32 [0.59, 2.96] 0.15 [0.01, 2.75] 0.20 [0.01, 4.01] 0.20 [0.01, 4.01] 0.20 [0.01, 4.01] 0.25 [0.00, 0.38] 0.05 [0.00, 0.38] 0.20 [0.00, 0.38] 0.20 [0.00, 0.38] 0.20 [0.00, 0.38] 0.20 [0.00, 0.38] 0.20 [0.00, 0.38] 0.10 [0.04, 0.23] Not estimable 0.04 [0.00, 0.65] 0.05 [0.00, 0.78] 0.01 [0.00, 0.17] 0.11 [0.01, 2.05] 0.10 [0.11, 2.05] 0.20 [0.00, 0.41] 0.20 [0.00, 0.41]
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Fig. 5 Forest plots of toxicity endpoints for the monotherapy

did not result in a significant prolongation of PFS or OS in platinum-resistant or -refractory ovarian cancer [27]. The 2019 NCCN Guidelines showed that PLD plus bevacizumab constitutes a potential treatment option for patients with platinum-resistant recurrent ovarian cancer, and the 2020 NCCN Guidelines suggest that bevacizumab is effective in both platinum-sensitive and platinum-resistant recurrent ovarian cancer. Nevertheless, treatment of platinum-resistant or -refractory recurrent ovarian cancer as palliative care still necessitates more chemotherapy options.

The principal and common adverse effects of monotherapy PLD were mucositis/stomatitis and hand-foot syndrome. We laterally compared the incidence of side effects at two different PLD doses (grade 3–4 toxicity), and showed that mucositis/stomatitis (40 mg/m² vs. 50 mg/m²) PLD (4.2% vs. 10.2%, respectively) was a dosedependent side effect of PLD. At the same doses (3.4% vs 17.6%, respectively), the results showed that handfoot syndrome was also a significant dose-dependent side effect of PLD.

Thus, our updated meta-analysis showed that PLD was well-tolerated at the 40 mg/m^2 (lower-dose) regimen which did not adversely affect survival compared with other single regimens—and confirmed PLD as a good choice for women in whom monotherapy was a treatment option.

Strengths and limitations of PLD in the treatment of ovarian Cancer

The most concerning potential side effect of doxorubicin and PLD is often cited as congestive heart failure, and doxorubicin is in fact closely associated with congestive heart failure. PLD's parent drug is doxorubicin, but PLD can effectively reduce cardiac toxicity. Studies show that PLD reduced the incidence of cardiotoxicity five-to-six fold even at doses $\geq 500 \text{ mg/m}^2$. This is because of pegylation, which coats the liposome with a hydrophilic protective coating, and allows the drug to remain in circulation for a prolonged time due to its ability to evade immunologic elimination. Both lower plasma levels and improved ability to target tumor tissue allow for the sparing of cardiac toxicity with PLD [28]. One study depicted no significant incidence of cardiotoxicity (as defined by 2D strain on 3D left-ventricular ejection fraction), even with high cumulative doses of PLD up to 2500 mg, and therefore long-term use appears safe [29]. Thus PLD exerts a cardioprotective effect and is more beneficial for patients with poor heart function and for elderly patients.

Contemporary studies have shown that prolonged treatment with PLD is associated with the development of secondary squamous cell carcinoma of the oral mucosa in a number of case reports [9]. In another trial, we showed that the cumulative doses of PLD in our patients prior to the development of squamous cell carcinoma were 1350 mg/m² and 1142 mg/m², respectively, and that it was necessary to reduce the dose, prolong the administration, and provide regular oral-cavity examinations along with complete skin examinations [30]. We recommend using a PLD dose as low as possible, and to prolong the administration so as to reduce the incidence of hand-foot syndrome—thereby reducing the incidence of secondary squamous cell carcinoma of the oral mucosa.

Conclusions

PLD plus carbo for platinum-sensitive disease produced a better PFS than standard-regimen PAC plus carbo and was well tolerated. However, there was no difference in overall survival. The findings of this meta-analysis support the continued use of PLD plus carbo as first-line chemotherapy for platinum-sensitive recurrent ovarian cancer, and PLD at 30 mg/m^2 every 4 weeks can be used as the initial dose. As a single-agent therapy, PLD manifested survival similar to other agents and was well tolerated. The findings of this meta-analysis support the continued use of PLD monotherapy as first-line chemotherapy for platinum-resistant or -refractory recurrent ovarian cancer, and we recommend using PLD at a dose of 40 mg/m² every 4 weeks as the initial dose.

Abbreviations

NCCN: National comprehensive cancer network; PLD: Pegylated liposomal doxorubicin; PAC: Paclitaxel; Carbo: Carboplatin; LIFA: Lifastuzumab vedotin; OS: Overall survival; PFS: Progression-free survival; HR: Hazard ratios; RR: Risk ratios; 95% Cl: 95% Confidence interval.

Supplementary Information

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Additional file 1.	
Additional file 2.	

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Authors' contributions

All authors contributed to the design of the review. X.R.L and L.X.P completed the initial data search. Y.Z and J.M.H designed methods and completed the Statistical analysis. G.N.Z co-designed methods and revised the article. X.R.L wrote the first manuscript draft and all authors approved the final manuscript.

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Availability of data and materials

The dataset used or analyzed in this study is available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication

Not applicable.

Competing interests

All the authors declare no competing interests.

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References

- 1. Reid BM, Permuth JB, Sellers TA. Epidemiology of ovarian cancer: a review. Cancer biology and. Medicine. 2017;14:9–32.
- Piao J, Lee EJ, Lee M. Association between pelvic inflammatory disease and risk of ovarian cancer: An updated meta-analysis. Gynecol Oncol. 2020;157:542-8.
- Bookman MA, Okamoto A, Stuart G, Yanaihara N, Aoki D, Bacon M, et al. Harmonising clinical trials within the gynecologic cancer intergroup: consensus and unmet needs from the fifth ovarian cancer consensus conference. Ann Oncol. 2017;28:viii30–5.
- McGee J, Bookman M, Harter P, Marth C, McNeish I, Moore KN, et al. Fifth ovarian cancer consensus conference: Individualized therapy and patient factors. Ann Oncol. 2017;28:702–10.
- Landrum LM, Brady WE, Armstrong DK, Moore KN, DiSilvestro PA, O'Malley DM, et al. A phase I trial of pegylated liposomal doxorubicin (PLD), carboplatin, bevacizumab and veliparib in recurrent, platinum-sensitive ovarian, primary peritoneal, and fallopian tube cancer: An NRG oncology/ gynecologic oncology group study. Gynecol Oncol. 2016;140:204–9.
- Buechel M, Herzog TJ, Westin SN, Coleman RL, Monk BJ, Moore KN. Treatment of patients with recurrent epithelial ovarian cancer for whom platinum is still an option. Ann Oncol. 2019;30:721–32.
- Corrado G, Salutari V, Palluzzi E, Distefano MG, Scambia G, Ferrandina G. Optimizing treatment in recurrent epithelial ovarian cancer. Expert Rev Anticancer Ther. 2017;17:1147–58.
- Madrid Paredes A, Vallejo I, Carrasco M, Valencia C, Artime F, Calleja M. Prescription profile and impact after the pegylated liposomal doxorubicin shortage alert. Eur J Hosp Pharm. 2015;22:A16.
- Cannon TL, Lai DW, Hirsch D, Delacure M, Downey A, Kerr AR, et al. Squamous cell carcinoma of the oral cavity in nonsmoking women: A new and unusual complication of chemotherapy for recurrent ovarian cancer? Oncologist. 2012;17:1541–6.
- Gibson JM, Alzghari S, Ahn C, Trantham H, La-Beck NM. The role of pegylated liposomal doxorubicin in ovarian cancer: a meta-analysis of randomized clinical trials. Oncologist. 2013;18:1022–31.
- Lawrie TA, Bryant A, Cameron A, Gray E, Morrison J. Pegylated liposomal doxorubicin for relapsed epithelial ovarian cancer. Cochrane Database Syst Rev. 2013;7:CD006910.

- Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E, Gebski V, Heywood M, Vasey PA, et al. Pegylated liposomal doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. J Clin Oncol. 2010;28:3323–9.
- Gladieff L, Ferrero A, De Rauglaudre G, Brown C, Vasey P, Reinthaller A, et al. Carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in partially platinum-sensitive ovarian cancer patients: Results from a subset analysis of the CALYPSO phase III trial. Ann Oncol. 2012;23:1185–9.
- Mahner S, Meier W, Du Bois A, Brown C, Lorusso D, Dell'Anna T, et al. Carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in very platinum-sensitive ovarian cancer patients: Results from a subset analysis of the CALYPSO phase III trial. Eur J Cancer. 2015;51:352–8.
- 15. Bafaloukos D, Linardou H, Aravantinos G, Papadimitriou C, Bamias A, Fountzilas G, Kalofonos HP, Kosmidis P, Timotheadou E, Makatsoris T, Samantas E, Briasoulis E, Christodoulou C, Papakostas P, Pectasides D, Dimopoulos AM. A randomized phase II study of carboplatin plus pegylated liposomal doxorubicin versus carboplatin plus paclitaxel in platinum sensitive ovarian cancer patients: a Hellenic Cooperative Oncology Group study. BMC Med. 2010;8:3.
- Mutch DG, Orlando M, Goss T, Teneriello MG, Gordon AN, McMeekin SD, et al. Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer. J Clin Oncol. 2007;25:2811–8.
- Ferrandina G, Ludovisi M, Lorusso D, Pignata S, Breda E, Savarese A, et al. Phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in progressive or recurrent ovarian cancer. J Clin Oncol. 2008;26:890–6.
- Vergote I, Finkler NJ, Hall JB, Melnyk O, Edwards RP, Jones M, et al. Randomized phase III study of canfosfamide in combination with pegylated liposomal doxorubicin compared with pegylated liposomal doxorubicin alone in platinum-resistant ovarian cancer. Int J Gynecol Cancer. 2010;20:772–80.
- Colombo N, Kutarska E, Dimopoulos M, Bae DS, Rzepka-Gorska I, Bidzinski M, et al. Randomized, open-label, phase III study comparing patupilone (EPO906) with pegylated liposomal doxorubicin in platinum-refractory or -resistant patients with recurrent epithelial ovarian, primary fallopian tube, or primary peritoneal cancer. J Clin Oncol. 2012;30:3841–7.
- Banerjee S, Oza AM, Birrer MJ, Hamilton EP, Hasan J, Leary A, et al. Anti-NaPi2b antibody-drug conjugate lifastuzumab vedotin (DNIB0600A) compared with pegylated liposomal doxorubicin in patients with platinumresistant ovarian cancer in a randomized, open-label, phase II study. Ann Oncol. 2018;29:917–23.
- Kaye SB, Lubinski J, Matulonis U, Ang JE, Gourley C, Karlan BY, et al. Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer. J Clin Oncol. 2012;30:372–9.
- Wilson MK, Pujade-Lauraine E, Aoki D, Mirza MR, Lorusso D, Oza AM, et al. Fifth ovarian cancer consensus conference of the gynecologic cancer intergroup: recurrent disease. Ann Oncol. 2017;28:727–32.
- Rolim LC, da Silva EMK, Flumignan RLG, Abreu M, Dib SA. Cochrane systematic review of acetyl-L-Carnitine for the treatment of diabetic polyneuropathy. Eur J Vasc Endovasc Surg. 2019;58:e342–3.
- Colombo N, Sessa C, du Bois A, Ledermann J, McCluggage WG, McNeish I, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. Ann Oncol. 2019;30:672–705.
- Bergamini A, Pisano C, Di Napoli M, Arenare L, Della Pepa C, Tambaro R, et al. Cisplatin can be safely administered to ovarian cancer patients with hypersensitivity to carboplatin. Gynecol Oncol. 2017;144:72–6.
- Crespo G, Sierra M, Losa R, Berros JP, Villanueva N, Fra J, et al. Pegylated liposomal doxorubicin and gemcitabine in a fixed dose rate infusion for the treatment of patients with poor prognosis of recurrent ovarian cancer: A phase lb study. Int J Gynecol Cancer. 2011;21:478–85.
- McGuire WP, Penson RT, Gore M, Herraez AC, Peterson P, Shahir A, Ilaria R Jr. Randomized phase II study of the PDGFRα antibody olaratumab plus liposomal doxorubicin versus liposomal doxorubicin alone in patients with platinum-refractory or platinum-resistant advanced ovarian cancer. BMC Cancer. 2018;18:1292.
- Gabizon AA, Patil Y, La-Beck NM. New insights and evolving role of pegylated liposomal doxorubicin in cancer therapy. Drug Resist Updat. 2016;29:90–106.

- Blank N, Laskov I, Kessous R, Kogan L, Lau S, Sebag IA, et al. Absence of cardiotoxicity with prolonged treatment and large accumulating doses of pegylated liposomal doxorubicin. Cancer Chemother Pharmacol. 2017;80: 737–43.
- Pease DF, Peterson BA, Gilles S, Hordinsky MK, Bohjanen KA, Skubitz KM. Development of cutaneous squamous cell carcinoma after prolonged exposure to pegylated liposomal doxorubicin and hand-foot syndrome: a newly recognized toxicity. Cancer Chemother Pharmacol. 2019;84:217–21.

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