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Pegylated liposomal doxorubicin for relapsed epithelial ovarian cancer (Review)

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[Intervention Review]

Pegylated liposomal doxorubicin for relapsed epithelial ovarian cancer

Rebecca Newhouse[1a], Ellen Nelissen[2a], Karim Hussien El-Shakankery[3a], Ewelina Rogozińska[4], Esme Bain[5], Susana Veiga[5], Jo Morrison[1]

[1]Department of Gynaecological Oncology, Musgrove Park Hospital, Taunton, UK. [2]Department of Gynaecological Oncology, The Royal Marsden, London, UK. [3]Medical Oncology, University College London Hospitals NHS Trust, London, UK. [4]The Evidence-Based Medicine Consultancy Ltd, Bath, UK. [5]Department of Gynaecological Oncology, North Bristol NHS Trust, Bristol, UK

[a]These authors should be considered joint first author

Contact: Jo Morrison, jo_morrison@doctors.org.uk.

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ABSTRACT

Background

Cancer of ovarian, fallopian tube and peritoneal origin, referred to collectively as ovarian cancer, is the eighth most common cancer in women and is often diagnosed at an advanced stage. Women with relapsed epithelial ovarian cancer (EOC) are less well and have a limited life expectancy, therefore maintaining quality of life with effective symptom control is an important aim of treatment. However, the unwanted effects of chemotherapy agents may be severe, and optimal treatment regimens are unclear. Pegylated liposomal doxorubicin (PLD), which contains a cytotoxic drug called doxorubicin hydrochloride, is one of several treatment modalities that may be considered for treatment of relapsed EOCs. This is an update of the original Cochrane Review which was published in Issue 7, 2013.

Objectives

To evaluate the efficacy and safety of PLD, with or without other anti-cancer drugs, in women with relapsed high grade epithelial ovarian cancer (EOC).

Search methods

We searched CENTRAL, MEDLINE (via Ovid) and Embase (via Ovid) from 1990 to January 2022. We also searched online registers of clinical trials, abstracts of scientific meetings and reference lists of included studies.

Selection criteria

We included randomised controlled trials (RCTs) that evaluated PLD in women diagnosed with relapsed epithelial ovarian cancer.

Data collection and analysis

Two review authors independently extracted data to a pre-designed data collection form and assessed the risk of bias according to the *Cochrane Handbook for Systematic Reviews of Interventions* guidelines. Where possible, we pooled collected data in meta-analyses.

Main results

This is an update of a previous review with 12 additional studies, so this updated review includes a total of 26 RCTs with 8277 participants that evaluated the effects of PLD alone or in combination with other drugs in recurrent EOC: seven in platinum-sensitive disease (2872 participants); 11 in platinum-resistant disease (3246 participants); and eight that recruited individuals regardless of platinum sensitivity status (2079 participants). The certainty of the evidence was assessed for the three most clinically relevant comparisons out of eight comparisons identified in the included RCTs.

Recurrent platinum-sensitive EOC

PLD with conventional chemotherapy agent compared to alternative combination chemotherapy likely results in little to no difference in overall survival (OS) (hazard ratio (HR) 0.93, 95% confidence interval (CI) 0.83 to 1.04; 5 studies, 2006 participants; moderate-certainty evidence) but likely increases progression-free survival (PFS) (HR 0.81, 95% CI 0.74 to 0.89; 5 studies, 2006 participants; moderate-certainty evidence). The combination may slightly improve quality of life at three months post-randomisation, measured using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (mean difference 4.80, 95% CI 0.92 to 8.68; 1 study, 608 participants; low-certainty evidence), but this may not represent a clinically meaningful difference.

PLD in combination with another chemotherapy agent compared to alternative combination chemotherapy likely results in little to no difference in the rate of overall severe adverse events (grade ≥ 3) (risk ratio (RR) 1.11, 95% CI 0.95 to 1.30; 2 studies, 834 participants; moderate-certainty evidence). PLD with chemotherapy likely increases anaemia (grade ≥ 3) (RR 1.37, 95% CI 1.02 to 1.85; 5 studies, 1961 participants; moderate-certainty evidence). The evidence is very uncertain about the effect of PLD with conventional chemotherapy on hand-foot syndrome (HFS)(grade ≥ 3) (RR 4.01, 95% CI 1.00 to 16.01; 2 studies, 1028 participants; very low-certainty evidence) and neurological events (grade ≥ 3) (RR 0.38, 95% CI 0.20 to 0.74; 4 studies, 1900 participants; very low-certainty evidence).

Recurrent platinum-resistant EOC

PLD alone compared to another conventional chemotherapy likely results in little to no difference in OS (HR 0.96, 95% CI 0.77 to 1.19; 6 studies, 1995 participants; moderate-certainty evidence). The evidence is very uncertain about the effect of PLD on PFS (HR 0.94, 95% CI 0.85 to 1.04; 4 studies, 1803 participants; very low-certainty evidence), overall severe adverse events (grade ≥ 3) (RR ranged from 0.61 to 0.97; 2 studies, 964 participants; very low-certainty evidence), anaemia (grade ≥ 3) (RR ranged from 0.19 to 0.82; 5 studies, 1968 participants; very low-certainty evidence), HFS (grade ≥ 3) (RR ranged from 15.19 to 109.15; 6 studies, 2184 participants; very low-certainty evidence), and the rate of neurological events (grade ≥ 3)(RR ranged from 0.08 to 3.09; 3 studies, 1222 participants; very low-certainty evidence).

PLD with conventional chemotherapy compared to PLD alone likely results in little to no difference in OS (HR 0.92, 95% CI 0.70 to 1.21; 1 study, 242 participants; moderate-certainty evidence) and it may result in little to no difference in PFS (HR 0.94, 95% CI 0.73 to 1.22; 2 studies, 353 participants; low-certainty evidence). The combination likely increases overall severe adverse events (grade ≥ 3) (RR 2.48, 95% CI 1.98 to 3.09; 1 study, 663 participants; moderate-certainty evidence) and anaemia (grade ≥ 3) (RR 2.38, 95% CI 1.46 to 3.87; 2 studies, 785 participants; moderate-certainty evidence), but likely results in a large reduction in HFS (grade ≥ 3) (RR 0.24, 95% CI 0.14 to 0.40; 2 studies, 785 participants; moderate-certainty evidence). It may result in little to no difference in neurological events (grade ≥ 3) (RR 1.40, 95% CI 0.85 to 2.31; 1 study, 663 participants; low-certainty evidence).

Authors' conclusions

In platinum-sensitive relapsed EOC, including PLD in a combination chemotherapy regimen probably makes little to no difference in OS compared to other combinations, but likely improves PFS. Choice of chemotherapy will therefore be guided by symptoms from previous chemotherapy and other patient considerations. Single-agent PLD remains a useful agent for platinum-resistant relapsed EOC and choice of agent at relapse will depend on patient factors, e.g. degree of bone marrow suppression or neurotoxicity from previous treatments. Adding another agent to PLD likely increases overall grade ≥ 3 adverse events with little to no improvement in survival outcomes. The limited evidence relating to PLD in combination with other agents in platinum-resistant relapsed EOC does not indicate a benefit, but there is some evidence of increased side effects.

PLAIN LANGUAGE SUMMARY

What are the harms and benefits of using pegylated liposomal doxorubicin in women with recurrent epithelial ovarian cancer, alone or in combination with other drugs?

What is the aim of this review?

The aim of this Cochrane Review update was to summarise benefits and unwanted effects of using a coated form of a chemotherapy drug, pegylated liposomal doxorubicin (PLD), for treatment of women with epithelial ovarian cancer (EOC) that had progressed/returned after initial treatment. The review authors collected and analysed all relevant studies to answer this question and found 26 studies, adding 12 studies to the original version of this review.

Key messages

Women whose EOC returned more than six months after finishing their last treatment who were treated with PLD alongside other chemotherapy survived for a similar length of time to women treated with alternative combinations. It may also take longer for their cancer to re-grow than with alternative combinations. Quality of life may slightly improve with PLD treatment. Apart from anaemia, which was more common in women taking the PLD treatment, severe side effects were similar to those seen in women on alternative combinations.

In women whose EOC returned within six months of finishing their last platinum treatment, PLD alongside other chemotherapy, versus alterative combination chemotherapy, probably works as well in terms of improving how long they live, but we are uncertain about other unwanted effects and benefits. PLD alongside other chemotherapy versus PLD alone likely makes little difference in how long women

survive, and may make little difference in how long it takes for their cancer to re-grow, but the combination likely increases overall severe unwanted effects and the risk of severe anaemia.

What was studied in this review?

The choice of chemotherapy in women with relapsed EOC is influenced by the duration of platinum-free interval (length of time from the last platinum-based chemotherapy to the time of disease progression). This is because a short 'platinum-free interval' suggests that their disease will no longer respond to platinum-based chemotherapy. Women who relapse within one month of receiving platinum therapy, or who progress on therapy have 'platinum-refractory' disease; women who relapse between one and six months after platinum therapy have 'platinum-resistant' disease; and women who relapse more than six months after platinum therapy have 'platinum-sensitive' disease.

Doxorubicin hydrochloride is an anti-cancer drug that works by interfering with cancer cell DNA. However, it can have unwanted effects on the heart. Coating the drug within a protective shell allows it to reach higher concentrations in cancer cells whilst protecting the heart. This coated chemotherapy is called pegylated liposomal doxorubicin (PLD).

We wanted to determine how PLD could be used best in women with EOC that has returned, Most of these women will have a limited life expectancy, so consideration of quality of life is important in making treatment choices. One specific side effect of PLD is called hand-foot syndrome (HFS). This is reddening, swelling, numbness and skin peeling of the palms of the hands and soles of the feet.

What are the main results of the review?

We added 12 studies to the previous review, so now include 26 studies with a total of 8277 women with recurrent EOC. Seven studies looked at platinum-sensitive disease (2827 women); 11 platinum-resistant disease (3246 women); and eight recruited women who had both platinum-sensitivity and platinum resistant disease (2079 women).

Recurrent platinum-sensitive EOC

We found five studies for women with platinum-sensitive disease using PLD in combination with chemotherapy versus alternative combination chemotherapy. The PLD combination likely makes little difference in how long women survive (overall survival, OS), but likely increases the time to further relapse (progression-free survival, PFS). There may be a slight improvement in quality of life. There may be little to no difference in the overall number of severe unwanted effects, although adding PLD causes more anaemia. We are uncertain about the effect of PLD with chemotherapy on other individual unwanted effects.

Recurrent platinum-resistant EOC

We found six studies for women with platinum-resistant disease using PLD alone compared to conventional chemotherapy. PLD alone likely makes little difference in OS. We are very uncertain about the effect on PFS, overall severe unwanted effects (i.e. those that require hospital treatment, e.g. blood transfusion), severe anaemia (grade ≥ 3), HFS, and the rate of severe unwanted effects on the nervous system (e.g. permanent numbness in fingers and toes).

We found two studies that compared PLD alongside other chemotherapy combination with PLD alone. PLD in combination likely makes little difference in OS, and it may make little difference in PFS. The combination likely increases overall severe unwanted effects and anaemia. Combination treatment likely results in a large reduction in HFS, but may result in little difference in unwanted effects on the nervous system.

Several studies compared PLD alone with new targeted agents or immunotherapy, but we are very uncertain about the benefit of adding these to PLD.

How up to date is this review?

We searched electronic databases and other resources for studies of PLD for relapsed EOC, and included 26 studies up to January 2022.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings 1: PLD with chemotherapy compared to alternative combination chemotherapy in recurrent platinum-sensitive EOC

Patient or population: adult women with recurrent platinum-sensitive EOC

Setting: specialist hospital

Intervention: PLD with conventional chemotherapy

Comparison: conventional chemotherapy alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comment
	Risk with conventional chemotherapy alone	Risk with PLD with conventional chemotherapy				
Overall survival (OS) Assessed with: survival status Follow-up: median range 25.5 to 49 months	Average[a] 284 per 1000	310 per 1000 (260 to 361)	HR 0.93 (0.83 to 1.04)	2006 (5 RCTs)	⊕⊕⊕⊖ Moderate[b]	PLD with conventional chemotherapy likely results in little to no difference in OS.
Progression-free survival (PFS) Assessed with: progression free status according to RECIST Follow-up: median range 11.3 to 49 months	Average[c] 377 per 1000	454 per 1000 (412 to 495)	HR 0.81 (0.74 to 0.89)	2006 (5 RCTs)	⊕⊕⊕⊖ Moderate[d]	PLD with conventional chemotherapy likely increases PFS.
Quality of life (QoL) Assessed with: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30	The mean change from baseline in quality of life (Global Health score) was -2.2 points.	MD 4.8 points higher (0.92 higher to 8.68 higher)	-	608 (1 RCT)	⊕⊕⊖⊖ Low[e]	PLD with conventional chemotherapy evidence may slightly improve QoL.

Follow-up: 3 months post-randomisation						
Overall severe adverse events (grade ≥ 3) Assessed with: WHO classification where stated	222 per 1000	**245 per 1000** (211 to 289)	**RR 1.11** (0.95 to 1.30)	834 (2 RCTs)	⊕⊕⊕⊖ Moderate[d]	PLD with conventional chemotherapy likely results in little to no difference in overall severe adverse events (grade ≥3).
Anaemia (grade ≥ 3) Assessed with: WHO classification or CTCAE (v2.0-4.03) where stated	69 per 1000	**95 per 1000** (65 to 140)	**RR 1.37** (1.02 to 1.85)	1961 (5 RCTs)	⊕⊕⊕⊖ Moderate[d]	PLD with conventional chemotherapy likely increases anaemia (grade ≥ 3).
Hand-foot syndrome (grade ≥ 3) Assessed with: WHO classification or CTCAE (v2.0-4.03) where stated	4 per 1000	**15 per 1000** (4 to 60)	**RR 4.01** (1.00 to 16.01)[f]	1028 (2 RCTs)	⊕⊖⊖⊖ Very low[d,g]	The evidence is very uncertain about the effect of PLD with conventional chemotherapy on hand-foot syndrome (grade ≥ 3).
Neurological (grade ≥ 3) **Assessed with:** WHO classification or CTCAE (v2.0-4.03) where stated	33 per 1000	**19 per 1000** (4 to 100)	**RR 0.38** (0.20 to 0.74)	1900 (4 RCTs)	⊕⊖⊖⊖ Very low[b,d,h]	The evidence is very uncertain about the effect of PLD with conventional chemotherapy on neurological events (grade ≥ 3).

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EOC: epithelial ovarian cancer; HR: hazard ratio; MD: mean difference; OS: overall survival; PLD: pegylated liposomal doxorubicin; RECIST: Response Evaluation Criteria in Solid Tumors; RCT: randomised control trail; RR: risk ratio; WHO: World Health Organization
GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
Explanations
[a]The control risk is an average number of participants reported alive at 36 months in CALYPSO, Fujiwara 2019 and Fujiwara 2019 trials.
[b]Downgraded by one level due to imprecision (wide confidence interval around the effect estimate crossing a line of no difference).
[c]The control risk is an average number of participants reported alive at 12 months in CALYPSO, Fujiwara 2019 and Pfisterer 2020 trials.
[d]Downgraded by one level due to risk of bias (open-label design).
[e]Downgraded by two levels due to imprecision (very wide confidence interval around the effect estimate crossing line of no difference).
[f]Note: 3out of 5 trials contributed to synthesis reported no events of HFS. In the fourth trial, there was only a single event in PLD with conventional chemotherapy arm.

[g]Downgraded by two levels due to imprecision (very wide confidence interval around the effect estimate including the line of no difference).
[h]Downgraded by one level due to inconsistency (notable difference between the direction of the effect between different drugs as conventional chemotherapy, test for subgroup difference P = 0.01).

Summary of findings 2. Summary of findings 2: PLD alone compared to other conventional chemotherapy in recurrent platinum-resistant EOC

Patient or population: adult women with recurrent platinum-resistant EOC

Setting: specialist hospital

Intervention: PLD alone

Comparison: other conventional chemotherapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with conventional chemotherapy	Risk with PLD				
Overall survival **(OS)** Assessed with: survival status Follow-up: median range 10 to 29.2 months	Average[a]		HR 0.96 (0.77 to 1.19)	1995 (6 RCTs)	⊕⊕⊕⊖ Moderate[b,c,d]	PLD likely results in little to no difference in OS.
	24 per 1000	28 per 1000 (12 to 57)				
Progression-free survival **(PFS)** Assessed with: progression-free status per RECIST 1.1 Follow-up: median range 10 to 29.2 months	Average[e]		HR 0.94 (0.85 to 1.04)	1803 (4 RCTs)	⊕⊖⊖⊖ Very low[d,f,g]	The evidence is very uncertain about the effect of PLD on PFS.
	19 per 1000	24 per 1000 (16 to 34)				
Quality of life	-	-	-	-	-	Outcome not reported.
Overall severe adverse events (grade > 3) Assessed with: unclear method	Risk with gemcitabine		RR ranged from 0.61 to 0.97	964 (2 RCTs)	⊕⊖⊖⊖ Very low[d,f,h]	The evidence is very uncertain about the effect of PLD on overall severe adverse events (grade >3).
	60 per 1000	Ranged from 37 to 58				
	Risk with patupilone					

	600 per 1000	Ranged from 366 to 582				
Anaemia (grade ≥ 3) Assessed with: CTCAE v2.0 & 4.0 where reported	Risk with gemcitabine		RR ranged from 0.19 to 0.82	1968 (5 RCTs)	⊕⊖⊖⊖ Very low[d,f,h]	The evidence is very uncertain about the effect of PLD on anaemia (grade ≥ 3).
	50 per 1000	Ranged from 10 to 41				
	Risk with topotecan					
	280 per 1000	Ranged from 53 to 230				
Hand-foot syndrome (grade ≥ 3) Assessed with: CTCAE v2.0 & 4.0 where reported	No occurrences of hand-foot syndrome in the control arms of included studies.		RR ranged from 15.19 to 109.15	2184 (6 RCTs)	⊕⊖⊖⊖ Very low[f,h]	The evidence is very uncertain about the effect of PLD on hand-foot syndrome (grade ≥ 3).
	0 per 1000	Ranged from 55 to 230 per 1000				
Neurological **(grade ≥ 3)** Assessed with: CTCAE v2.0 where reported	Risk with patupilone		RR ranged from 0.08 to 3.09	1222 (3 RCTs)	⊕⊖⊖⊖ Very low[f,i,j]	The evidence is very uncertain about the effect of PLD on neurological events (grade ≥ 3).
	62 per 1000	Ranged from 5 to 192				

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EOC: epithelial ovarian cancer; HR: hazard ratio; PFS: progression-free survival; PLD: pegylated liposomal doxorubicin; RECIST: Response Evaluation Criteria in Solid Tumors; RCT: randomised control trial; RR: risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

[a]The control risk is an average number of participants reported alive at 36 months in CORAIL and Colombo 2012 trials.

[b]Note: Despite I^2 = 86% we decided not to downgrade the evidence due to inconsistency as the confidence intervals around the effects in the individual trials overlap and all trials show no evidence of an effect of PLD with conventional chemotherapy on overall survival.

[c]Note: 3 studies included participants with recurrent EOC regardless of platinum sensitivity status (Gordon 2001; MITO-3; NCT00653952, 624 participants).

[d]Downgraded by one level due to imprecision (wide confidence interval around the effect estimate crossing the line of no difference).

[e]The control risk is an average number of participants reported alive at 12 months in CORAIL and Colombo 2012 trials.

[f]Downgraded by one level due to the risk of bias (open-label design).
[g]Downgraded by one level due to indirectness (two trials contributing evidence included participants with recurrent EOC regardless of platinum sensitivity status).
[h]Downgraded by four levels due to imprecision (extreme values of effect estimates and confidence intervals).
[i]Differences depending on the type of conventional chemotherapy (P = 0.04).
[j]Downgraded by two levels due to imprecision (risk ratio estimates in the studies ranging from 0.08 to 3.09).

Summary of findings 3. Summary of findings 3: PLD with chemotherapy compared to PLD alone in recurrent platinum-resistant epithelial ovarian cancer

Patient or population: adult women with recurrent platinum-resistant epithelial ovarian cancer

Setting: specialist hospital

Intervention: PLD with conventional chemotherapy

Comparison: PLD alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with PLD alone	Risk with PLD with conventional chemotherapy				
Overall survival **(OS)** **Assessed with:** survival status **Follow-up:** median 17.4 months	Average[a]		HR 0.92 (0.70 to 1.21)	242 (1 RCT)	⊕⊕⊕⊖ Moderate[b]	PLD with conventional chemotherapy likely results in little to no difference in OS.
	12 per 1000	17 per 1000 (5 to 45)				
Progression-free survival **(PFS)** Assessed with: progression-free status per RECIST 1.1 assessed by BICR Follow-up: median 17.4 months	Average[c]		HR 0.94 (0.73 to 1.22)	353 (2 RCTs)	⊕⊕⊖⊖ Low[b,d]	PLD with conventional chemotherapy may result in little to no difference in PFS.
	41 per 1000	50 per 1000 (20 to 97)				
Quality of life	-	-	-	-	-	Outcome not reported.
Overall severe adverse events **(grade ≥ 3)** Assessed with: CTCAE v4.03	224 per 1000	556 per 1000 (444 to 693)	RR 2.48 (1.98 to 3.09)	663 (1 RCT)	⊕⊕⊕⊖ Moderate[d,e]	PLD with conventional chemotherapy likely increases overall severe adverse events (grade ≥ 3).

treatment-emergent AEs						
Anaemia **(grade ≥ 3)** Assessed with: CTCAE v4.03 treatment-emergent AEs	54 per 1000	129 per 1000 (79 to 210)	RR 2.38 (1.46 to 3.87)	785 (2 RCTs)	⊕⊕⊕⊖ Moderate[d]	PLD with conventional chemotherapy likely increases anaemia (grade ≥ 3).
Hand-foot syndrome **(grade ≥ 3)** Assessed with: CTCAE v4.03 treatment-emergent AEs	186 per 1000	45 per 1000 (26 to 74)	RR 0.24 (0.14 to 0.40)	785 (2 RCTs)	⊕⊕⊕⊖ Moderate[d,e]	PLD with conventional chemotherapy likely results in a large reduction in hand-foot syndrome (grade ≥ 3).
Neurological **(grade ≥ 3)** Assessed with: CTCAE v4.03 treatment-emergent AEs	73 per 1000	102 per 1000 (62 to 168)	RR 1.40 (0.85 to 2.31)	663 (1 RCT)	⊕⊕⊖⊖ Low[b,d]	PLD with conventional chemotherapy may result in little to no difference in neurological events (grade ≥ 3).

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

BICR: blinded independent central review; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EOC: epithelial ovarian cancer; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; PLD: Pegylated liposomal doxorubicin; RECIST: Response Evaluation Criteria in Solid Tumors; RR: risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

[a]The control risk is an average number of participants reported alive at 36 months in Colombo 2012 and CORAIL trials (arms with PLD alone).

[b]Downgraded by one level due to imprecision (wide confidence interval around the effect estimate crossing a line of no difference).

[c]The control risk is an average number of participants reported alive at 12 months in PRECEDENT (olaratumab), Colombo 2012 (PLD alone arm), and CORAIL (PLD alone arm) trials.

[d]Downgraded by one level due to risk of bias (open-label design).

[e]Note: evidence includes data from participants with recurrent EOC regardless of platinum sensitivity status.

BACKGROUND

Description of the condition

Ovarian cancer is the eighth most common cancer in women worldwide, responsible for approximately 313,959 new cancer cases per annum (GLOBOCAN 2020). In Europe, it is the eighth most common cancer in women, the fifth most common cause of cancer deaths, and the most lethal gynaecological cancer (ECIS 2020). The cumulative risk of being diagnosed with ovarian cancer is approximately 1% in Europe and North America, and 0.6% to 0.7% in the rest of the world (GLOBOCAN 2020); this risk increases with age.

Women with ovarian cancer classically fail to develop symptoms that are recognised as suspicious until the development of advanced disease. This absence of obvious symptoms in early stages results in 60% to 70% of women presenting with the International Federation of Gynecology and Obstetrics (FIGO) stages III to IV disease (Gaitskell 2022), characterised by widespread tumour dissemination within and/or beyond the abdominal cavity (Jemal 2008; see Table 1 for FIGO staging).

Overall, considering the estimated survival of all women and all stages of ovarian cancer, the five-year survival rate is between 35% and 45% amongst high-income countries (ICBP 2019). This rate has increased over time, owing to general improvements in healthcare and novel treatments in recent years, such as maintenance poly (ADP-ribose) polymerase (PARP) inhibitors. When considering survival stratified by diagnostic staging, women with FIGO stage I ovarian cancer in England are estimated to have a five-year survival rate of around 94%. In contrast, the five-year survival rate for stage IV disease is less than 20% (Cancer Research UK 2019).

Over 90% of all malignant ovarian tumours are epithelial in origin, termed epithelial ovarian cancer (EOC). Of these, the most common subtype is high-grade serous carcinoma (HGSC; ESMO 2019). Internationally, current guidelines and treatment paradigms for EOC recommend surgical removal and cytoreduction of the tumour alongside any other visible macroscopic disease, at primary diagnosis if feasible. In most cases, determined by tumour stage and histological subtype, treatment with platinum-based chemotherapy is also advised in the neo-adjuvant or adjuvant setting, if performance status permits. This chemotherapy is usually carboplatin and paclitaxel combination therapy, although single-agent platinum may be considered, determined by a variety of clinical features (ESMO 2019).

HGSC is typically characterised as having marked sensitivity to platinum-based conventional chemotherapies in the first-line setting. However, although most tumours (70% to 80%) will initially respond to first-line chemotherapy, most will subsequently relapse and require further chemotherapy (NICE 2003). At this time, the choice of which chemotherapy women will then be treated with is influenced by the woman's platinum-free interval (PFI), regarded as the length of time from completion of the last platinum-based chemotherapy to the time of disease progression. Typically, women who are still classified as platinum-sensitive (PFI > 12 months) or partially platinum-sensitive (PFI 6 to 12 months) would be rechallenged with platinum-based chemotherapy in combination with another agent, including paclitaxel, gemcitabine or pegylated liposomal doxorubicin (PLD; ESMO 2019; NICE 2016; Pfisterer 2006). Conversely, women regarded as platinum-resistant (PFI < six months) or platinum-refractory (PFI < one month or progression during first-line therapy) should be treated with non-platinum single agents, including paclitaxel, topotecan, gemcitabine and PLD (ESMO 2019; Pfisterer 2006; Naumann 2011). However, response rates in this group are poor (10% to 15%) and the median overall survival (OS) is approximately 12 months (Naumann 2011). Despite considerable research in this setting in recent years, no improvements in survival have been achieved.

Description of the intervention

For the treatment of women with platinum-resistant ovarian cancer, PLD had been traditionally recommended as monotherapy at a starting dose of 50 mg/m^2, given intravenously every four weeks, for up to six cycles. Early termination of the course may occur in the event of unacceptable toxicity, clinical disease progression, or radiological disease progression (EMA 2010). Several recent studies have investigated using lower PLD doses (30 to 45 mg/m^2), particularly when combined with other agents, such as carboplatin (in platinum-sensitive disease) or dexamethasone (CALYPSO; HeCOG 2010; OVA-301), in an attempt to ameliorate side effects and toxicity. In this setting, a dose of 40 mg/m^2 given four-weekly is commonly used in clinical practice.

The most common side effect of PLD is nausea (EMA 2010); however, other frequently associated toxicities include palmar-plantar erythrodysesthesia (PPE; also known as hand-foot syndrome (HFS)), stomatitis/mucositis and neutropenia (CAELYX PI; EMA 2010). Hand-foot syndrome, characterised by palmar-plantar erythema, desquamation, (redness and skin peeling of palms and soles)and pain, usually occurs after two or three cycles and can be severely disabling; its presence often results in PLD dose reduction or discontinuation. Severe PPE (Common Terminology Criteria for Adverse Events (CTCAE) Grade 3/4) is reported to occur in approximately 20% of women who commence PLD therapy at the 50 mg/m^2 dose (Lorusso 2007). Numerous approaches to hand-foot syndrome management have been described; however, there is an absence of high-quality evidence to support these strategies, and treatment is mostly supportive (von Moos 2008).

How the intervention might work

Available since the 1960s, doxorubicin hydrochloride is an anthracycline cytotoxic chemotherapy drug that belongs to the anthracycline class (EMA 2010). Its main mode of action is through binding with both the enzyme topoisomerase II and DNA, forming a complex resulting in lethal double-stranded DNA breaks (Zunino 2002). Although anthracyclines are key anti-tumour agents and shown to be effective, those treated are at risk of cardiotoxicity and other adverse effects (Zunino 2002). Liposomal doxorubicin was subsequently developed, with the aim of reducing cardiotoxicity risk whilst preserving anti-tumour efficacy, relative to conventional doxorubicin (Theodoulou 2004).

Pegylated liposomal doxorubicin is a formulation of liposomal doxorubicin coated in polyethylene glycol, a hydrophilic coating that protects the liposomes from detection by the body's reticular endothelial system. This coating subsequently reduces the active substance's degradation rate and increases its circulating half-life, compared to conventional and liposomal doxorubicin (Gabizon 2001). Pegylated liposomes are small enough to extravasate out of leaky tumour vasculature (CAELYX PI), and the absence of

functional lymphatic drainage within cancer tissues results in high uptake and retention of PLD by the tumour. In addition, the increased circulating half-lifetime, conferred by the pegylation, increases the number of passes the drug makes through the tumour microvasculature; this ultimately results in higher intratumoural delivery of cytotoxic agents (Gabizon 2001). The significantly lower risk of cardiotoxicity seen with PLD is thought to be due to the tight capillary junctions in the cardiac muscle, limiting the concentration of the drug able to penetrate cardiac tissues (Theodoulou 2004).

Why it is important to do this review

The European Society of Medical Oncology (ESMO) guidelines recommend PLD as a treatment option for women with recurrent disease, licensed in the UK as monotherapy or in combination with platinum-based compounds (ESMO 2019;https://www.nice.org.uk/guidance/ta389NICE 2016).

Within the last decade, difficulties in the production of PLD resulted in the disruption of patient care, alongside the suspension of some ongoing trials (INOVATYON; TRINOVA-2). Since production has been re-established, the potential for use of this drug as part of routine care has improved once more.

As new agents are being developed continually for the treatment of women with EOC, there remains a continual need to compare existing standards of care, including the role of PLD in both platinum-sensitive and platinum-resistant settings. The relative efficacy and toxicity of PLD compared to other new agents is unclear. This review aims to update the previous Cochrane Review (Lawrie 2013), incorporating new research findings in order to evaluate further the efficacy and safety of PLD compared with other chemotherapeutic agents.

OBJECTIVES

To evaluate the efficacy and safety of PLD, with or without other anti-cancer drugs, in women with relapsed high grade epithelial ovarian cancer (EOC).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) were eligible for inclusion.

Types of participants

We included women ≥ 18 years of age with relapsed high grade epithelial ovarian cancer of any stage, including women with both platinum-sensitive and platinum-resistant disease. We excluded studies of participants with low grade serous carcinoma or non-epithelial histology.

Types of interventions

1. PLD in combination with platinum-based therapy versus platinum-based therapy with another agent, e.g. PLD plus carboplatin versus paclitaxel (PAC) plus carboplatin.
2. Other chemotherapy agent(s) versus PLD, e.g. topotecan (TOP) versus PLD.
3. PLD plus other agent(s) versus PLD alone or with placebo, e.g. trabectedin (TBD) plus PLD versus PLD.

Types of outcome measures

The primary and secondary outcomes of this review are as follows.

Primary outcomes

- Overall survival (OS): survival until death from all causes
- Progression-free survival (PFS): survival until disease progression

Secondary outcomes

- Severe adverse events, classified according to commonly used toxicity scoring criteria (e.g. CTCAE 2017), including haematological, gastrointestinal, genitourinary, dermatological, neurological, pulmonary, and other severe adverse events
- Quality of life, measured by a validated scale, e.g. the European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life questionnaire (EORTC QLQ-C30)
- Symptom control, including dose reductions and delays

Search methods for identification of studies

We sought papers in all languages and obtained translations when necessary.

Electronic searches

We searched the following electronic databases on 4 January 2022 (also see Cochrane Gynaecological Cancer Group methods used in reviews):

- Cochrane Central Register of Controlled Trials (CENTRAL; Issue 12, 2021), in the Cochrane Library;
- MEDLINE via Ovid (1990 to 3 January 2022);
- Embase via Ovid (1990 to 2021 week 52).

The CENTRAL, MEDLINE and Embase search strategies, based on terms related to the review topic, are presented in Appendix 1, Appendix 2, and Appendix 3, respectively. As PLD has been recently developed, searches before 1990 would not have been relevant; therefore databases were searched from 1990 until January 2022. We identified all relevant articles on PubMed and, using the 'related articles' feature, we carried out a further search for newly published articles.

Searching other resources

We searched the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com/rct), www.clinicaltrials.gov and the Physicians Data Query (PDQ) (www.cancer.gov/clinicaltrials) for ongoing trials. We also searched the abstracts of the American Society for Clinical Oncology (ASCO) Annual Meetings from 2000 to 2022. Where necessary, we attempted to contact the main investigators of relevant ongoing trials for further information. In addition, we checked the citation lists of included studies to identify other reports/studies.

Data collection and analysis

Selection of studies

For this update of the review, we downloaded all titles and abstracts retrieved by electronic searching to Covidence 2019 and removed duplicates. At least two review authors (a combination of EN,

RN, EB, SV and JM) for this update of the review independently examined the remaining references. We excluded those studies that clearly did not meet the inclusion criteria, and obtained copies of the full text of potentially relevant references. At least two review authors (a combination of RN, EN, KE-S, EB and SV) for this update of the review independently assessed the eligibility of retrieved papers, with appeal to JM where there were disagreements and referral to Dr Miller for expert advice, as required (see Acknowledgements). We documented reasons for exclusion for key excluded papers.

Data extraction and management

For included studies, we extracted the following data where possible.

- Author, year of publication and journal citation (including language)
- Country
- Setting
- Inclusion and exclusion criteria
- Study design, methodology
- Study population
  - total number enrolled
  - participant characteristics
  - age
  - previous therapy (including platinum sensitivity or resistance)
  - comorbidities
- Ovarian cancer details at diagnosis
  - FIGO stage
  - histological cell type
  - tumour grade
  - performance status
  - extent of disease
- Total number of intervention groups
- Intervention details
  - details of PLD including dose, regimen, frequency and the number of cycles
  - comparison details including type of control and dose, regimen, frequency and number of cycles, if appropriate
- Proportion of participants who received all/part/none of the intended treatment
- Delays in treatment
- Risk of bias in study (see Assessment of risk of bias in included studies)
- Duration of follow-up
- Outcomes – overall survival, PFS, QoL, symptom control and adverse events
  - for each outcome: outcome definition (with diagnostic criteria if relevant)
  - unit of measurement (if relevant)
  - for scales: upper and lower limits, and whether high or low score is good
  - results: number of participants allocated to each intervention group
  - for each outcome of interest: sample size; missing participants

Data extraction of outcome data from each trial

We extracted data on outcomes as follows.

- For time-to-event data (OS and PFS), we extracted the hazard ratio (HR), log of the hazard ratio (log(HR)) and its standard error (SE) from trial reports where possible. If these were not reported, we attempted to estimate them from other reported statistics using available methods (Tierney 2007).
- For dichotomous outcomes (e.g. adverse events), we extracted the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at an endpoint, in order to estimate a risk ratio (RR).
- For continuous outcomes (e.g. QoL measures), we extracted the mean difference (MD) and standard deviation (SD) between the final value of the outcome measure in each treatment arm at the end of follow-up. If SDs of final values were not available, we used change scores if their SDs were available. If no SDs were available, we omitted these trials from the analyses.

Where possible, we extracted data relevant to an intention-to-treat analysis (ITT), in which participants were analysed in groups to which they were assigned. Where time-to-event outcomes were assessed by more than one method, e.g. independent radiology review, investigator assessment or independent oncology review, we used the independent radiology review data. We noted the time points at which outcomes were collected and reported. Where data from several time points were reported, we used the data from the last assessment in our meta-analyses if appropriate. Where a trial evaluated the same drug in two or more different doses, we extracted all the combined data but in the data synthesis used and only the estimated individual data for the most efficacious dose/regimen versus the comparator.

Two review authors (a combination of RN, EN, KE-S, EB and SV) independently extracted data from the selected trials using piloted data extraction forms specially designed for the review. Where there was disagreement between the two review authors, this was resolved by discussion with JM.

Assessment of risk of bias in included studies

We assessed the risk of bias in included RCTs using Cochrane's RoB 1 tool and the criteria specified in chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This included assessment of the following domains.

- Selection bias
  - random sequence generation
  - allocation concealment
- Performance bias
  - blinding of participants and personnel (participants and treatment providers)
- Detection bias
  - blinding of outcome assessment
- Attrition bias
  - incomplete outcome data: we recorded the proportion of participants whose outcomes were not reported at the end of the study and considered greater than 20% attrition to be at a high risk of bias
- Reporting bias

- selective reporting of outcomes
- Other possible sources of bias

Two authors assessed the risk of bias independently (a combination of RN, EN, KE-S, EB and SV) and resolved differences by discussion or by appeal to a third review author (JM). Results are presented in a risk of bias summary graph. We interpreted the results of the meta-analyses in light of the findings with respect to risk of bias.

Measures of treatment effect

We used hazard ratio (HR) for time-to-event data, risk ratio (RR) for dichotomous outcomes and mean difference (MD) for continuous outcomes.

Unit of analysis issues

The unit of analysis was the individual participant.

Dealing with multi-arm trials

The JAVELIN Ovarian 200 trial had multiple treatment groups (three-arm trial), and so we divided the control group between the treatment groups and treated comparisons between each treatment group and a split control group as independent comparisons for all adverse event outcomes.

Dealing with missing data

We did not impute missing outcome data.

Assessment of heterogeneity

We assessed heterogeneity between trials by visual inspection of forest plots, by estimation of the percentage heterogeneity (I^2 statistic) between trials that cannot be ascribed to sampling variation (Higgins 2003), and by a formal statistical test of the significance of the heterogeneity - Chi^2 test (Deeks 2001). We regarded statistical heterogeneity as substantial if the I^2 was greater than 50% and either Tau^2 (a measure of between-study variance) was greater than 0, or the P value of the Chi^2 test was less than 0.10. If there was evidence of substantial heterogeneity, we investigated the possible reasons for this and reported it.

Assessment of reporting biases

There was an insufficient number of included studies to adequately evaluate the potential for small study effects, such as publication bias, using funnel plots.

Data synthesis

Where we deemed it clinically and methodologically appropriate, we meta-analysed the trial data. Our main approach was to pool data in a two-stage, fixed-effect, inverse-variance meta-analysis based on the assumption that all trials included in a given comparison were conducted under sufficiently similar conditions and in similar populations. We applied the random-effects, inverse variance model in comparisons with platinum-resistant EOC where we included data from trials that evaluated the effect of treatment options in populations with recurrent EOC regardless of platinum-sensitivity status. If the outcome was rare (few events), we used the Mantel-Haenszel models (fixed or random).

Dealing with non-proportional hazards

If studies identified non-proportional hazards, we used the reported hazards ratios as a measure of the effect, if reported. However, we indicated the detection of non-proportionality, reported value of the log-rank test and alternative measure of the effect (e.g. restricted mean survival times) if reported.

Approach to the synthesis of adverse events

Based on the availability of information on whether the reported adverse events were treatment-related or not, we synthesised the data as outlined earlier (all adverse events of the same kind). If the trial report did not provide this information, we examined the case-by-case suitability of using the data in the analysis.

Subgroup analysis and investigation of heterogeneity

We grouped the RCTs by Types of interventions. Where the types of interventions differed within a comparison, e.g. other drugs versus PLD, we subgrouped data by the comparator drug.

Sensitivity analysis

We performed sensitivity analyses on survival outcomes to explore the influence of our decision to incorporate data from the trials with recurrent EOC regardless of its platinum sensitivity status.

Summary of findings and assessment of the certainty of the evidence

Based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2017a), we prepared a summary of findings table to present the results of the following outcomes.

- Overall survival (OS)
- Progression-free survival (PFS)
- Quality of life (QoL)
- Adverse events: overall severe adverse events (Grade ≥ 3)
- Adverse events: anaemia (Grade ≥ 3)
- Adverse events: hand-foot syndrome (Grade ≥ 3)
- Adverse events: neurological (Grade ≥ 3)

For each assumed risk cited in the tables, we provided a rationale and used the GRADE system to rank the quality of the evidence (Schünemann 2017b). We downgraded evidence by -1 or -2 if the following limitations were present, according to their seriousness: study design limitations, inconsistency, imprecision, indirectness and publication bias. Where the evidence was based on single studies, or where there was no evidence on a specific outcome, we included the outcome in the summary of findings tables and graded or explained accordingly. We downgraded evidence of a clear effect derived from a single small study, and resolved any differences by discussion. We reported and interpreted results based on the Cochrane Effective Practice and Organisation of Care and interactive GRADEpro summary of findings table guidance (EPOC 2015; Schünemann 2019).

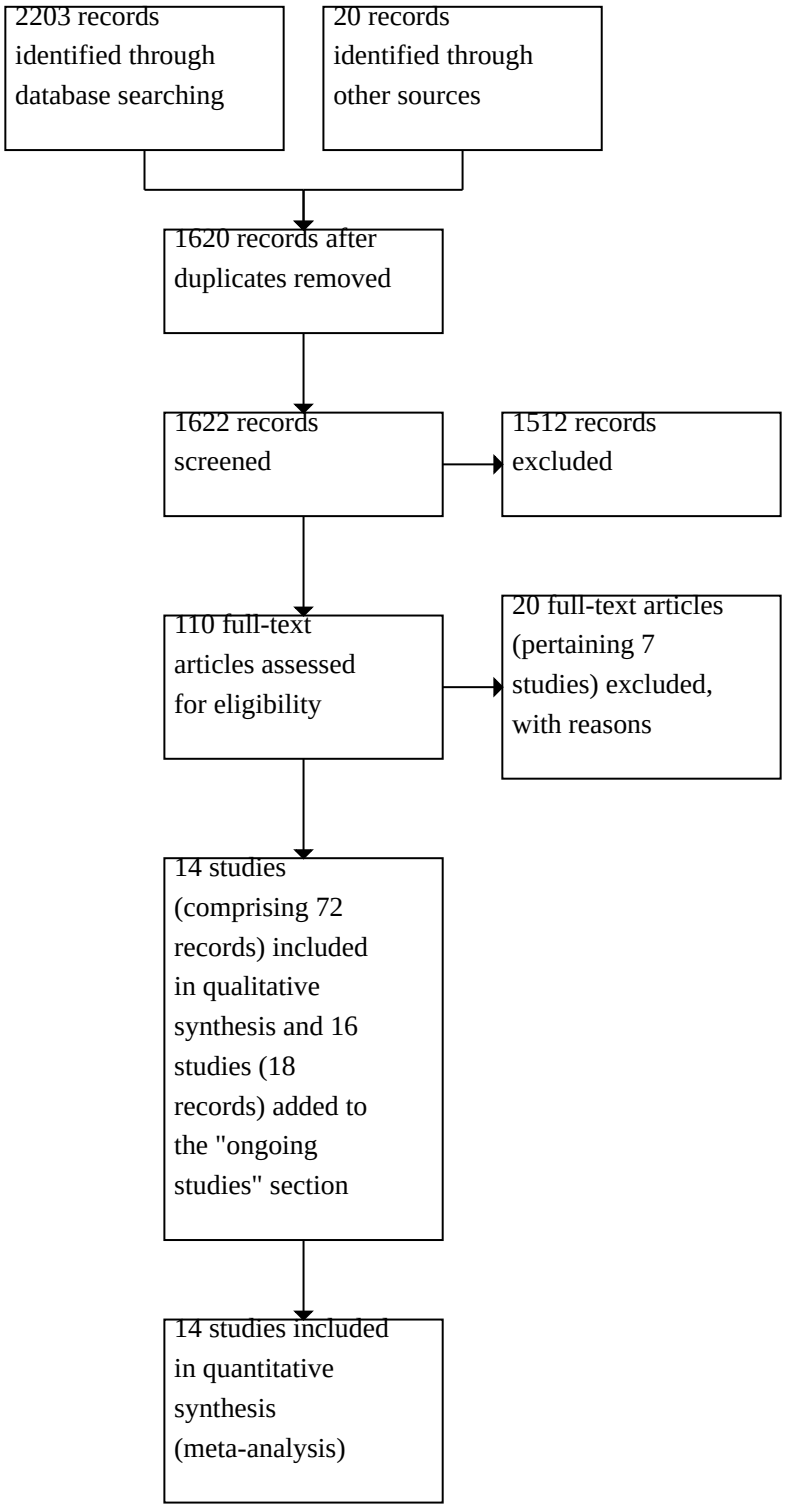
RESULTS

Description of studies

Results of the search

In the original version of the review, 1602 unique references were identified by the database searches, 17 trials by the trial registry searches, and an additional three studies from review of reference lists of included studies (1622 references in total) (Figure 1). Titles and abstracts of 1512 records were excluded and the full text of 110 potentially eligible publications obtained, including the trial registry records. After evaluating these full texts, seven studies were excluded (20 records) (see Characteristics of excluded studies) and the details of the 16 ongoing trials added to the Characteristics of ongoing studies section of the review (18 records). Fourteen completed RCTs (72 records) met the inclusion criteria. One of these was not yet published in full (PRECEDENT); the investigators were contacted and a copy of the unpublished manuscript obtained. Additional unpublished data were also obtained from the investigators of two other studies (Kaye 2012; MITO-3). Where studies included PLD as part of an arm, attempts were made to extract data separately for those who received PLD. The authors were contacted for data separated by PLD and included where provided.

Figure 1. PRISMA flow chart of original version of review (Lawrie 2013) - search to 15 October 2012



For the 2022 update (up to January 2022), we identified 683 unique references by database searches and trial registry searches, and found another six from other sources (Figure 2). After screening titles and abstracts, we identified 96 studies for full-text review. We excluded 55 studies: 17 studies were clearly irrelevant, as per Cochrane guidelines (Section 4.6.5; Lefebvre 2022), and we have not described these. We have detailed the other 38 records in the Characteristics of excluded studies table. In total, we included 12 further studies, detailed in the Characteristics of included studies table, some of which were identified as ongoing studies in the previous version of the review. In total, we now include 26 studies in this update, with 23 contributing data to the meta-analysis.

Figure 2. Flow diagram for search for review update from February 2013 to January 2022

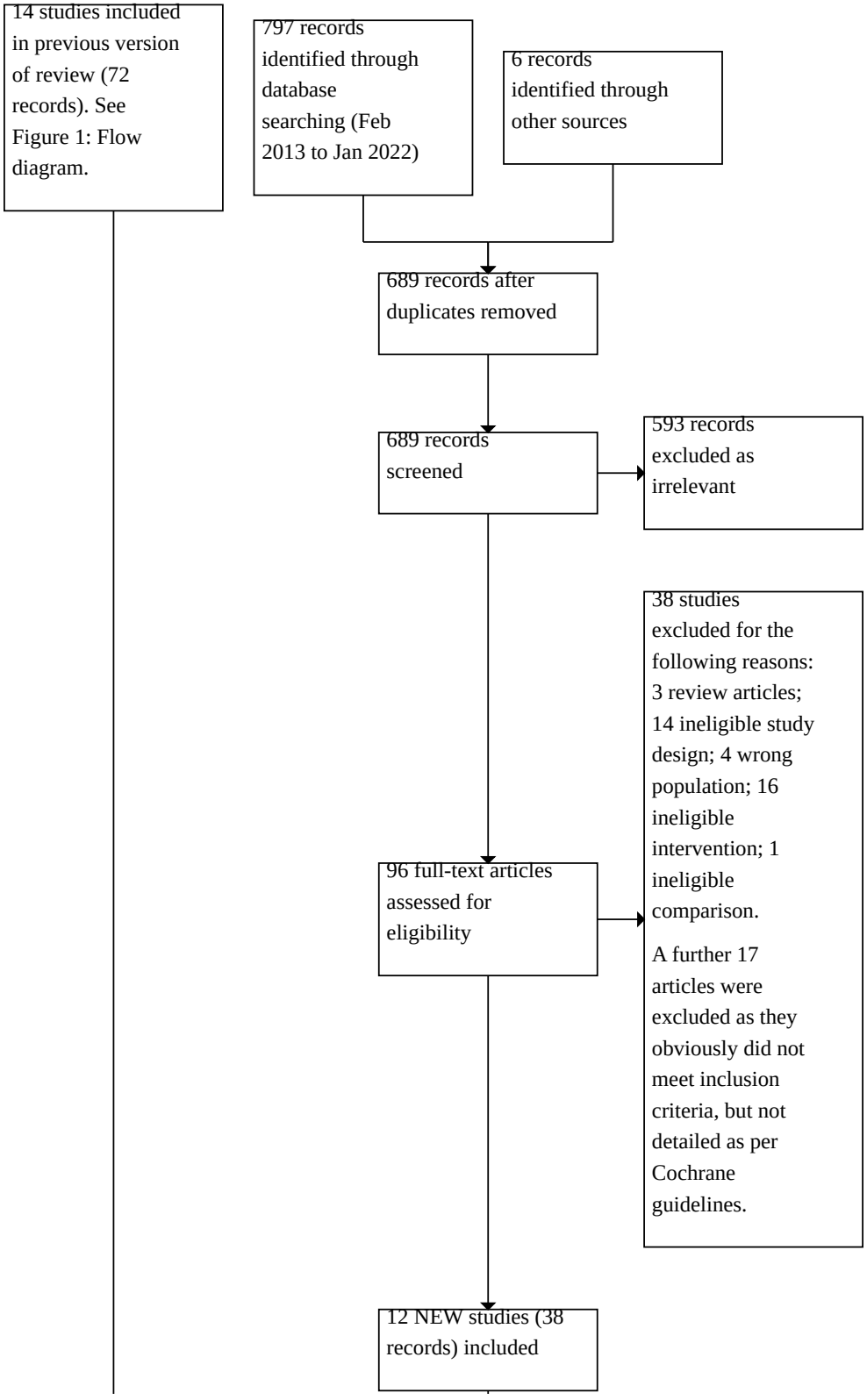
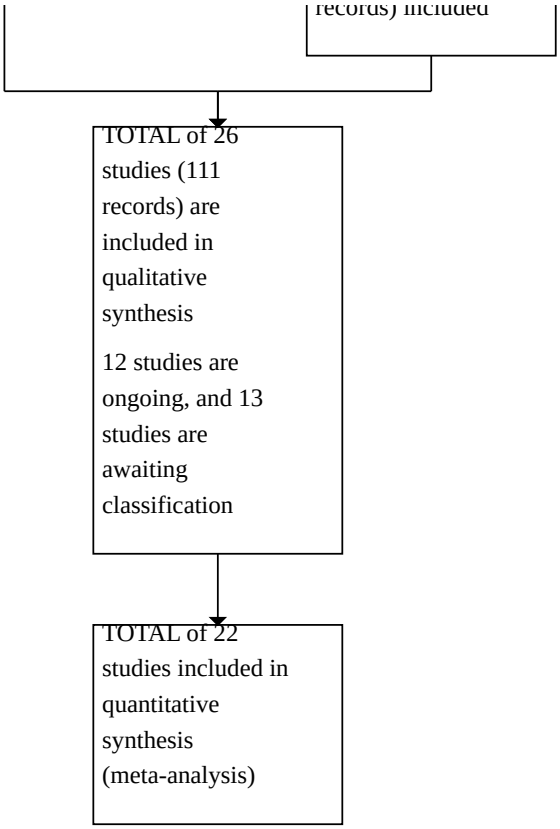


Figure 2. (Continued)



We identified a total of 12 Ongoing studies, and 13 studies are Studies awaiting classification pending further information from the authors, which we have requested, largely for separation of data for PLD-treated participants from a 'chemotherapy of physician's choice' arm.

Included studies

Treatment options for women with recurrent EOC vary depending on whether their disease is likely to respond to platinum-based chemotherapy. Women within each of these groups have differing prognoses and response rates to treatment compared to those within other treatment groups. We therefore divided our studies between those including women with:

1. platinum-sensitive relapsed EOC (relapse > 12 months after last platinum-base chemotherapy);
2. platinum-resistant or refractory relapsed EOC (no response to last platinum-based chemotherapy (refractory) or relapse within six months of last platinum-based chemotherapy (resistant); and
3. regardless of platinum-resistance (including those with partially-platinum-resistant EOC (relapse between six and 12 months of last platinum-based chemotherapy).

Please see Table 2 for details of included studies by comparison groups and Table 3 for details of median survival times in included studies.

Overall, we included 26 studies with a total of 8277 participants (APPROVE; ASSIST-3; ASSIST-5; Banerjee 2018; CALYPSO; Colombo 2012; CORAIL; Fujiwara 2019; Gordon 2001; HeCOG 2010; JAVELIN Ovarian 200; Kaye 2012; M200; McGuire 2018; MITO-3; Monk 2017; Monk 2020; Mutch 2007; NCT00653952; NCT01840943; OVA-301; Pfisterer 2020; PRECEDENT; PROCEED 2014; SWOG S0200; TRINOVA-2).

Several studies were included in the previous version of the review as ongoing studies (McGuire 2018; Monk 2017; PROCEED 2014; TRINOVA-2), or included studies without data (NCT00653952, formerly O'Byrne 2002 in the previous version of the review), and are now included.

Platinum-sensitive EOC

We included seven studies (2872 participants; ITT efficacy data reported for 2807) evaluating the effect of PLD in women with platinum-sensitive recurrent epithelial ovarian cancer. These were grouped by the type of comparison treatment; conventional chemotherapy or targeted therapy (CALYPSO; Fujiwara 2019; HeCOG 2010; Monk 2020; Pfisterer 2020; SWOG S0200; TRINOVA-2).

PLD with conventional chemotherapy compared to other combination chemotherapy

SWOG S0200 is a phase III multicentre open-label RCT comparing carboplatin with PLD 30 mg/m^2 against PLD alone. It was terminated early due to poor accrual after 61 women were recruited, slowed by the publication of the ICON-4 study showing

the benefit of adding paclitaxel to carboplatin. Unpublished survival data were shared by authors. PFS was significantly improved by the addition of PLD to carboplatin. The final OS was not statistically significantly different between treatment arms.

CALYPSO is a phase III multicentre non-inferiority RCT comparing carboplatin with PLD 30 mg/m^2 against carboplatin with paclitaxel. The study included 976 women. All participants had platinum sensitive disease and had previously received taxane therapy. It was standard for corticosteroids and anti-emetics to be given as pre-medication with the addition of clemastine and ranitidine in the carboplatin-paclitaxel arm. Significantly more women in the carboplatin-paclitaxel arm discontinued treatment before six cycles had been completed (110/507 versus 70/466), mainly due to toxicity (73/507 women versus 27/466 women; P < 0.001).

HeCOG 2010 is a phase II randomised control trial including 189 women with platinum sensitive disease. Participants were randomised to carboplatin and PLD 45 mg/m^2 or carboplatin and paclitaxel. Most participants had received prior taxane therapy (88% in the carboplatin and paclitaxel group; 93% in the carboplatin and pegylated liposomal doxorubicin). Both groups received dexamethasone, dyphenhydramine and ranitidine pre-medication - this was given via both IV and oral routes to paclitaxel recipients.

Fujiwara 2019 conducted a phase II multicentre open-label RCT. This recruited 100 women in Japan to either carboplatin and PLD 30mg/m^2 or carboplatin and gemcitabine (1000 mg/m^2 days 1 and 8). The primary outcome was PFS with ORR, OS, toxicity and dose administration as secondary outcomes. There were no obvious differences in toxicity, but PLD had a more favourable risk-benefit profile. The PLD arm required fewer dose reductions (relative dose intensity 88.9% versus 53.1%) and had a higher six-cycle completion rate (63.3% versus 31.4%), the most common reason being neutropenia or thrombocytopenia in the gemcitabine arm.

Pfisterer 2020 was an international open-label phase III multicentre RCT that recruited 682 participants with platinum-sensitive recurrent EOC (stratified to recurrence six to 12 months or > 12 months post platinum) to receive bevacizumab and carboplatin with either PLD 30 mg/m^2 or gemcitabine. After six cycles of treatment, both arms then received maintenance bevacizumab. Nearly half of participants had previously received anti-angiogenic treatment (47.7% in the carboplatin/gemcitabine/bevacizumab group versus 47.2% in the carboplatin/PLD/bevacizumab). The primary outcome was PFS by Response Evaluation Criteria in Solid Tumors (RECIST), and secondary outcomes PFS by serum cancer antigen 125 (CA-125), OS and QoL (EORCT QLQ-C30 or ovarian cancer-specific module (QLQ-OV28)).

PLD with conventional chemotherapy compared to PLD alone

Monk 2020 was an international, multicentre open-label phase III RCT, in which 576 participants were assigned to either PLD 30 mg/m^2 and trabectedin or PLD alone 50 mg/m^2. The primary outcome was OS and secondary outcomes were PFS and ORR. Participants were stratified by time from platinum to recurrence (six to 12 months, 12 to 24 months or > 24 months). Eighty per cent of participants had received a previous taxane.

PLD with targeted therapy compared to PLD alone

TRINOVA-2 was a randomised phase III double-blind, placebo-controlled trial that allocated 223 participants to PLD 50 mg/m^2 with trebananib or with placebo. Stratification was by platinum free interval (0 to 6 months or 6 to 12 months). Owing to PLD shortages, enrolment was paused and the study then terminated.

Platinum-resistant EOC

Eleven studies (3246 participants; ITT efficacy data reported for 3234) evaluated the effect of PLD in participants with platinum-resistant recurrent EOC. These were grouped by the type of comparison treatment; conventional chemotherapy (ASSIST-3; ASSIST-5; Colombo 2012; CORAIL; Mutch 2007), targeted therapy (APPROVE; Banerjee 2018; McGuire 2018; PRECEDENT; PROCEED 2014) or immunotherapy (JAVELIN Ovarian 200). JAVELIN Ovarian 200 had two arms, and so was included in the comparison of immunotherapy versus PLD and of PLD with immunotherapy versus PLD alone.

Conventional chemotherapy alone compared to PLD alone

Mutch 2007 was a phase III open-label multicentre RCT, in which 195 women with platinum-resistant disease that had reoccurred within six months were assigned to either gemcitabine (n = 99) or PLD 50 mg/m^2 (n = 96). If participants experienced disease progression or unacceptable toxicity, or if cumulative PLD dose exceeded 500 mg/m^2, they could cross over to the alternative drug. Cross-over therapy was administered to 130 participants, with 66 participants receiving gemcitabine and 64 participants receiving PLD. In the gemcitabine group, 60.6% had received one prior platinum regimen and 39.4% had received two prior regimens; in the PLD group, 67.7% had received one prior platinum regimen and 32.3% had received two prior regimens. Quality of life was assessed by the Functional Assessment of Cancer Therapy–Ovarian (FACT-O) questionnaire.

ASSIST-3 was a phase III multicentre RCT. The available conference abstract reported that 247 participants, with disease recurrence within six months, were randomised to either canfosfomide with carboplatin or PLD 50 mg/m^2. The methods of randomisation and allocation were not described, and full results were not available.

Colombo 2012 was a phase III open-label international multicentre RCT that recruited 829 women with platinum resistant disease. They were assigned to patupilone or PLD 50 mg/m^2. The primary outcome was OS and secondary outcomes were PFS, overall response rate (ORR) and serious adverse events (SAE). Progression was determined by a blinded, central review of results. Quality of life was measured using the FACT-O questionnaire.

CORAIL was a randomised phase III study of lurbinectedin versus PLD 50 mg/m^2 or topotecan in people with platinum-resistant disease. 442 participants were stratified by platinum free interval (one to three months, over three months). The primary end point was PFS, determined by independent review committee. Data for PLD alone were included in the supplementary material.

PLD with conventional chemotherapy compared to PLD alone

ASSIST-5 was a phase III multicentre RCT in which 125 participants with platinum-resistant disease were allocated to canfosfamide with PLD 50 mg/m^2 or PLD 50 mg/m^2 alone. The study was paused whilst the results of ASSIST-1 were reviewed and then

terminated, meaning the planned enrolment of 244 participants was not reached. The PFS was performed on interim analysis data, and OS was not reported.

Targeted therapy alone compared to PLD alone

Banerjee 2018 was an international, multicentre, randomised, open-label, phase II study that randomised 95 participants to lifastuzumab or PLD 40 mg/m^2. Lifastuzumab is an antibody–drug conjugate comprising humanised IgG1 anti-NaPi2b monoclonal antibody and an antimitotic agent which blocks the polymerisation of tubulin. The drug targets the sodium-dependent phosphate transporter NaPi2b. QoL was measured by the two-item global health status/quality of life (GHS/QOL) questionnaire.

PLD with targeted therapy compared to PLD alone

APPROVE was a multicentre open-label phase II trial study evaluating the effect of adding apatinib to PLD 40 mg/m^2. Apatinib is a tyrosine kinase inhibitor that selectively inhibits vascular endothelial growth factor (VEGF) receptor 2 administered orally. The trial randomised 152 women with platinum-resistant disease. All participants had previously received a taxane, and 3.8% of participants in the apatinib arm had received prior antiangiogenic therapy versus 0% in the PLD alone arm.

McGuire 2018 was a multicentre open-label phase II trial study evaluating the effect of adding olaratumab, an antiplatelet derived growth factor receptor alpha (PDGFR-alpha) antibody to PLD 40 mg/m^2. The trial randomised 123 women with platinum-resistant recurrent EOC were randomised to receive PLD with or without olaratumab. PDGFRα activity has pro-angiogenic activity and modulates the tumour or stromal microenvironment to promote metastases, hence blocking this pathway might slow disease progression.

PROCEED 2014 was a randomised double-blind phase III trial comparing PLD 50 mg/m^2 with vintafolide against PLD alone in the treatment of platinum resistant disease. Following ther review of interim data at the first scheduled futility analysis, the study was temporarily halted and then permanently stopped. The trial randomised 321 participants. Overall survival data were not included in the final analysis and the median follow-up duration was only 2.8 months.

PRECEDENT compared vintafolide and PLD 50 mg/m^2 in the treatment of platinum resistant disease. This phase II open-label multicentre RCT randomised 162 women at a 2:1 ratio to PLD with or without vintafolide. Participants were categorised according to folate receptor status (100% positive, 10% to 90% or 0% folate receptor (FR)-positive lesions) and a threshold analysis performed based on these results. Progression was assessed by blinded independent review.

Immunotherapy alone compared to PLD alone

JAVELIN Ovarian 200 was a multicentre international phase III open-label study that randomised 566 participants 1:1:1 to receive avelumab, avelumab and PLD or PLD alone (40 mg/m^2). We included the two independent comparisons within this study in separate comparison groups of this review.

PLD with immunotherapy compared to PLD alone

One of the comparison arms of JAVELIN Ovarian 200 compared PLD in combination with avelumab versus PLD alone. Participants were randomised 1:1:1 to receive avelumab (188), avelumab and PLD (188) or PLD alone (190).

Platinum-resistant and platinum-sensitive recurrent EOC

We included eight studies with 2079 participants (ITT efficacy data reported for 2075) with both platinum sensitive and resistant disease (Gordon 2001; Kaye 2012; M200; MITO-3; Monk 2017; NCT00653952; NCT01840943; OVA-301). Four studies compared the use of PLD alone with a single-agent conventional chemotherapy (Gordon 2001; MITO-3; NCT00653952; NCT01840943). One study compared PLD alone with a single targeted therapy (Kaye 2012). OVA-301 compared PLD in combination with the chemotherapy agent trabectedin with PLD alone, whereas M200 and Monk 2017 compared PLD in combination with volociximab and motolimod, respectively, with PLD alone and PLD with conventional chemotherapy compared to PLD alone in recurrent platinum-resistant or platinum-sensitive EOC.

OVA-301 randomised 572 participants 1:1 to receive either trabectedin with PLD 30 mg/m^2 or PLD 50mg/m^2 alone. Response was assessed by blinded, independent reviewers. The trial assessed QoL assessment using the e QLQ-C30 questionnaire. 42% of participants in the trabectedin arm required granulocyte colony-stimulating factor (G-CSF) compared with 17% for PLD alone. Women in the trabectedin arm were given an anti-emetic premedication which was not routinely administered for PLD alone.

Conventional chemotherapy alone compared to PLD alone

Gordon 2001 randomised 481 participants to receive either topotecan or PLD 50 mg/m^2. QLQ-C30 was used to assess quality of life. Those receiving PLD were significantly less likely to experience dose delays.

MITO-3 was a phase III randomised multicentre trial comparing gemcitabine (n = 77) to PLD 40 mg/m^2 (n = 76) Recurrence of EOC had occurred within six months of prior platinum therapy for 43 participants in each arm and between seven and 12 months for 34 and 33 participants in the gemcitabine and PLD arms, respectively. Methyprednisolone IV premedication was given to those receiving PLD. The trial measured QoL using the QoL-C30 questionnaire. G-CSF was required in 14% of participants receiving gemcitabine and 5% receiving PLD.

NCT00653952 was a phase III open-label randomised study comparing PLD and paclitaxel in participants with first relapse after chemotherapy with a platinum-based regimen, stratified by platinum-sensitivity. Participants were randomised to receive either PLD 50 mg/m^2 every 28 days or paclitaxel 175 mg/m^2 every 21 days. Participants were to have been treated for up to one year. The study was halted to new recruits in 1999 due to low accrual after 50% of planned participants were recruited (216 participants), after paclitaxel was approved for use in combination with platinum-based therapy for the first-line treatment of ovarian cancer by the European Agency for the Evaluation of Medicinal Products. Reported outcomes were therefore limited to OS and adverse event forms received prior to the database lock on 8 January 2004, and are limited to a clinical study report.

NCT01840943 was a phase III open-label randomised comparative bridging study. The study aimed to recruit 120 participants with both platinum resistant and sensitive disease to receive either topotecan or PLD 50 mg/m^2. The trial recruited 32 participants and of these, 26 were randomised; 25 participants did not complete the study: 11 participants withdrew, eight were lost to follow up and six did not complete due to the physician's decision. The study was terminated due to a medication supply issue. The study has been included in our review but has not been included in the data analysis due to high risk of bias.

Target therapy alone compared to PLD alone

Kaye 2012 was a phase II open-label multicentre RCT in which 97 participants with BRCA1 or BRCA2 mutations were randomised 1:1:1 to receive olaparib 200 mg bd, 400 mg bd or PLD 50 mg/m^2. The primary outcome was reported for the olaparib arms combined and individually, versus the PLD arm. All participants were within 12 months of previous platinum therapy, 56.3%, 50.0% and 42.4%, respectively, had platinum resistant disease.

PLD with target therapy compared to PLD alone

M200 was an open-label study that recruited participants to receive PLD 40mg/m^2 alone, PLD with the anti-angiogenic integrin inhibitor, volociximab (PLD + V), or volociximab alone (V). The trial randomised 127 participants with platinum-sensitive or resistant disease to the arms PLD (n = 66), PLD + V (n = 34) and V (n = 27). Only a conference abstract was available.

PLD with immunotherapy compared to PLD alone

Monk 2017 conducted a phase 2, placebo-controlled trial of PLD (40 mg/m^2) with the toll-like receptor 8 agonist, motolimod, or with placebo. The trial randomly assigned 297 participants 1:1. Participants were stratified by platinum free interval (< 6 months or 6 to 12 months); 51.2% had platinum resistant disease.

Details of study funding and potential conflicts of interest are outlined in Characteristics of included studies and summarised in Other potential sources of bias.

Excluded studies

We excluded 38 studies with reasons, as per Cochrane guidelines (Section 4.6.5; Lefebvre 2022), which are detailed in the Characteristics of excluded studies table.

- Review articles: A'hern 1995 review of addition of doxorubicin to chemotherapy regimes; Bookman 2002 review of incorporation of new cytotoxic agents; Graybill 2014 review of vintafolide.
- Ineligible study design: not an RCT (Aracil 2013; Basu 2013; Kavanagh 2004; Khokhlova 2012; NCT03639246 2018); prospective study (Basu 2011); exploratory analysis (Colombo 2014a); prediction model (Cherchi 2003; Herzog 2014; Palaia 2006; PiSARRO 2016; Scarfone 2006; Trillsch 2016; Wydra 2014).
- Ineligible population as they evaluated PLD for first-line drug treatment of EOC (GOG0182/ICON 5; MITO-2 2011) or as maintenance treatment after successful first-line treatment (AGOG06-001). MILO ENGOT-ov11 was a study in low-grade serous ovarian carcinoma, which we excluded a priori in this update.
- Ineligible intervention: Bakrin 2018 intraperitoneal PLD-based chemotherapy versus intravenous chemotherapy; Bhowmik 2018 branded PLD versus generic PLD; Colombo 2014 PLD in both arms; Lai 2018 PLD and carboplatin versus no treatment; INOVATYON PLD and carboplatin versus PLD and trabectidin; Marme 2019 PLD both arms with atezolizumab or placebo, NCT02891824 2016 PLD or other physician's choice chemotherapy with carboplatin and either atezolizumab or placebo; Monk 2016 and NCT02641639 2015 PLD and bevacizumab both arms with CA4P or placebo; NCT03632798 2018 and NCT03699449 2018 multiple-arm comparison of durvalumab with other agents; NCT03949283 2019 treatment according to cancer stem cell assay; Shoji 2018 chemotherapy with or without bevacizumab; Yabuno 2019 PLD dose comparison; Lorusso 2014 doxorubicin not PLD; Nagao 2016 low-dose paclitaxel added to other chemotherapy.
- Ineligible comparison: Lindemann 2017 used chemotherapy versus hormonal treatment.

For further details of these excluded studies, see Characteristics of excluded studies.

Studies Awaiting Classification

Thirteen studies are awaiting classification (ASSIST-1 2009; AURELIA 2012; FORWARD I; HECTOR; MITO-16 MANGO OV2b; MITO-23; MITO-8 2017; MORAb-003; NCT03690739; Oza 2019; PROVE 2011; SOLO3; Volasertib Trial). For details of these studies see Table 4. Some of these were previously in Ongoing studies and have now had data published in abstract form at least (MITO-23; MITO-8 2017; Oza 2019).

In all of these cases, participants in the arm containing PLD received either PLD or an alternative therapeutic agent; many of these studies compared 'chemotherapy of physician's choice (CPC)' to CPC plus another agent. We contacted the authors of each of these studies to request the data of those who received PLD; however, this extracted data has not yet been made available to us for inclusion in this review. As we were not able to separate PLD from other therapies, these studies remain in the awaiting classification section.

ASSIST-1 2009 randomised participants to either canfosfomide or active control arm. In the active control arm participants received either PLD 50 mg/m^2 or topotecan dependent on their previous failed second line therapy.

AURELIA 2012 randomised 361 participants with platinum resistant disease to receive bevacizumab with one of paclitaxel, PLD (40 mg/m^2) or topotecan (n = 179) or chemotherapy alone (n = 182). Investigators selected the chemotherapy agent on an individual participant basis: 126 were given PLD, 115 paclitaxel and 120 topotecan.

FORWARD I randomised 366 people with platinum resistant disease and whose tumours were positive for FRa expression 2:1 to receive either mirvetuximab, soravtansine or investigator's choice chemotherapy (paclitaxel (n = 80), PLD 40 mg/m^2 (n = 110) or topotecan n = 58)). The primary outcomes was blinded assessment of PFS. QoL was assessed by QLQ-OV28.

HECTOR was a phase III multicentre randomised control trial in which topotecan and carboplatin were compared with standard platinum-based chemotherapy in people with platinum-sensitive recurrent ovarian cancer. 550 participants were randomised 1:1

to receive carboplatin and topotecan or investigator's choice of paclitaxel (n = 79), gemcitabine (n = 191) or PLD (n = 5) with carboplatin.

In MITO-16 MANGO OV2b, 406 participants with platinum sensitive recurrent ovarian cancer were randomised to receive investigator's choice chemotherapy (PLD 30 mg/m^2, gemcitabine or paclitaxel) and carboplatin, gemcitabine with or without bevacizumab. The PFS for this study was reported by chemotherapy backbone.

MITO-8 2017 was an open-label, prospective, randomised, superiority trial in which participants with platinum sensitive disease were randomised to receive either the non-platinum based chemotherapy (NPBC) followed by PBC or the standard reverse treatment sequence. NPBC agents included PLD 40 mg/m^2, topotecan and gemcitabine. PBC included carboplatin with paclitaxel and carboplatin with gemcitabine.

Preliminary data from MITO-23 have been presented as a meeting abstract. Participants were randomised to receive trabectedin 1.3 mg/m^2 every 21 days or CPC (including PLD, carboplatin, gemcitabine, weekly paclitaxel, or topotecan).

MORAb-003 randomised participants with platinum sensitive first relapse and a low CA125 to farletuzumab or placebo in addition to either carboplatin and paclitaxel or carboplatin and PLD.

PROVE 2011 randomised 96 participants to receive panitumumab in addition to carboplatin and gemcitabine and carboplatin and PLD 40 mg/m^2. Only a conference abstract is available.

In Oza 2019, participants with platinum resistant disease received either guadecitabine and carboplatin or treatment of choice (topotecan, PLD (40 to 50 mg/m^2), paclitaxel, or gemcitabine). Participants were randomised 1:1 to either arm. Results were not available for PLD alone.

SOLO3 was a phase II study of olaparib versus physician's choice single-agent non-platinum chemotherapy (PLD 50 mg/m^2 n = 47, paclitaxel n = 20, gemcitabine n = 13, or topotecan n = 8) in participants with platinum sensitive disease and a germline BRCA mutation. Objective response rate was reported by individual chemotherapy agent, but no other PLD-alone data were available.

The Volasertib Trial was a phase II randomised trial of volasertib versus investigator's choice chemotherapy. There were no restrictions on the chemotherapy agent but PLD, topotecan, paclitaxel, and gemcitabine were recommended.

As this review includes studies over a significant time-frame, different classification systems for adverse events were used. These are detailed in Table 5.

Risk of bias in included studies

Figure 3 lists all included studies alongside the authors' judgements about risk of bias for each.

Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study

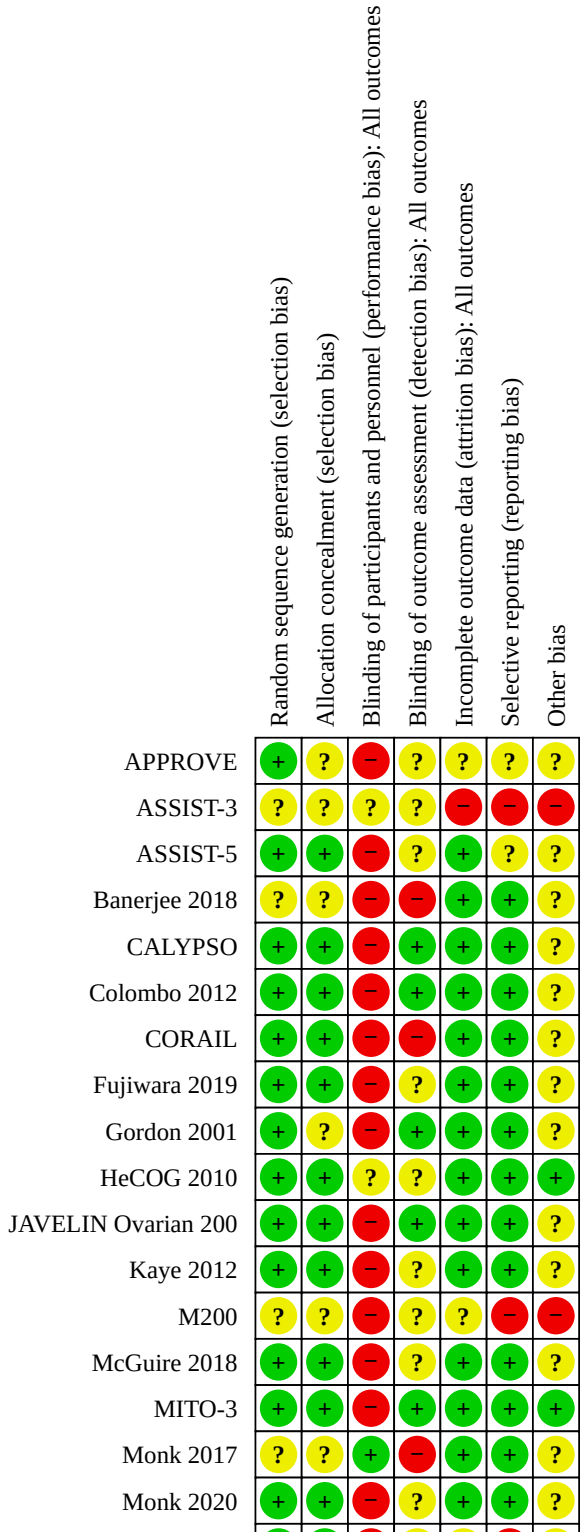
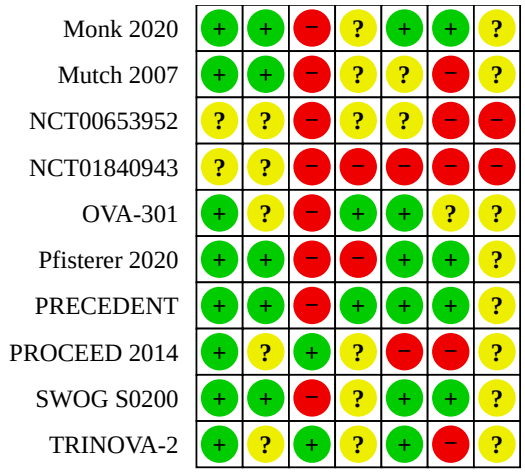


Figure 3. (Continued)



Allocation

Most included studies were multicentre studies, with central randomisation and treatment allocation after registration with the organising centre. Therefore, the risk of selection bias was low. The methods of randomisation were not described in six studies (ASSIST-3; Banerjee 2018; M200; Monk 2017; NCT00653952; NCT01840943)

Methods of allocation concealment were unclear in eleven studies (APPROVE; ASSIST-3; Banerjee 2018; Gordon 2001; M200; Monk 2017; NCT00653952; NCT01840943; OVA-301; PROCEED 2014; TRINOVA-2).

Blinding

Almost all the included studies were open-label, i.e. the participants and attending healthcare professionals were aware of the associated group allocation; therefore, all studies were at a high risk of performance bias. As an exception to this, three studies were double-blinded (Monk 2017; PROCEED 2014; TRINOVA-2). Method of blinding was not documented for one full-text publication, with trial no protocol available (HeCOG 2010), and unclear in another (ASSIST-3), as this was not described.

All but one included study (NCT00653952 - as described above) assessed disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST) and/or Gynecologic Cancer Intergroup (GCIG) criteria (CA-125) (Therasse 2000; Rustin 1996); however, in most studies, it was unclear what methods, if any, were used to minimise detection bias - only seven studies reported assessor blinding or independent radiologist or oncologist review (CALYPSO; Colombo 2012; Gordon 2001; JAVELIN Ovarian 200; MITO-3; OVA-301; PRECEDENT).

Incomplete outcome data

Attrition rates were high in ASSIST-3 for primary outcomes, and these data were not included. A high risk of bias was assigned to NCT01840943 as 11/26 participants withdrew and 8/26 were lost to follow up, and to PROCEED 2014 as only interim data were available. Three other studies did not clearly state the total numbers of participants evaluated per outcome (i.e. denominators were missing) (M200; Mutch 2007; NCT00653952). APPROVE was assigned an unclear risk of bias as 57/74 and 53/72 did not complete six cycles of PLD.

Two trials that reported QoL data had low attrition rates(JAVELIN Ovarian 200; Pfisterer 2020). However, attrition rates for QoL outcomes were high (> 20%) in seven of the nine studies that reported this outcome (CALYPSO; Colombo 2012; Gordon 2001; Kaye 2012; MITO-3; Mutch 2007; OVA-301). As attrition rates for other outcomes in these studies were low, overall we adjudged the attrition bias to be low for these studies. We retained the 'unclear' rating for Mutch 2007 due to the unclear denominator.

Selective reporting

Most included studies reported their prespecified outcomes. NCT00653952 was closed early due to accrual problems, after 50% of participants were recruited. Only OS and adverse event data were presented, via an online clinical study report, after agreement with the sponsor company's Oncology Division. NCT01840943 reporting was incomplete when compared to the planned protocol.

Two studies reported only limited data in the abstracts of conference proceedings that could not be adequately evaluated for reporting bias (ASSIST-3; M200); to our knowledge, these studies have not been published in full. ASSIST-5 was temporarily put on hold in June 2007 to review the results of the single-agent trial (ASSIST-1 2009). The clinical hold was released in October 2007, but the sponsor decided not to enrol any additional patients and closed the trial early (planned enrolment = 244, actual enrolment = 125). Overall survival data for ASSIST-5 have not been published and, to our knowledge, neither have the review findings, despite closing over a decade ago. Similarly, preliminary data from ASSIST-3 were presented in 2007, but further data have not been published.

Mutch 2007 was judged at high risk of bias as they did not describe hazard ratios, number of events, and censoring for the primary outcome (PFS) or OS and only limited (non-comparative) QoL data were reported. PROCEED 2014 was judged as high risk of bias due to high censoring rates and short follow-up period.

Finally, in the TRINOVA-2 trial we noted a discrepancy in the reported secondary outcomes; we did not have access to the study protocol, but secondary outcomes are published differently to

those listed on clinicaltrials.gov (OS, ORR and duration of response, vs OS only). This may be attributed to reporting bias.

Other potential sources of bias

We judged four studies to be at high risk of other potential risks of bias (ASSIST-3; M200; NCT00653952; NCT01840943). The results of ASSIST-3, M200 and NCT00653952 have not been published in full, there is a potentially high risk of bias associated with the non-publication of these studies. NCT00653952 enrolled women with relapsed EOC (platinum-sensitive or platinum-resistant) to PLD or PAC. As previous therapy with PLD or PAC was an exclusion criterion, once PAC/carboplatin became a first-line chemotherapy combination option for EOC (NICE 2003), accrual was slow and the study became largely irrelevant. However, 220 women (out of a target of 438) were randomised and started on treatment and, ideally, the results of this terminated study should have been published. We were unsuccessful in our attempts to obtain these data or further information. Similarly, we were unable to obtain missing data for ASSIST-3, despite previous attempts to contact the investigators and Telik.

SWOG S0200 (PLD/carboplatin versus carboplatin alone for platinum-sensitive relapsed EOC) was another study that closed early due to slow accrual following the release of the initial ICON-4 results, which showed the combination of PAC/carboplatin to be superior to carboplatin alone for women with platinum-sensitive relapsed EOC, and for other reasons. SWOG S0200 is therefore limited by a small sample size (61 evaluable participants). However, unlike NCT00653952, the investigators of SWOG S0200 published their final results in full. We therefore judged this study to be at unclear risk of other bias.

In OVA-301, bias may have occurred as a result of discrepancies in the premedications given to the intervention arm (notably dexamethasone), or the lower PLD dose in the intervention arm, which may have influenced outcomes. We judged this study to be at unclear risk of bias.

NCT01840943 has been included in the review, but not in the meta-analysis, due to overall high risk of bias in the study. This study was closed early and only included 32 participants. Reporting of the methodology was extremely scanty or unclear.

All but two studies (HeCOG 2010 and MITO-3) were funded by drug manufacturers with a commercial interest in either PLD or the comparator drugs. We therefore judged the remaining 18 studies to be at unclear risk of bias (APPROVE; ASSIST-5; Banerjee 2018; CALYPSO; Colombo 2012; CORAIL; Fujiwara 2019; Gordon 2001; JAVELIN Ovarian 200; Kaye 2012; McGuire 2018; Monk 2017; Monk 2020; Mutch 2007; OVA-301; Pfisterer 2020; PRECEDENT; PROCEED 2014; SWOG S0200; TRINOVA-2), unless they were at high risk for other reasons, as described above.

Effects of interventions

See: **Summary of findings 1** Summary of findings 1: PLD with chemotherapy compared to alternative combination chemotherapy in recurrent platinum-sensitive EOC; **Summary of findings 2** Summary of findings 2: PLD alone compared to other conventional chemotherapy in recurrent platinum-resistant EOC; **Summary of findings 3** Summary of findings 3: PLD with chemotherapy compared to PLD alone in recurrent platinum-resistant epithelial ovarian cancer

Twenty-six included studies evaluated the effect of PLD in recurrent EOC: six in women with recurrent platinum-sensitive disease (2604 participants), and 11 in women with recurrent platinum-resistant disease (3153 participants). In the remaining nine studies participants were included regardless of platinum-sensitivity status (2520 participants). We graded the certainty of the evidence of the three most clinically relevant comparisons. As per the methods section (Data synthesis), we combined data from trials that evaluated the effect of treatment options in populations with recurrent EOC regardless of platinum-sensitivity status with those with platinum-resistant recurrence in meta-analyses, and performed sensitivity analysis to determine the effect of excluding studies including the mixed population.

Recurrent platinum-sensitive EOC

PLD with conventional chemotherapy compared to other combination chemotherapy

See Summary of findings 1.

Overall survival (OS)

PLD with chemotherapy likely results in little to no difference in OS (HR 0.93, 95% CI 0.83 to 1.04; P = 0.18, I^2 = 23%; 5 studies, 2006 participants; moderate-certainty evidence; Analysis 1.1) compared to chemotherapy alone.

Progression-free survival (PFS)

PLD with chemotherapy likely increases PFS (HR 0.81, 95% CI 0.74 to 0.89; P < 0.0001, I^2 = 16%; 5 studies, 2006 participants; moderate-certainty evidence; Analysis 1.2) compared to chemotherapy alone.

Quality of life (QoL)

PLD with chemotherapy compared to chemotherapy alone may slightly improve QoL at three months post-randomisation measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (MD 4.80, 95% CI 0.92 to 8.68; 1 study, 608 participants; low-certainty evidence; Analysis 1.3), but this may not represent a clinically meaningful difference.

Adverse events

Trials contributing to this comparison did not report the following safety outcomes: diarrhoea (grade ≥ 3), and dose reductions or dose delays.

PLD with chemotherapy compared to chemotherapy alone likely results in little to no difference in overall severe adverse events (grade ≥ 3) (RR 1.11, 95% CI 0.95 to 1.30; P = 0.17, I^2 = 0%; 2 studies, 834 participants; moderate-certainty evidence; Analysis 1.4).

PLD with chemotherapy likely increases anaemia (grade ≥ 3) (RR 1.37, 95% CI 1.02 to 1.85; P = 0.04, I^2 = 22%; 5 studies, 1961 participants; moderate-certainty evidence; Analysis 1.5) and neutropenia (grade ≥ 3) (RR 0.78, 95% CI 0.70 to 0.88; P < 0.0001; I^2 = 75%; 5 studies, 1961 participants; Analysis 1.8).

PLD with conventional chemotherapy likely results in a large decrease in hypersensitivity reactions (grade ≥ 3) (RR 0.27, 95% CI 0.15 to 0.48; P < 0.0001, I^2 = 0%; 5 studies, 1961 participants; Analysis 1.14) and may result in a large increase in stomatitis (grade ≥ 3) (RR 2.52, 95% CI 1.01 to 6.28; P = 0.05, I^2 = 0%; 3 studies, 1801

participants; Analysis 1.10) and arthralgia (grade ≥ 3) RR 0.19, 95% CI 0.04 to 0.85; P = 0.03, I^2 = 0%; 4 studies, 1862 participants; Analysis 1.13).

PLD with conventional chemotherapy may result in little to no difference in vomiting (grade ≥ 3) (RR 1.26, 95% CI 0.78 to 2.02; P = 0.34, I^2 = 0%; 4 studies, 1862 participants; Analysis 1.11), fatigue (grade ≥ 3) (RR 1.00, 95% CI 0.67 to 1.50; P = 0.99, I^2 = 0%; 4 studies, 1862 participants; Analysis 1.12), discontinuation of treatment due to toxicity (RR 0.93, 95% CI 0.75 to 1.15; P = 0.50, I^2 = 93%; 4 studies, 1862 participants; Analysis 1.16) and need for G-CSF (RR 1.14, 95% CI 0.85 to 1.54; P = 0.38, I^2 = 0%; 2 studies, 838 participants; Analysis 1.18).

The evidence is very uncertain about the effect of PLD with conventional chemotherapy on hand-foot syndrome (grade ≥ 3) (RR 4.01, 95% CI 1.00 to 16.01; P = 0.05, I^2 = 0%; 2 studies, 1028 participants; very low-certainty evidence; Analysis 1.6), neurological events (grade ≥ 3) RR 0.38, 95% CI 0.20 to 0.74; P = 0.004, I^2 = 67%; 4 studies, 1900 participants; very low-certainty evidence; Analysis 1.7), thrombocytopenia (grade ≥ 3) (RR 1.14, 95% CI 0.90 to 1.44; P = 0.28, I^2 = 90%; 5 studies, 1961 participants; Analysis 1.9), treatment-related death due to serious adverse events (RR 1.44, 95% CI 0.29 to 7.15; P = 0.66, I^2 = 33%; 3 studies, 1801 participants; Analysis 1.15), and need for antibiotics (RR 1.12, 95% CI 0.57 to 2.21; P = 0.73, I^2 = 37%; 2 studies, 1144 participants; Analysis 1.17).

PLD with conventional chemotherapy compared to PLD alone

The evidence in this comparison is limited to a combination of PLD with trabectedin (Monk 2020; OVA-301).

Overall survival (OS)

PLD with trabectedin likely results in little to no difference in OS compared to PLD alone (HR 0.87, 95% CI 0.74 to 1.02; P = 0.09, I^2 = 0%; 2 studies, 1006 participants; Analysis 2.1).

Progression-free survival (PFS)

PLD with trabectedin likely increases PFS slightly compared to PLD alone (HR 0.85, 95% CI 0.72 to 1.00; P = 0.05, I^2 = 53%; 2 studies, 1006 participants; Analysis 2.2).

Quality of life (QoL)

Outcome not reported.

Adverse events

Trials contributing to this comparison did not report the following safety outcomes: neurological events (grade ≥ 3), diarrhoea (grade ≥ 3), arthralgia/myalgia (grade ≥ 3), hypersensitivity reactions (grade ≥ 3), treatment-related death due to serious adverse events, discontinuation of treatment due to toxicity, dose reductions or delays, and need for antibiotics or G-CSF.

PLD with trabectedin compared to PLD alone likely results in a large reduction in hand-foot syndrome (grade ≥ 3) (RR 0.30, 95% CI 0.15 to 0.59; 1 study, 568 participants; Analysis 2.5) and likely increases overall severe adverse events (grade ≥ 3) (RR 1.33, 95% CI 1.20 to 1.47; 1 study, 568 participants; Analysis 2.3) compared to PLD alone.

PLD with trabectedin compared to PLD alone may result in a large increase in anaemia (grade ≥ 3) (RR 3.01, 95% CI 1.87 to 4.85; 1 study, 568 participants; Analysis 2.4), neutropenia (grade ≥ 3) (RR 2.07, 95% CI 1.59 to 2.70; 1 study, 568 participants; Analysis 2.6) and fatigue (grade ≥ 3) (RR 4.37, 95% CI 1.96 to 9.75; 1 study, 568 participants; Analysis 2.10), although risk of stomatitis (grade ≥ 3) was decreased by the combination of PLD and trabectedin compared with PLD alone (RR 0.21, 95% CI 0.08 to 0.56; 1 study, 568 participants; Analysis 2.8).

PLD with trabectedin compared to PLD alone likely results in an increase in vomiting (grade ≥ 3) (RR 3.55 95% CI 1.34 to 9.43; 1 study, 568 participants; Analysis 2.9) compared to PLD alone.

The evidence is very uncertain about the effect of PLD with trabectedin on thrombocytopenia (grade ≥ 3) (RR 14.13, 95% CI 4.44 to 45.03; 1 study, 568 participants; Analysis 2.7).

Recurrent platinum-resistant EOC

PLD alone compared to conventional chemotherapy

See Summary of findings 2.

Overall survival (OS)

PLD likely results in little to no difference in OS (HR 0.96, 95% CI 0.77 to 1.19; P = 0.70, I^2 = 84%; 6 studies, 1995 participants; moderate-certainty evidence; Analysis 3.1) compared to chemotherapy alone. Findings of sensitivity analysis using studies that recruited only individuals with platinum-resistant EOC were consistent with the main analysis (HR 1.08, 95% CI 0.96 to 1.23 ; 3 studies, 1369 participants).

Progression-free survival (PFS)

The evidence is very uncertain about the effect of PLD on PFS (HR 0.94, 95% CI 0.85 to 1.04; P = 0.23, I^2 = 0%; 4 studies, 1803 participants; very low-certainty evidence; Analysis 3.2) compared to chemotherapy alone. Findings of sensitivity analysis using studies that recruited only individuals with platinum-resistant EOC were consistent with the main analysis (HR 0.95, 95% CI 0.83 to 1.09; 2 studies, 1176 participants).

Quality of life (QoL)

Outcome not reported.

Adverse events

Trials contributing to this comparison did not report the following safety outcomes: arthralgia/myalgia (grade ≥ 3), treatment-related death due to serious adverse events, treatment discontinuation due to toxicity, and a need for antibiotics or G-CSF.

The evidence is very uncertain about the effect of PLD compared to chemotherapy alone on overall severe adverse events (grade >3) (RR ranged from 0.61 to 0.97; 2 studies, 964 participants; very low-certainty evidence; Analysis 3.3), anaemia (grade ≥ 3) (RR ranged from 0.19 to 0.82; 5 studies, 1968 participants; very low-certainty evidence; Analysis 3.4), hand-foot syndrome (grade ≥ 3) (RR ranged from 15.19 to 109.15; 6 studies, 2184 participants; very low-certainty evidence; Analysis 3.5), neurological events (grade ≥ 3)(RR ranged from 0.08 to 3.09; 3 studies, 1222 participants; very low-certainty evidence; Analysis 3.6), neutropenia (grade ≥ 3)(RR ranged from 0.16 to 3.36; 5 studies, 2055 participants; Analysis 3.7), thrombocytopenia (grade ≥ 3) (RR ranged from 0.04 to 0.53; 4

studies, 1157 participants; Analysis 3.8), stomatitis (grade ≥ 3) (RR ranged from 2.53 to 20.15; 6 studies, 2184 participants; Analysis 3.9), vomiting (grade ≥ 3) (RR ranged from 0.14 to 0.74; 4 studies, 1494 participants; Analysis 3.10), diarrhoea (grade ≥ 3) (RR ranged from 0.09 to 0.60; 4 studies, 1494 participants; Analysis 3.11), fatigue (grade ≥ 3) (RR ranged from 0.40 to 0.80; 5 studies, 1556 participants; Analysis 3.12), rate of hypersensitivity reactions (grade ≥ 3) (RR 2.96, 95% CI 0.32 to 27.77; 1 study, 143 participants; Analysis 3.13), rate of dose reductions (RR 1.04, 95% CI 0.54 to 2.01; P = 0.91, I^2 = 91%; 4 studies, 1773 participants; Analysis 3.14), and dose delays (RR 0.97, 95% CI 0.55 to 1.69; P = 0.90, I^2 = 80%; 5 studies, 962 participants; Analysis 3.15).

PLD with conventional chemotherapy compared to PLD alone

See Summary of findings 3.

Overall survival (OS)

PLD with conventional chemotherapy likely results in little to no difference in OS (HR 0.92, 95% CI 0.70 to 1.21; 1 study, 242 participants, moderate-certainty evidence; Analysis 4.1).

Progression-free survival (PFS)

PLD with conventional chemotherapy may result in little to no difference in PFS (HR 0.94, 95% CI 0.73 to 1.22; P = 0.64, I^2 = 0%; 2 studies, 353 participants; low-certainty evidence; Analysis 4.2).

Quality of life (QoL)

Outcome not reported.

Adverse events

Trials contributing to this comparison did not report the following safety outcomes: diarrhoea (grade ≥ 3), arthralgia (grade ≥ 3), hypersensitivity reactions (grade ≥ 3), treatment discontinuation due to toxicity and a need for antibiotics or G-CSF.

PLD with conventional chemotherapy likely increases overall severe adverse events (grade ≥ 3) (RR 2.48, 95% CI 1.98 to 3.09; 1 study, 663 participants; moderate-certainty evidence; Analysis 4.3), anaemia (grade ≥ 3) (RR 2.38, 95% CI 1.46 to 3.87; P = 0.0005, I^2 = 0%; 2 studies, 785 participants; moderate-certainty evidence; Analysis 4.4), and neutropenia (grade ≥ 3) (RR 2.75, 95% CI 2.23 to 3.38; P < 0.00001, I^2 = 0%; 2 studies, 785 participants; Analysis 4.7) compared to PLD alone.

PLD with conventional chemotherapy likely results in a large reduction in hand-foot syndrome (grade ≥ 3) (RR 0.24, 95% CI 0.14 to 0.40; P < 0.00001, I^2 = 48%; 2 studies, 785 participants; moderate-certainty evidence; Analysis 4.5) compared to PLD alone.

PLD with conventional chemotherapy may result in a large increase in thrombocytopenia (grade ≥ 3) (RR 7.70, 95% CI 3.90 to 15.19; P < 0.00001, I^2 = 0%; 2 studies, 785 participants; Analysis 4.8), vomiting (grade ≥ 3) (RR 3.77, 95% CI 1.91 to 7.41; P = 0.0001, I^2 = 54%; 2 studies, 785 participants; Analysis 4.10) and fatigue (grade ≥ 3) (RR 2.20, 95% CI 1.02 to 4.76; 1 study, 663 participants; Analysis 4.11); and may result in a large reduction in stomatitis (grade ≥ 3) (RR 0.30, 95% CI 0.13 to 0.70; P = 0.005, I^2 = 60%; 2 studies, 785 participants; Analysis 4.9).

PLD with conventional chemotherapy may increase the rate of dose delays (RR 1.50, 95% CI 1.00 to 2.26; 1 study, 535 participants; Analysis 4.13), and may result in little to no difference in neurological events (grade ≥ 3) (RR 1.40, 95% CI 0.85 to 2.31; 1 study, 663 participants; low-certainty evidence; Analysis 4.6) and rate of dose reductions (RR 1.07, 95% CI 0.53 to 2.14; 1 study, 535 participants; Analysis 4.14).

The evidence is very uncertain about the effect of PLD with conventional chemotherapy on treatment-related death due to serious adverse events (RR 2.48, 95% CI 0.48 to 12.68; 1 study, 663 participants; Analysis 4.12).

PLD compared to targeted therapy alone

Overall survival (OS)

PLD likely results in little to no difference in OS (HR 0.99, 95% CI 0.44 to 2.25; 1 study, 65 participants; Analysis 5.1) compared to targeted therapy.

Progression-free survival (PFS)

PLD likely results in little to no difference in PFS (HR 1.23, 95% CI 0.82 to 1.84; P = 0.31, I^2 = 0%; 2 studies, 160 participants; Analysis 5.2) compared to targeted therapy.

Quality of life (QoL)

Outcome not reported.

Adverse events

Trials contributing to this comparison did not report the following safety outcomes: thrombocytopenia (grade ≥ 3), arthralgia (grade ≥ 3), hypersensitivity reactions (grade ≥ 3), treatment-related death due to serious adverse events, treatment discontinuation due to toxicity, dose delays and need for antibiotics or G-CSF.

PLD may result in a large reduction in anaemia (grade ≥ 3) (RR 0.12, 95% CI 0.02 to 0.97; P = 0.05, I^2 = 0%; 2 studies, 157 participants; Analysis 5.4) compared to targeted therapy.

PLD may result in little to no difference in overall severe adverse events (grade ≥ 3) (RR 1.12, 95% CI 0.73 to 1.71; 1 study, 93 participants; Analysis 5.3) and the rate of dose reductions (RR 0.90, 95% CI 0.42 to 1.92; 1 study, 64 participants; Analysis 5.12) compared to targeted therapy.

The evidence is very uncertain about the effect of PLD compared to targeted therapy on hand-foot syndrome (grade ≥ 3) (RR 25.00, 95% CI 1.54 to 405.08; P = 0.02, I^2 = 0%; 2 studies, 157 participants; Analysis 5.5), neurological events (grade ≥ 3) (RR 0.98, 95% CI 0.06 to 15.19; 1 study, 93 participants; Analysis 5.6), neutropenia (grade ≥ 3) (RR 0.33, 95% CI 0.07 to 1.53; 1 study, 93 participants; Analysis 5.7), stomatitis (grade ≥ 3) (RR 5.87, 95% CI 0.72 to 47.84; P = 0.10; 2 studies (1 of which had 0 events), 157 participants; Analysis 5.8), vomiting (grade ≥ 3) (RR 1.31, 95% CI 0.30 to 5.70; P = 0.72, I^2 = 0%; 2 studies, 157 participants; Analysis 5.9), diarrhoea (grade ≥ 3) (RR 2.06, 95% CI 0.27 to 15.56; P = 0.48, I^2 = 0%; 2 studies, 157 participants; Analysis 5.10), and fatigue (grade ≥ 3) (RR 1.18, 95% CI 0.38 to 3.72; P = 0.78, I^2 = 0%; 2 studies, 157 participants; Analysis 5.11).

PLD with targeted therapy compared to PLD alone

Overall survival (OS)

PLD with targeted therapy likely results in little to no difference in OS (HR 0.93, 95% CI 0.75 to 1.15; P = 0.53, I^2 = 0%; 4 studies, 647 participants; Analysis 6.1) compared to PLD alone. Findings of sensitivity analysis using studies that recruited only individuals with platinum-resistant EOC were consistent with the main analysis (HR 0.84, 95% CI 0.56 to 1.27; 2 studies, 301 participants).

Progression-free survival (PFS)

PLD with targeted therapy may result in little to no difference in PFS (HR 0.78, 95% CI 0.58 to 1.04; P = 0.09, I^2 = 63%; 5 studies, 877 participants; Analysis 6.2) compared to PLD alone. Sensitivity analysis using studies that recruited only individuals with platinum-resistant EOC showed some evidence of beneficial effects from combined treatment compared to PLD alone (HR 0.65, 95% CI 0.42 to 1.00; 3 studies, 531 participants).

Quality of life (QoL)

Outcome not reported.

Adverse events

Trials contributing to this comparison did not report the following safety outcomes: arthralgia/myalgia (grade ≥ 3), hypersensitivity reactions (grade ≥ 3), treatment discontinuation due to toxicity, dose delays, and need for antibiotics or G-CSF. Reported adverse events are mainly treatment-emergent.

PLD with targeted therapy may increase hand-foot syndrome (grade ≥ 3) (RR 1.75, 95% CI 1.07 to 2.88; P = 0.03, I^2 = 0%; 4 studies, 647 participants; Analysis 6.5) compared to PLD alone.

PLD with targeted therapy may result in little to no difference in anaemia (grade ≥ 3) (RR 0.63, 95% CI 0.32 to 1.26; P = 0.19, I^2 = 0%; 4 studies, 647 participants; Analysis 6.4) and neutropenia (grade ≥ 3) (RR 1.09, 95% CI 0.69 to 1.74; P = 0.70, I^2 = 16%; 4 studies, 647 participants; Analysis 6.7) compared to PLD alone.

The evidence is very uncertain about the effect of PLD with targeted therapy on overall severe adverse events (grade ≥ 3) (RR 1.15, 95% CI 0.90 to 1.48; P = 0.27, I^2 = 69%; 4 studies, 794 participants; Analysis 6.3); neurological events (grade ≥ 3) (RR 4.25, 95% CI 0.23 to 77.45; P = 0.33; 2 studies, 378 participants; Analysis 6.6); thrombocytopenia (grade ≥ 3) (RR 1.03, 95% CI 0.11 to 9.49; P = 0.98, I^2 = 51%; 2 studies, 303 participants; Analysis 6.8); stomatitis (grade ≥ 3) (RR 0.97, 95% CI 0.43 to 2.19; P = 0.93, I^2 = 12%; 4 studies, 647 participants; Analysis 6.9); vomiting (grade ≥ 3) (RR 0.81, 95% CI 0.35 to 1.87; P = 0.63, I^2 = 0%; 3 studies, 490 participants; Analysis 6.10); diarrhoea (grade ≥ 3) (RR 0.64, 95% CI 0.18 to 2.24; P = 0.49, I^2 = 0%; 2 studies, 344 participants; Analysis 6.11); fatigue (grade ≥ 3) (RR 2.08, 95% CI 0.30 to 14.52; P = 0.46, I^2 = 67%; 3 studies, 490 participants; Analysis 6.12); rate of treatment-related death due to serious adverse events (RR 1.02, 95% CI 0.33 to 3.20; P = 0.97, I^2 = 0%; 5 studies, 956 participants; Analysis 6.13) and rate of dose reductions (RR 14.00, 95% CI 1.89 to 103.76; 1 study, 148 participants; Analysis 6.14).

PLD compared to immunotherapy

Overall survival (OS)

PLD likely results in little to no difference in OS (HR 0.88, 95% CI 0.68 to 1.13; 1 study, 378 participants; Analysis 7.1) compared to immunotherapy.

Progression-free survival (PFS)

PLD likely increases PFS (HR 0.60, 95% CI 0.42 to 0.84; 1 study, 378 participants; Analysis 7.2) compared to immunotherapy.

Quality of life (QoL)

Outcome not reported.

Adverse events

Trials contributing to this comparison did not report the following safety outcomes: arthralgia/myalgia (grade ≥ 3), hypersensitivity reactions (grade ≥ 3), treatment-related death due to serious adverse events, treatment discontinuation due to toxicity, dose delays and need for antibiotics or G-CSF. The rate of neurological events (grade ≥ 3) was noted in JAVELIN Ovarian 200, but no events of this grade occurred during the course of the trial. Reported adverse events are mainly treatment-emergent.

PLD likely results in a large increase in overall severe adverse events (grade ≥ 3) (RR 1.97, 95% CI 1.33 to 2.92; 1 study, 364 participants; Analysis 7.3) compared to immunotherapy.

The evidence is very uncertain about the effect of PLD on anaemia (grade ≥ 3) (RR 3.17, 95% CI 0.87 to 11.52; 1 study, 364 participants; Analysis 7.4); hand-foot syndrome (grade ≥ 3) (RR 20.07, 95% CI 1.18 to 342.24; 1 study, 364 participants; Analysis 7.5); neutropenia (grade ≥ 3) (RR 20.07, 95% CI 1.18 to 342.24; 1 study, 364 participants; Analysis 7.6); thrombocytopenia (grade ≥ 3) (RR 3.17, 95% CI 0.13 to 77.27; 1 study, 364 participants; Analysis 7.7); stomatitis (grade ≥ 3) (RR 8.45, 95% CI 1.07 to 66.89; 1 study, 364 participants; Analysis 7.8); vomiting (grade ≥ 3) (RR 3.17, 95% CI 0.33 to 30.19; 1 study, 364 participants; Analysis 7.9); diarrhoea (grade ≥ 3) (RR 0.10, 95% CI 0.01 to 1.72; 1 study, 364 participants; Analysis 7.10); fatigue (grade ≥ 3) (RR 7.39, 95% CI 0.38 to 142.12; 1 study, 364 participants; Analysis 7.11); and the rate of dose reductions (RR 5.07, 95% CI 1.98 to 13.00; 1 study, 364 participants; Analysis 7.12).

PLD with immunotherapy compared to PLD alone

Overall survival (OS)

PLD with immunotherapy likely results in little to no difference in OS (HR 0.89, 95% CI 0.69 to 1.15; P = 0.38, I^2 = 0%; 2 studies, 675 participants; Analysis 8.1) compared to PLD alone. Findings of sensitivity analysis using studies that recruited only individuals with platinum-resistant EOC were consistent with the main analysis (HR 0.89, 95% CI 0.69 to 1.15; 1 study, 378 participants).

Progression-free survival (PFS)

PLD with immunotherapy may result in little to no difference in PFS (HR 0.78, 95% CI 0.54 to 1.14; P = 0.20, I^2 = 0%; 2 studies, 675 participants; Analysis 8.2) compared to PLD alone. Findings of sensitivity analysis using studies that recruited only individuals with platinum-resistant EOC were consistent with the main analysis (HR 0.78, 95% CI 0.54 to 1.14; 1 study, 378 participants).

Quality of life (QoL)

Outcome not reported.

Adverse events

Trials contributing to this comparison did not report the following safety outcomes: arthralgia/myalgia (grade ≥ 3), hypersensitivity reactions (grade ≥ 3), treatment discontinuation due to toxicity, dose delays and a need for antibiotics or G-CSF.

PLD with immunotherapy may increase the rate of dose reductions (RR 1.90, 95% CI 1.22 to 2.98; 1 study, 359 participants; Analysis 8.14).

PLD with immunotherapy may result in little to no difference in overall severe adverse events (grade ≥ 3) (RR 1.12, 95% CI 0.96 to 1.30; P = 0.14, I^2 = 62%; 2 studies, 653 participants; Analysis 8.3); anaemia (grade ≥ 3) (RR 0.65, 95% CI 0.27 to 1.57; P = 0.34, I^2 = 0%; 2 studies, 653 participants; Analysis 8.4); hand-foot syndrome (grade ≥ 3) (RR 1.07, 95% CI 0.81 to 1.42; P = 0.62, I^2 = 62%; 2 studies, 653 participants; Analysis 8.5); neurological events (grade ≥ 3) (RR 0.98, 95% CI 0.70 to 1.37; P = 0.90, I^2 = 0%; 2 studies, 653 participants; Analysis 8.6); neutropenia (grade ≥ 3) (RR 1.07, 95% CI 0.47 to 2.48; P = 0.87, I^2 = 0%; 2 studies, 653 participants; Analysis 8.7); stomatitis (grade ≥ 3) (RR 1.39, 95% CI 0.62 to 3.11; P = 0.43, I^2 = 0%; 2 studies, 653 participants; Analysis 8.9), and vomiting (grade ≥ 3) (RR 0.99, 95% CI 0.38 to 2.60; P = 0.99, I^2 = 23%; 2 studies, 653 participants, Analysis 8.10).

The evidence is very uncertain about the effect of PLD with immunotherapy on thrombocytopenia (grade ≥ 3) (RR 0.32, 95% CI 0.01 to 7.91;1 study, 359 participants; Analysis 8.8); diarrhoea (grade ≥ 3) (RR 3.64, 95% CI 0.60 to 21.92; P = 0.16, I^2 = 0%; 2 studies, 653 participants; Analysis 8.11); fatigue (grade ≥ 3) (RR 2.75, 95% CI 1.00 to 7.55; P = 0.05, I^2 = 0%; 2 studies, 653 participants; Analysis 8.12); and the rate of treatment-related death due to serious adverse events (RR 3.00, 95% CI 0.12 to 73.05; 1 study, 294 participants; Analysis 8.13).

DISCUSSION

Summary of main results

In this update to the review, we include 26 RCTs with a total of 8277 participants recruited that evaluated the effects of PLD alone or in combination with other drugs in recurrent EOC (ITT efficacy data reported for 8116).

- Seven in platinum-sensitive disease (2872 participants; ITT efficacy data reported for 2807)
- Eleven in platinum-resistant disease (3246 participants; ITT efficacy data reported for 3234)
- Eight that recruited individuals regardless of platinum sensitivity status (2079 participants; ITT efficacy data reported for 2075)

We assessed the certainty of the evidence for the three most clinically relevant comparisons, out of eight comparisons identified in the included RCTs.

Recurrent platinum-sensitive EOC

PLD with conventional chemotherapy compared to alternative conventional chemotherapy likely results in little to no difference in OS, but likely increases progression-free survival (PFS). The combination of PLD and chemotherapy may slightly improve the quality of life at three months post-randomisation, measured using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30, but this may not represent a clinically meaningful difference.

PLD added to chemotherapy compared to chemotherapy alone likely results in little to no difference in the rate of overall severe adverse events (grade ≥ 3). PLD with chemotherapy likely increases anaemia (grade ≥ 3). The evidence is very uncertain about the effect of PLD with conventional chemotherapy on hand-foot syndrome (HFS) (grade ≥ 3) and neurological events (grade ≥ 3).

Recurrent platinum-resistant EOC

PLD alone compared to conventional chemotherapy likely results in little to no difference in OS. The evidence is very uncertain about the effect of PLD on PFS, overall severe adverse events (grade ≥3), anaemia (grade ≥3), HFS (grade ≥3), and the rate of neurological events (grade ≥3). However, there were no cases of HFS in the non-PLD arm and between 55 and 104 cases per 1,000 in the PLD arm.

PLD with conventional chemotherapy compared to PLD alone likely results in little to no difference in OS, and it may result in little to no difference in PFS. The combination likely increases overall severe adverse events (grade ≥3) and anaemia (grade ≥ 3), but likely results in a large reduction in HFS (grade ≥ 3). It may result in little to no difference in neurological events (grade ≥ 3).

Several studies included PLD either as a comparison to, or with or without, targeted agents or immunotherapy. This is because novel agents are often first tested in participants with relapsed disease, and PLD is commonly used in these settings, so is a frequent 'physician's choice' chemotherapy. Due to the heterogeneity of treatments and their targets, we have not formally included them within our summary of findings, as the certainty of these treatment combinations is low or very low. The data for individual comparisons is presented in the results and analyses sections.

Overall completeness and applicability of evidence

We included 26 studies where data were available for the use of PLD in women with relapsed EOC. A number of other studies used PLD as part of treatment, either as monotherapy or in combination, which examined the effect of adding another agent to the physicians choice of chemotherapy treatment. We were not able to obtain data from these studies for those treated with PLD in the intervention or comparison arm, so a review of individual participant data, including data from these studies, may alter our findings.

We are relatively confident that we have captured the majority of studies assessing PLD in relapsed EOC, having identified ongoing studies in a previous review and compared included studies to recent systematic reviews. In addition, this review has been performed alongside other reviews of targeted agents in ovarian cancer. Studies have been shared between review teams where there was found to be overlap, so the search net has effectively been wider than the search strategy of each individual review. However,

treatment of relapsed EOC is a fast-moving field, so studies may have been missed.

The studies included in the review are applicable to many women with relapsed EOC, as they include those with platinum-sensitive and resistant disease. However, the age of women in studies is younger than those outside of clinical trials, which should be noted when making decisions about individual patient care, as this may affect the benefit and risks of treatment.

Data for disease response, including survival outcomes, is reported more consistently than harms and quality of life outcomes. This is common across oncology studies and remains disappointing, limiting the ability of women to make truly informed decisions about their treatment options.

In summary, PLD may have similar levels of benefit to other chemotherapy options, either alone or in combination with other chemotherapy and targeted treatments, but has a differing side effect profile. Optimal choice of treatment for women with relapsed EOC will therefore depend on patient factors, comorbidity, residual side effects to other treatments and individual preference.

Quality of the evidence

This is a comprehensive review of literature on the effect of PLD in the treatment of relapsed EOC. Nevertheless, the certainty of evidence for survival outcomes was moderate to very low, with the certainty of harms and quality of life outcomes mainly very low. The main difficulty in the assessment of study limitations was suboptimal or inadequate reporting of important features of trial design, such as randomisation sequence generation (in 6 of 26 studies this domain was unclear) or allocation concealment (unclear in 11 of 26 studies).

Only three studies clearly blinded participants and personnel (Monk 2017; PROCEED 2014; TRINOVA-2), with another two at unclear risk for this domain (ASSIST-3; HeCOG 2010). The rest of the studies were open-label in design, which put the studies at high risk of bias for blinding for all outcomes except OS (Figure 3). Overall, no study was deemed at low risk of bias in all evaluated domains and only one study in six domains (MITO-3).

Reporting of adverse outcomes was inconsistent, impeding combination of data in meta-analyses, which reduces the certainty of our findings.

Potential biases in the review process

We attempted to prevent bias in the review by including grey literature and making every effort to obtain missing data from the investigators. However, as discussed above, we were unable to obtain data for PLD-treated participants in several studies, which remain Studies awaiting classification. PLD is a commonly used treatment in recurrent EOC, so we may not have identified all studies, despite a systematic approach, and welcome further data from other studies not included in this review.

The majority of the authors, including the senior author, have no links to drug companies, any financial interest in the prescription of chemotherapeutic agents, nor were they involved in the conduct of the included studies.

Agreements and disagreements with other studies or reviews

When considering this review in the context of the published literature studying the benefits of PLD in EOC, existing systematic reviews generally agree with our outcomes (where comparison was possible), but there are also some disagreements, as highlighted below.

PLD with conventional chemotherapy compared to conventional chemotherapy alone in recurrent platinum-sensitive EOC

Four published systematic reviews compare the combination of PLD and platinum-based chemotherapy (primarily carboplatin) with other platinum-based combinations (Edwards 2015 (16 studies (28 publications), including 5368 participants);Li 2021 (described as including 10 studies with 3747 participants); Shi 2020 (7 studies, including 3676 participants); Staropoli 2014 (14 studies, including 5760 participants)). Three of these investigated the value of PLD in both the platinum-sensitive and platinum-resistant setting, whereas Shi 2020 only focussed on the role of PLD in the platinum-sensitive setting, combined with carboplatin.

Considering combination platinum/PLD chemotherapy, studies by Li 2021 and Shi 2020 agree that PLD-containing regimens likely produce no difference in OS, when compared to carboplatin/paclitaxel (HR 1.00, and HR 0.98, respectively). Staropoli 2014 drew similar conclusions (HR 0.96, 95% CI 0.82 to 1.12). However, their analysis also included a study comparing carboplatin/PLD to platinum monotherapy, alongside studies using combination platinum/paclitaxel chemotherapy. In addition, their analysis included studies treating women in the first-line setting, so was not limited to the relapsed, platinum-sensitive patient cohort. Edwards 2015 noted an overall survival advantage of platinum/PLD combination chemotherapy, but this was when compared to platinum monotherapy alone (HR 1.267, favouring PLD, 95% CI 1.03 to 1.55).

Regarding PFS in this population, all reviews agreed with our findings, suggesting likely improvement in PFS with PLD. Edwards 2015, Li 2021 and Shi 2020 estimated preference for PLD/carboplatin over PLD/paclitaxel combination chemotherapy, with HR 0.82, HR 0.85, and HR 0.87, respectively; no 95% confidence intervals crossed 1.0. In addition, Li 2021 noted that no difference in PFS was observed when PLD was dosed at 30 mg/m^2, in combination with carboplatin, compared to 45 mg/m^2. Six out of the seven included studies in Shi 2020 also used the 30 mg/m^2 dose, possibly attributing to the non-inferiority of the lower dose in this setting. Staropoli 2014 observed an increased PFS with PLD/carboplatin combined chemotherapy (HR 0.83, 95% CI 0.74 to 0.94); this comparison was confined to studies using either carboplatin monotherapy or carboplatin/paclitaxel.

Considering adverse events and treatment toxicities in this population, Shi 2020 concluded that anaemia grade ≥ 3 was more likely with platinum/PLD, compared to platinum/paclitaxel (RR 0.52, 95% CI 0.38 to 0.70), in agreement with our findings. Grade ≥ 3 neutropenia was not significantly different with platinum/PLD (RR 1.03, 95% 0.78-1.35). In contrast to our uncertainty around grade ≥ 3 thrombocytopenia, Shi 2020 reported RR 0.30 favouring platinum/paclitaxel (95% CI 0.19 to 0.47). They found that G3/4 allergy was

also more common with platinum/PLD (RR 1.86, 95% CI 1.06 to 3.24).

Li 2021 included a comprehensive analysis of treatment toxicities using combination chemotherapies in relapsed, platinum-sensitive EOC. They also agree that platinum/PLD is more likely to result in grade ≥ 3 allergy (RR 0.38 favouring platinum/paclitaxel, 95% CI 0.19 to 0.78) and grade ≥ 3 anaemia (RR 1.86, 95% CI 1.22 to 2.71). In contrast with our results, G3/4 neutropenia was less likely when using carboplatin/PLD (over carboplatin/paclitaxel; RR 0.76, 95% CI 0.67 to 0.86). Interestingly, they also reported no significant difference in the incidence of G3/4 anaemia and G3/4 thrombocytopenia at PLD 30 mg/m^2 versus 45 mg/m^2. In agreement with Shi 2020, G3/4 thrombocytopenia was also more common with PLD/platinum, over paclitaxel/platinum (HR 2.67, 95% CI 1.94 to 3.67).

Regarding HFS and mucositis, Li 2021 assessed these toxicities considering CTCAE grade 2 and above. They noted HFS was higher in carboplatin/PLD than carboplatin/paclitaxel (RR 6.12, 95% CI 3.84 to 9.76), as was G2 and above mucositis (RR 2.12, 95% CI 1.53 to 2.93). Interestingly, grade 3/4 HFS rates were comparable between carboplatin/PLD and carboplatin/paclitaxel (RR 2.76, 95% CI 0.50 to 15.60).

Edwards 2015, a health technology assessment for the National Institute for Healthcare Research, also included a network meta-analysis (NMA) and cost-effectiveness analysis of treatment for recurrent EOC. The cost-effectiveness analysis included 21 economic evaluations. They concluded that in platinum-sensitive disease treated with non-platinum-based therapies, it was unclear whether PLD would be considered cost-effective compared with paclitaxel at a threshold of GBP 30,000 per additional Quality Adjusted Life Year (QALY), and that the addition of trabectedin to PLD was unlikely to be considered cost-effective. For women with platinum-resistant recurrence, it was unlikely that topotecan would be considered cost-effective compared with PLD.

PLD with conventional chemotherapy compared to PLD alone in recurrent platinum-sensitive EOC and platinum-resistant EOC

No previously published systematic reviews or meta-analyses exist comparing PLD monotherapy with PLD plus another conventional chemotherapy. This is the case for both platinum-sensitive and platinum-resistant settings.

PLD compared to conventional chemotherapy alone in recurrent platinum-resistant EOC, and PLD compared to targeted therapy alone in recurrent platinum-resistant EOC

Our review suggests that PLD likely results in no change in overall survival, alongside reporting uncertainty regarding PFS and the benefit of PLD monotherapy, when compared to other conventional chemotherapy monotherapies.

Comparison with existing literature and previously published reviews is limited in this setting. Staropoli 2014 compared PLD to chemotherapy monotherapy, but only included one study in this PFS subgroup analysis (Colombo 2012). When comparing OS, they included two studies and predicted PLD had little influence (HR 1.06. 95% CI 0.92 to 1.23). Li 2021 grouped all monotherapies together under the one analysis (PLD versus conventional chemotherapy monotherapy, and PLD versus targeted treatment monotherapy). For this subgroup, though they identified no difference in PFS (HR 1.02, 95% CI 0.90 to 1.16) or OS (HR 0.88, 95% CI 0.77 to 1.01), their data cannot be directly compared with our own results, which split chemotherapy and targeted therapy monotherapy subgroups, and analysed them separately. Finally, Edwards 2015 concluded that in the platinum-resistant/refractory setting, PLD monotherapy resulted in no statistically significant differences in PFS or OS, compared to comparators.

When considering adverse events, it is once again not possible to directly compare our results to existing reviews and meta-analyses. For adverse event analysis, Staropoli 2014 grouped together platinum-resistant trials with two studies that used non-conventional chemotherapies, and these trials also used a cohort including both platinum-resistant and partial platinum-sensitive patients. They did note, in this grouped analysis, that PLD was not superior even when considering toxicity profiles, but further comparison is limited.

Li 2021 also analysed treatment toxicities for PLD versus other monotherapy, but as all other monotherapies were grouped together (including PARP inhibitors and antibody-drug conjugates) comparison with our data is limited. In their grouped analysis, they did report worse grade ≥ 3 mucositis/stomatitis with PLD (RR 0.10 favouring other agents, 95% CI 0.04 to 0.23) and HFS (RR 0.03 favouring other agents, 95% CI 0.01 to 0.09), alongside noting no difference in grade 3/4 anaemia, grade 3/4 thrombocytopenia, and grade 3/4 neutropenia. Further subgroup analysis of toxicities in the context of PLD versus other monotherapy also concluded that there was a dose-dependent relationship for mucositis and PPE severity, considering the two different PLD doses of 30 mg/m^2 and 50 mg/m^2.

PLD with targeted therapy compared to PLD alone in recurrent platinum-resistant EOC

No previously published systematic reviews or meta-analyses exist comparing PLD monotherapy with PLD plus a targeted therapy. This is the case for both platinum-sensitive and platinum-resistant settings.

PLD compared to immunotherapy in recurrent platinum-resistant EOC, and PLD with immunotherapy compared to PLD alone in recurrent platinum-resistant EOC

No previously published systematic reviews or meta-analyses investigating PLD in EOC have included immunotherapy trials. This is the case for both platinum-sensitive and platinum-resistant settings.

AUTHORS' CONCLUSIONS

Implications for practice

In platinum-sensitive recurrence, pegylated liposomal doxorubicin (PLD), in combination with a platinum agent, has similar efficacy to other combinations, in terms of overall survival (OS), although likely improves progression-free survival (PFS). The side effect profiles differ and this, in conjunction with consideration of patient-factors (residual toxicities of previous treatment, disease-related symptoms, other comorbidities), is likely to determine best options for treatment.

In platinum-resistant relapse, PLD alone appears to have similar efficacy to other chemotherapy regimens and addition of another chemotherapy agent to PLD has minimal benefit over PLD alone, but likely increases severe adverse events. Given those with relapsed epithelial ovarian cancer (EOC) have life-limiting disease, treatment options that minimise toxicities and improve quality of life are preferable.

Effectiveness and harms of targeted therapy and immunotherapy remain uncertain and require further examination in clinical trials.

Most importantly, women with relapsed ovarian cancer have a life-limiting illness. Evidence shows that doctors tend to be overly optimistic about prognosis, both with themselves and even more so with patients, and may be reluctant to have conversations about end of life (e.g. Barclay 2010; Lamont 2001; Stone 2007). The median OS and PFS times in the studies, outlined in Table 3, are of women fit enough to enter clinical studies, who have generally better performance status and fewer comorbidities than the general ovarian cancer patient population. Therefore, the survival of the average woman with relapsed ovarian cancer is likely to be shorter. Involvement of palliative care, alongside active treatment, may be appropriate, as discussed recently by Temkin 2022. However, nearly half (47.1%) of participants with advanced ovarian cancer, who had no further routine treatment options and were taking part in phase 1 studies, had no specialist palliative care alongside their experimental treatment (Moroney 2019).

Implications for research

Treatment of advanced and recurrent cancers requires a careful balance of risks and benefits, the details of which need to be understood by both patient and clinician in order to make decisions about the best treatment for individuals. Without good evidence for both efficacy and harms, these decisions will be made with insufficient information, which may not be in the patient's best interest. It is therefore disappointing that toxicity and quality of life data continue to be so poorly reported, with over-reliance on surrogate outcomes, rather than those more meaningful to patients, as previously discussed (Tattersall 2022). Agreement of minimum reporting standards and core outcomes, especially those important to patients, with study protocols published in advance, should be a requirement for all future clinical studies. Early involvement of patient advocacy groups in clinical trial design is critical to this, and should be mandated. Furthermore, standardised reporting of harms data would help to inform patients and facilitate analysis in secondary research, as outlined by the CoRe Outcomes in Women's and Newborn health (CROWN) initiative.

As PLD is a recognised treatment in recurrent EOC, studies are likely to continue to include PLD in their arms, either in combination with, or in comparison to, another treatment. This is often as part of a 'physician choice' chemotherapy, which may mean that study arms contain a variety of chemotherapy treatments within each arm. Open sharing of data, broken down by specific treatment, should be a requirement of clinical studies. We are disappointed that further study data could not be included in this review, despite contacting authors for data limited to those treated with PLD. We hope that publication of this review will encourage more open sharing in the future, so these data will be able to inform patient care in the future.

There is now a bewildering array of options for treatment of EOC in second- and third-line settings, and those beyond. Studies using genomic sequencing and liquid-based biomarkers to predict which chemotherapy agent to use are ongoing (as reviewed by Khan 2021). Ideally, these studies should be brought together, with the aid of meta-analysis and machine-learning, in order to produce decision-aids, to help clinicians and their patients to make informed choices, based on evidence of effectiveness and harms.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

APPROVE

Study characteristics	
Methods	Multicentre, randomised, controlled, open-label, phase II trial
Participants	152 PR
Interventions	Intervention: apatinib 250 mg orally once daily and PLD (40 mg/m^2) IV every 4 weeks Control: PLD (40 mg/m^2) IV every 4 weeks
Outcomes	**Primary Outcome** PFS **Secondary outcomes** OS Objective response rate (ORR) Disease control rate (DCR) Safety
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned (1:1) via an interactive web response system.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment methods not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	RECIST criteria used but unclear if assessors blinded.
Incomplete outcome data (attrition bias)	Unclear risk	57/74 and 53/72 did not complete 6 cycles of PLD.

APPROVE *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	OS data immature.
Other bias	Unclear risk	57/74 and 53/72 did not complete 6 cycles of PLD Drs She, Guan, and Hou reported personal fees from Jiangsu Hengrui Pharmaceutical Co outside the submitted work. Dr Wu reported grants from National Key R&D Program of China during the conduct of the study as well as nonfinancial support from Jiangsu Hengrui Pharmaceuticals Co Ltd and the CSPC Pharmaceutical Group Co Ltd outside the submitted work. No other disclosures were reported.

ASSIST-3

Study characteristics	
Methods	Phase III multicentre RCT (ID not found on trial registries); abstract only; no further methodological details.
Participants	247 women with PR ROC (resistant and refractory) with measurable disease (RECIST), who had progressed on 2 platinum regimens.
Interventions	**Intervention** CAN (750 mg/m^2) and carboplatin (AUC 5) (carbo) **Control** PLD (50 mg/m^2) IV every 4 weeks until progression
Outcomes	ORR PFS Safety QoL
Notes	Published results included the following statements with little supporting data. • "Overall median PFS was 3.5 months for both CAN/carbo and PLD" (no HRs given). • "Most common toxicities for CAN/carbo were haematologic and as expected for each drug alone". Overall median survival had not been reached at the time of the 2007 ASCO proceedings where these results were reported. Subgroup analyses of women with time from last carboplatin dose (TFP) = 6 months 'reported large differences in ORR and QoL and statistical significance in PFS and survival' in favour of the experimental group (CAN/carboplatin), but this subgroup consisted of 19 women in each group and 58% (11/19) of the CAN/carboplatin arm were censored (compared with 3/19 in the PLD arm). We emailed Dr Rose and Telik, Inc in November 2012 for further information and final survival and safety data but received no response.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

ASSIST-3 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	ORR results differed between clinician and independent radiological assessments, however it is not stated which assessment was used in the analyses.
Incomplete outcome data (attrition bias) All outcomes	High risk	Insufficient data. The abstract states "25% of patients discontinued treatment without documented progression." Final results not reported. Censoring imbalance.
Selective reporting (reporting bias)	High risk	Preliminary results were reported at ASCO 2007 with scant useful data. Overall survival was not reported.
Other bias	High risk	Publication bias. We were unable to obtain any useful data despite several attempts to contact the first author and Telik. We assessed the overall risk of bias of this study as high. This study was sponsored by Telik. Authors reported to stocks in Telik and received honararia. Telik is the company that developed the study drug (TLK286).

ASSIST-5

Study characteristics	
Methods	Phase III multicentre RCT (US, Brazil, Belgium, UK). Accrual from September 2006 to June 2007. Followed up every 8 weeks. (ID: NCT00350948)
Participants	125 women with PR ROC. Included if: ≥ 18 years old; 1 or 2 previous platinum-based chemotherapy regimens given; measurable disease defined by RECIST; ECOG PS 0,1 or 2; and adequate bone marrow reserves and cardiac, renal and hepatic function were required. Bulky disease was defined as tumour mass ≥ 5cm.
Interventions	**Intervention** Canfosfomide (CAN) (1000 mg/m^2) IVI for 30 min followed by PLD (50 mg/m^2) on day 1 every 28 days **Control** PLD (50 mg/m^2) IVI for 60 min on day 1 every 28 days
Outcomes	**Primary outcome** PFS **Secondary outcome** ORR, SAE (NCI-CTCAE v3.0)

ASSIST-5 *(Continued)*

Notes	This study was temporarily put on hold in June 2007 to review the results of the single-agent trial (ASSIST-1) in PR ROC. The clinical hold was released in October 2007, but the sponsor decided not to enrol any additional patients. Patients requiring dose reductions for HFS and stomatitis were 15% and 4%, respectively, in the intervention arm compared with 42% and 25%, respectively, in the PLD arm; i.e. CAN appeared to decrease the rate of HFS and stomatitis when combined with PLD. Premedication (ondansetron and IV corticosteroids) was the same in both arms. For the exploratory subgroup of PR ROC women with platinum-refractory or primary platinum resistance (i.e. excluding secondary platinum resistance), the difference in PFS was significantly in favour of arm 1 (HR = 0.55; P value 0.0425). Also in this subgroup, median survival for arm 1 was 11.8 months versus 7.8 months in arm 2.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation with stratification for ECOG PS, prior best response to platinum-based chemotherapy and bulky disease.
Allocation concealment (selection bias)	Low risk	Central allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not stated whether assessors were blind to group allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/60 women in the PLD arm did not receive any study drug and so were not included in the SAE analyses.
Selective reporting (reporting bias)	Unclear risk	OS was not reported as there was an insufficient number of death events at the time of reporting. We requested final OS data from Telik Inc but have as yet received no reply to our queries. Although immature OS data are not necessarily a high risk of selective reporting, this study completed over a decade ago, so this is judged to be at high risk of bias.
Other bias	Unclear risk	This trial closed early. Planned enrolment n = 244, actual enrolment n = 125. See notes above. As a result of the clinical hold, 35 patients (21 in combination arm and 14 in PLD arm) were not able to complete their assigned therapy as per protocol.

Banerjee 2018

Study characteristics

Methods	International, multicentre, randomised, open-label, phase II study
Participants	95 participants with PR ROC. No more than 1 previous CT for ROC

Banerjee 2018 *(Continued)*

	Inclusion criteria ≥ 18 years of age Eastern Cooperative Oncology Group (ECOG) performance status 0-1 Received no more than one line of chemotherapy for platinum resistant disease and up to three lines total Primary platinum-refractory disease defined as disease progression during or within 2 months of a first-line, platinum-containing chemotherapy regimen Suitable to start treatment with PLD Adequate organ function measured within 10 days of randomisation Highly effective form of contraception through the course of study treatment and for 6 months after the last dose of study treatment Willing and able to perform a patient-reported outcome survey **Exclusion criteria** Other malignancy within the last 5 years, except adequately treated squamous carcinoma of the skin, limited basal cell skin cancer, carcinoma in situ of the cervix or synchronous primary endometrial cancer or prior primary endometrial cancer Antitumor therapy, including chemotherapy, biologic, experimental, or hormonal therapy, within 4 weeks. Palliative radiation within 2 weeks. Major surgical procedure within 4 weeks. Prior anthracycline therapy, including prior treatment with PLD in any setting. Prior treatment with NaPi2b or SCL34A2 (solute carrier family 34 member 2 gene) targeted therapy. History of severe allergic or anaphylactic reactions to monoclonal antibody therapy (or recombinant antibody-related fusion proteins) Grade >1 toxicity (except alopecia and anorexia) from prior therapy or Grade >1 neuropathy from any cause Left ventricular ejection fraction below the lower limit of normal. Significant cardiovascular disease or pulmonary disease Untreated or active CNS metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control) Known active infection, or any major episode of infection requiring treatment with IV antibiotics or hospitalisation within 4 weeks Clinically significant liver disease, including viral or other hepatitis, current alcohol abuse, or cirrhosis. HIV seropositive status, hepatitis B or C Pregnant or breastfeeding
Interventions	**Intervention** Lifastuzumab 2.4 mg/kg IV every 3 weeks. **Control** PLD 40 mg/m^2 IV every 4 weeks.
Outcomes	**Primary outcome** PFS

Banerjee 2018 *(Continued)*

	Secondary outcomes ORR (RECIST) Duration of OR, OS, SAE Area under the concentration time curve lifastuzumab Maximum concentration of lifastuzumab Clearance of lifastuzumab Elimination half-time of lifastuzumab Volume of distribution at steady state of lifastuzumab Percentage of participants with anti-therapeutic antibodies against lifastuzumab
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Equal assignment to each of the two arms (1:1). Method not described.
Allocation concealment (selection bias)	Unclear risk	Method not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	95 patients randomised, 93 patients received at least one dose of study drug. At data cutoff there were 64 PFS events, 23 OS events, and 22 patients remained on study.
Selective reporting (reporting bias)	Low risk	Same outcome measures reported in study protocol and final results.
Other bias	Unclear risk	Funding by Genentech, Inc., South San Francisco, CA, USA (no grant number applies). Authorwise: PT, KL, ES, AV, YC, JCM, DJM, VL, YW, and EWH are employees of Genentech, Inc., and shareholders of Roche. There may be some bias that the study was funded by Genentech, done by Genentech, and produced by Roche.

CALYPSO

Study characteristics	
Methods	Phase III open-label multicentre non-inferiority RCT. Accrual from April 2005 to September 2007. (ID: NCT00538603)

CALYPSO *(Continued)*

Participants	976 women with PS ROC (recurrence > 6 months after first or second line platinum-based chemotherapy and had received a taxane). Included if ECOG ≤ 2; previous taxane therapy; measurable or assessable disease; life-expectancy of at least 12 weeks; and adequate bone marrow, renal and hepatic function. Patients with pre-existing peripheral neuropathy grade > 1 were excluded.
Interventions	**Intervention** (509 women): carboplatin (AUC 5) + PAC (175 mg/m^2) every 3 weeks **Control** (466 women): carboplatin (AUC 5) + PLD (30 mg/m^2) every 4 weeks Premedication of antiemetics (5HT agonist) and dexamethasone was to given to all women; those in the carboplatin /PAC arm also received clemastine and ranitidine.
Outcomes	**Primary outcome** PFS **Secondary outcomes** OS SAE QoL (QLQ C30 and OV 28) assessed at baseline, 3,6, 9 and 12 months
Notes	Overall, severe non-haematological toxicity occurred in 36.8% of the PAC/carboplatin arm compared with 28.4% of the PLD/carboplatin arm (P < 0.01). Significantly fewer severe allergic reactions (grade 3 to 4) were observed in the PLD/carboplatin arm than in the PAC/carboplatin arm: 2.4% versus 8.8%, respectively (P < 0.001) (in reference Joly et al. Gynecologic Oncology 2011;122(2):226-32). Significantly more women in the PAC/carboplatin arm discontinued treatment before six cycles had been completed (110/507 versus 70/466), mainly due to toxicity (73/507 women versus 27/466 women; P < 0.001). In total, 90% of women received post-progression treatment, 69% received two or more lines. The proportion of women in the PAC/carboplatin arm who received PLD as post-study therapy (68%) was significantly higher than the proportion of women in the PLD/carboplatin arm who received PAC (43%; P < 0.001); this may have influenced OS HRs in the direction of the PAC/carboplatin arm. We obtained unpublished data on non-haematological adverse effects (grade 3 to 4) from the investigators.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally randomised. Randomisation was in permuted blocks of 6, with stratification by measurable disease, treatment-free interval (6 to 12 versus > 12 months) and centre.
Allocation concealment (selection bias)	Low risk	Central allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.

CALYPSO *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Evaluation assessments were independently reviewed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition for survival and toxicity outcomes. Regarding QoL data, 79% of women in the carbo/PAC arm and 84% of women in the carbo/PLD arm had QoL data at baseline and one other point in the study. The most complete data set (< 20% missing data) was available at 3 months post-randomisation, therefore we used these data.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.
Other bias	Unclear risk	Baseline characteristics were similar and arms were well balanced for stratification factors. Imbalance in treatment allocation (509 versus 467) was consistent with chance. Industry funded "Supported by a research grant from Schering-Plough" and COI statement as follows: "Employment or Leadership Position: None Consultant or Advisory Role:Jalid Sehouli, Ovarian Cancer (C); Gunnar Kristensen, Boehringer Ingelheim (C), AstraZeneca (C), Roche (C); Christian Jackisch, Essex Pharma Germany (C), Schering-Plough (C) Stock Ownership: None Honoraria: Eric Pujade-Lauraine, Schering-Plough; Uwe Wagner, Essex Pharma GmbH; Mark Heywood, Schering-Plough Canada; Sandro Pignata, Schering-Plough, Roche; Jalid Sehouli, GlaxoSmithKline, Essex Pharma; Gunnar Kristensen, Schering-Plough; Andreas du Bois, Schering-Plough Research Funding: Sandro Pignata, ATRC; Jalid Sehouli, Ovarian Cancer; Andreas du Bois, Schering-Plough, GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca, Eli Lilly Expert Testimony: None Other Remuneration: Uwe Wagner, Essex Pharma GmbH"

Colombo 2012

Study characteristics	
Methods	Phase III open-label RCT conducted in 22 countries; accrual between November 2005 and March 2009 ID: NCT00262990
Participants	829 women with PR ROC following ≤ 3 platinum-taxane based regimens. Measurable and non-measurable disease (but CA125 elevated at baseline); ovarian, fallopian and primary peritoneal cancer included. Excluded if peripheral neuropathy, unresolved bowel obstruction or diarrhoea within 7 days of start of treatment.
Interventions	**Intervention** PAT (10 mg/m^2) IVI q3wk **Control** PLD (50 mg/m^2) IVI q4wk No routine premedication was given to either arm.
Outcomes	**Primary outcome** OS **Secondary outcomes**

Colombo 2012 *(Continued)*

	PFS
	ORR
	SAE
Notes	Women were assessed 8-weekly; median follow-up was 27 months.
	Arms received a median of 4.5 and 3 cycles for PAT and PLD respectively.
	Median TTP was 15.9 weeks for both arms.
	Median time to death was 56.6 weeks versus 54.4 weeks in favour of PAT.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation.
Allocation concealment (selection bias)	Low risk	Allocation via an interactive voice response system.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded central review of results.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Very few women lost to follow-up and low attrition (< 20%) in most analyses. As with other studies, QoL data suffered from high attrition rates, and therefore we could not use it in the meta-analyses.
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported.
Other bias	Unclear risk	Baseline characteristics were similar. Supported by Novartis Pharmaceuticals (clinical studies and medical editorial assistance). Conflicts of interst statements "Employment or Leadership Position: Dirk Weber, Novartis Pharmaceuticals (C); Mona El-Hashimy, Novartis Pharmaceuticals (C); Farida Souami, Novartis Pharmaceuticals (C); Patricia Wing, Novartis Pharmaceuticals (C) Consultant or Advisory Role: Aristotelis Bamias, Novartis Pharmaceuticals (C) Stock Ownership: Dirk Weber, Novartis Pharmaceuticals; Mona El-Hashimy, Novartis Pharmaceuticals; Jingjin Li, Novartis Pharmaceuticals; Patricia Wing, Novartis Pharmaceuticals Honoraria: Aristotelis Bamias, Novartis Pharmaceuticals Research Funding: None Expert Testimony: None Other Remuneration: None".

CORAIL

Study characteristics

CORAIL *(Continued)*

Methods	Randomised international multicentre phase III study
Participants	442 participants with PR ROC **Inclusion criteria** Histologically or cytologically confirmed unresectable epithelial ovarian, primary peritoneal or fallopian tube cancer. ≥ 18 years of age Measurable disease by RECIST criteria Eastern Cooperative Oncology Group (ECOG) performance status 0-2 Received no more than three lines of chemotherapy Platinum refractory or platinum sensitive disease (PFI < 1 or > 6 m) Adequate organ function Not pregnant and on medically acceptable form of contraception Voluntary, written informed consent **Exclusion criteria** Other malignancy within the last 3 years, except curatively treated basal cell carcinoma or squamous cell carcinoma of the skin, carcinoma in situ of the breast or cervix Therapy within 3 weeks Prior therapy with PM01183, trabectedin, or with both PLD and topotecan Grade ≤ 1 from any previous treatment (excluding grade ≤ 2 alopecia or peripheral neuropathy) History of cardiac disease Bowel obstruction Brain or leptomeningeal metastases Active uncontrolled infection Patients with any immunodeficiency, HIV, hepatitis or cirrhosis, hepatitis B or C Pregnant or breastfeeding
Interventions	**Intervention** Lurbinectedin given 3.2 mg/m^2 IV as a 1-hour infusion on Day 1 every 3 weeks (3 weeks = one treatment cycle) **Control** PLD given if previous treatment with topotecan, or topotecan given if previous treatment with PLD. PLD (50 mg/m^2, every 4 weeks) or topotecan (1.5 mg/m^2, every 3 weeks)
Outcomes	**Primary outcome** PFS **Secondary outcomes** PFS

CORAIL *(Continued)*

	OS
	ORR
	DoR
	Best response according to Ca 125
	AE & SAE
	All-cause mortality
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation method using Medidata Balance, 1:1.
Allocation concealment (selection bias)	Low risk	Randomised allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Unblinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reported on planned outcomes.
Selective reporting (reporting bias)	Low risk	Planned outcome data complete.
Other bias	Unclear risk	Study sponsored by PharmaMar, manufacturers of Lurbinectedin.

Fujiwara 2019

Study characteristics

Methods	A phase II multicentre, open-label, randomised controlled study in Japan
Participants	100 women with PS ROC, > 19 years, PS ≤ 2, life expectancy at least 4 months, and adequate bone marrow, renal, and hepatic function. **Inclusion criteria** Ovarian, primary peritoneal or fallopian tube cancer ≥ 20 years of age Measurable disease or assessable lesions by RECIST criteria

Fujiwara 2019 *(Continued)*

	Eastern Cooperative Oncology Group (ECOG) performance status 0-2 Adequate bone marrow and organ function Life expectancy of 16 weeks or more **Exclusion criteria** Elevated CA125 without measurable disease or assessable lesions
Interventions	**Intervention** PLD 30 mg/m^2 plus carboplatin AUC 5 mg/ mL/min on day 1, every 4 weeks **Control** GEM 1000 mg/m^2 on days 1 and 8 plus carboplatin AUC 4 mg/mL/min on day 1, every 3 weeks for at least 6 cycles
Outcomes	**Primary outcome** PFS 6 month/1 year survival rate **Secondary outcomes** ORR OS SAE Dose administration
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned.
Allocation concealment (selection bias)	Low risk	Centrally randomised.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Results reported for response efficacy 42/49 and 39/50.

Fujiwara 2019 *(Continued)*

Selective reporting (reporting bias)	Low risk	Planned outcomes reported.
Other bias	Unclear risk	Janssen supported study and is producer of PLD.

Gordon 2001

Study characteristics	
Methods	Phase III multicentre open-label RCT with 104 sites in the USA and Europe that recruited participants between May 1997 and March 1999.
Participants	481 women with ROC (PS or PR) who had recurred or failed first-line platinum-based chemotherapy; with measurable disease, or measurable and assessable disease; adequate bone marrow, renal, hepatic and cardiac function; Karnofsky performance status ≥ 60%; expected to live > 3 months
Interventions	**Intervention** PLD 50 mg/m^2 IV over 1 hour, every 4 weeks **Control** TOP 1.5 mg/m^2/d IV over 30 min x 5d, every 3 weeks
Outcomes	**Primary outcome** PFS **Secondary outcome** ORR, OS, SAE, QoL (QLQ-C30)
Notes	Seven women received no treatment after randomisation and were excluded from most analyses. G-CSF was given to women who experienced febrile neutropenia, prophylactically in the following cycles; 29.1 % TOP versus 4.6% PLD received G-CSF. The Investigators concluded that PLD was the treatment of choice among non-platinum agents for women with ROC, especially platinum-sensitive disease. 72% and 74% of women in the TOP and PLD groups, respectively, received prior taxane therapy. Median TTP was 17 weeks versus 16.1 weeks in favour of the TOP arm. Median time to death was 59.7 weeks versus 62.7 weeks in favour of the PLD arm.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central randomisation; stratified by platinum sensitivity and bulky disease.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described.
Blinding of participants and personnel (performance bias)	High risk	Open-label.

Gordon 2001 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Independent radiological review used for primary outcome (PFS).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition low for primary outcomes (high for QoL data).
Selective reporting (reporting bias)	Low risk	All expected outcomes reported. Censoring = 13%.
Other bias	Unclear risk	Funded by drug manufacturer.

HeCOG 2010

Study characteristics	
Methods	Phase II RCT of the Hellenic Cooperative Oncology Group. Accrual from October 1999 to December 2005.
Participants	189 women with PS ROC (≥ 6 months after platinum-based chemotherapy). Included if ECOG 0-2; life expectancy ≥ 3 months; and adequate bone marrow, renal, hepatic function. Patients with residual neurotoxicity from previous platinum and/or taxane chemotherapy and those with other cancers were excluded.
Interventions	**Intervention** Carboplatin (AUC 5) + PAC 175 mg/m^2 over 3 hours, every 3 weeks **Control** Carboplatin (AUC 5) + PLD 45 mg/m^2, every 4 weeks Standard premedication included dexamethasone, dyphenhydramine and ranitidine for both groups, although the PAC group received both an oral (12 hours prior) and an IV dose (30 min prior to PAC administration). Six cycles intended.
Outcomes	**Primary outcome** ORR (WHO criteria or CA-125 Rustin's criteria) and toxicity **Secondary outcomes** TTP OS
Notes	204 women were randomised but 15 were subsequently considered to be ineligible and excluded. Median follow-up 43.6 months (95% CI 0.1 to 74.8). 88% and 93%, respectively, received previous taxane-containing therapy.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

HeCOG 2010 *(Continued)*

Random sequence generation (selection bias)	Low risk	Central randomisation.
Allocation concealment (selection bias)	Low risk	Central randomisation/allocation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition (< 20%). Fifteen post-randomisation exclusions due to non-eligibility including other cancers, non-measurable disease without CA-125 elevations. Eleven lost medical records, (5 in CP arm and 6 in CLD arm); 8 and 5 women lost to follow-up respectively.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported.
Other bias	Low risk	None noted. Baseline characteristics were similar.

JAVELIN Ovarian 200

Study characteristics	
Methods	Phase 3, randomised, open-label study, multicentre, international (USA, Australia, Austria, Belgium, Canada, Czechia, Denmark, France, Greece, Honk Kong, Hungary, Ireland, Israel, Italy, Japan, Korea, Netherlands, Norway, Poland, Russia, Singapore, Spain, Switzerland, Taiwan, United Kingdom)
Participants	566 women with PR ROC **Inclusion criteria** Histologically confirmed epithelial ovarian, primary peritoneal or fallopian tube cancer, including malignant mixed Müllerian tumors with high grade serous component. ≥ 18 years of age Measurable disease by RECIST criteria that has not previously been irradiated Received up to three lines of chemotherapy for platinum sensitive disease, most recently platinum containing, and no prior systemic therapy for platinum resistant disease **Exclusion criteria** Non epithelial tumor or ovarian tumors with low malignant potential (ie, borderline tumors). Other malignancy within the last 5 years, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or of the cervix. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti CD137, or anti-cytotoxic T lymphocyte associated antigen 4 antibody Severe gastrointestinal conditions such as bowel obstruction, or uncontrolled diarrhoea within 4 weeks or history of inflammatory bowel disease.

JAVELIN Ovarian 200 *(Continued)*

	Symptomatic brain metastases requiring steroids Active autoimmune disease that might deteriorate when receiving an immunostimulatory agents
Interventions	Randomisation 1:1:1 **Arm 1** n = 188 Avelumab 10 mg/kg monotherapy as a 1-h IV infusion once every 2 weeks **Arm 2** n = 188 Avelumab 10 mg/kg every 2 weeks plus PLD 40 mg/m2 every 4 weeks, each as 1-h IV infusions **Arm 3** n = 190 PLD 40 mg/m^2 alone as a 1-h IV infusion every 4 weeks.
Outcomes	**Primary outcomes** OS PFS **Secondary outcomes** ORR (BICR and investigator) PFD (RECIST) DoR (BICR) Disease control SAE TEAE QoL (EORTC QLQ-C30) Time to deterioration in abdominal/GI Symptom (subscale of EORTC QLQ-OV28) Change from baseline in EQ-VAS score at end of treatment
Notes	**Main result** The checkpoint inhibitor, avelumab, alone or with PLD, did not significantly improve PFS or OS versus PLD.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignment by Interactive Response Technology (IRT) system in 1:1:1 ratio to avelumab alone (Arm A), avelumab plus PLD, (Arm B) or PLD alone (Arm C).
Allocation concealment (selection bias)	Low risk	Central randomisation.
Blinding of participants and personnel (performance bias)	High risk	Open-label study.

JAVELIN Ovarian 200 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessed by blinded independent central review (BICR).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Flow table provided, with all patients included in full analysis set.
Selective reporting (reporting bias)	Low risk	Outcomes on study protocol and outcomes on published results match.
Other bias	Unclear risk	The study was sponsored by Pfizer.

Kaye 2012

Study characteristics	
Methods	Phase II open-label multicentre RCT; 1:1:1 ratio (ID: NCT00628251)
Participants	97 women with ROC within 12 months of receiving platinum-based chemotherapy with confirmed BRCA1/2 germline mutations; one or more measurable lesion; ECOG PS 0-2; estimated life expectancy ≥ 16 weeks; adequate bone marrow, hepatic and renal function. Excluded if previous PARP inhibitors or anthracyclines; brain metastases; other malignant disease; persistent toxic effects of treatment; LVEF < 50%
Interventions	**Arm 1** OLA 200 mg twice daily continuously (32 women) **Arm 2** OLA 400 mg twice daily continuously (32 women) **Arm 3** PLD 50 mg/m^2 IVI every 4 weeks (33 women)
Outcomes	**Primary outcome** PFS (RECIST-assessed) **Secondary outcomes** ORR Duration of treatment response Tumour size OS SAE QoL (FACT-O)
Notes	PARP nuclear enzymes facilitate DNA repair. Olaparib is a PARP inhibitor selective for homologous-recombination-deficient cells, such as those with BRCA1/2 deficiency.

Kaye 2012 *(Continued)*

The primary outcome was reported for the olaparib arms combined and individually, versus the PLD arm. We used the results from the OLA 400 mg arm versus PLD. Median time to progression was 38 weeks versus 30 weeks in favour of OLA. Median time to death was not calculable for the OLA group and was 76 weeks for the PLD group (unpublished data).

Corticosteroids and serotonin antagonists were given to 22/33 (67%) and 14/33 (42%) of the women in the PLD group respectively versus 12.5 % and 12.5% of the OLA group respectively, but it was not possible to determine whether they were given as premedication or at another time (unpublished information).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, block randomisation, stratified according to BRCA status and platinum sensitivity (≤ 6 months and > 6 months).
Allocation concealment (selection bias)	Low risk	Allocation via an Interactive Voice Response System.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	'Centrally reviewed tumour assessments' were used for analyses; investigator-assessed primary outcome; assessor blinding/independence not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	In the PLD arm, 5/33 discontinued treatment for unknown reasons versus 1/64 in the olaparib arm. Otherwise, attrition rates seem low.
Selective reporting (reporting bias)	Low risk	All expected outcomes reported. Results are not reported for platinum-sensitive subgroups; these data were requested from the lead investigator on the 6 December 2012.
Other bias	Unclear risk	Baseline characteristics were similar except that more women in Arm 2 had received > 2 prior chemotherapy regimens. The study was supported by AstraZeneca, the manufacturer of Olaparib. Employment or Leadership Position: Mark Wickens, AstraZeneca (C); Elizabeth S. Lowe, AstraZeneca (C); James Carmichael, AstraZeneca (C) Consultant or Advisory Role: Stan B. Kaye, AstraZeneca (C); Charlie Gourley, GlaxoSmithKline (C), Roche (C), Schering-Plough (C); Michael Friedlander, AstraZeneca Advisory Board (C); Bella Kaufman, AstraZeneca (U) Stock Ownership: Mark Wickens, AstraZeneca; Elizabeth S. Lowe, AstraZeneca; James Carmichael, AstraZeneca Honoraria: Stan B. Kaye, AstraZeneca Advisory Board; Charlie Gourley, Chugai Pharmaceutical, GlaxoSmithKline, PharmaMar, Roche, Schering-Plough Research Funding: Ursula Matulonis, AstraZeneca; Charlie Gourley, AstraZeneca; Beth Y. Karlan, AstraZeneca; Michael Friedlander, AstraZeneca Expert Testimony: None Other Remuneration: Charlie Gourley, MSD (Schering-Plough), PharmaMar

M200

Study characteristics	
Methods	Multicentre open-label RCT; enrolment in the USA from July 2007 to Oct 2008. (ID: NCT00635193)
Participants	127 women with stage III/IV PS or PR ROC. Maximum of 2 prior chemotherapy treatments (at least one of which was platinum/taxane based); at least one measurable lesion to assess response by RECIST.
Interventions	Volociximab (M200) is an anti-angiogenic integrin inhibitor/monoclonal antibody. Two dosage regimes were tested combined with PLD versus PLD alone: **Arm 1** PLD 40 mg/m^2 every 4 weeks (66 women) **Arm 2** M200 15 mg/kg weekly + PLD 40 mg/m^2 every 4 weeks (34 women) **Arm 3** M200 15 mg/kg every 2 weeks + PLD 40 mg/m^2 every 4 weeks (27 women)
Outcomes	Efficacy, safety and tolerability
Notes	No useable data. Results were reported as follows: "The most common Grade 3 to 4 AEs (≥ 5% in any group) were abdominal pain, intestinal obstruction, ascites, fatigue, hypoalbuminemia, and cytopenias. The incidence of AEs was balanced across treatment groups. There were no CRs; PRs were 16%, 18%, and 19%....Preliminary analysis of PFS suggested that there was a low probability of detecting a statistically significant difference in favor of V [Volociximab] +PLD, so the study was closed to enrollment."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Efficacy and safety were not clearly detailed in the ASCO 2009 abstract which is the only publication for this study.
Selective reporting (reporting bias)	High risk	Baseline data were not reported. Study outcomes not reported, except in abstract.
Other bias	High risk	Funding: Biogen Idec and Protein Design Labs, Inc.

M200 *(Continued)*

	Limited information was available and results have not been published in full. Dr Obrocea of Abbott Laboratories was emailed on 28 November 2012 for final study data.

McGuire 2018

Study characteristics	
Methods	Randomised multicentre open-label phase II study
Participants	123 participants with PR ROC from the USA, UK and Spain. They were recruited between June 2009 and February 2014. **Inclusion criteria** Histologically or cytologically confirmed epithelial ovarian, primary peritoneal, fallopian tube cancer, or ovarian clear cell carcinoma Measurable disease by RECIST Eastern Cooperative Oncology Group (ECOG) performance status 0-1 Adequate bone marrow, organ function and echocardiogram Informed consent Effective form of contraception **Exclusion criteria** Increased CA125 in the absence of concomitant clinical or radiographic progression Other malignancy within the last 3 years except curatively resected non-melanomatous skin cancer, curatively treated cervical carcinoma in-situ or other primary solid tumour treated with curative intent Major surgery, open biopsy or significant traumatic injury within the last 4 weeks. Participation in clinical trials of experimental agents within 4 weeks Prior treatment with more than 1 biologic and/or more than one hormonal therapy Prior treatment with other agents targeting PDGF or PDGF receptor. Received an anthracycline for any indication in the past. Radiotherapy, chemotherapy, or biologic therapy directed at the malignant tumour within 3 weeks prior to randomisation, or hormonal therapy directed at the malignant tumour within 1 week. Known allergies to compounds of chemical or biologic composition similar to that of IMC-3G3 Current Grade > 1 toxicity or ≥ Grade 2 side effects due to agents administered more than 28 days prior to randomisation. Unstable angina pectoris, angioplasty, cardiac stenting, or myocardial infarction 6 months prior to randomisation. Uncontrolled symptomatic congestive heart failure, uncontrolled hypertension, clinically significant arrhythmia Suspected impending bowel obstruction Brain metastases of leptomeningeal disease Uncontrolled intercurrent illness including, serious or nonhealing active wound, ulcer, or bone fracture.

McGuire 2018 *(Continued)*

	HIV seropositive status
	History of uncontrolled hereditary or acquired bleeding or thrombotic disorders
	Psychiatric illness/social situations that would limit compliance with study requirements
	Pregnant or breastfeeding
Interventions	**Intervention**
	Olaratumab (20 mg/kg IV every 2 weeks and PLD (40 mg/m^2 every 4 weeks)
	Control
	PLD (40 mg/m^2 every 4 weeks)
Outcomes	**Primary outcome**
	PFS
	Secondary outcomes
	OS
	ORR
	DoR
	Safety
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study site personnel randomised patients using either a call-in Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS). The IVRS/ IWRS assigned a unique identification number to each patient.
Allocation concealment (selection bias)	Low risk	Study site personnel randomized patients using either a call-in Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS). The IVRS/ IWRS assigned a unique identification number to each patient.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Patients underwent radiographic disease assessment approximately every 8 weeks. Not described how this was assessed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was one patient lost to follow-up.
Selective reporting (reporting bias)	Low risk	Study registered at clinicaltrials.gov. Outcomes reported in study protocol match outcome reported in results paper.
Other bias	Unclear risk	This work was sponsored by ImClone System LLC, a wholly owned subsidiary of Eli Lilly and Company. The study was designed by the funder, ImClone /Eli

McGuire 2018 *(Continued)*

	Lilly and Company, with input from ovarian cancer experts. The data were analysed and interpreted by ImClone /Eli Lilly and Company in collaboration with the academic authors. All authors had access to all the data and vouch for the accuracy and completeness of the data and analyses reported and for the fidelity of the study to the study protocol. All authors had final responsibility for the decision to submit for publication. All authors participated in the drafting of the manuscript and/or critical revisions of subsequent drafts. Writing and editorial assistance was provided by Syneos Health on behalf of ImClone / Eli Lilly and Company.

MITO-3

Study characteristics	
Methods	Phase III multicentre RCT; accrual from January 2003 to January 2007.
Participants	153 women with ROC that had relapsed within 12 months (PPS and PR ROC) of receiving one platinum/paclitaxel regimen. Women had measurable or assessable disease (RECIST), adequate hepatic, renal, cardiac and bone marrow function, no prior malignancies, and were expected to live > 3 months.
Interventions	**Intervention** GEM (1000 mg/m^2) days 1, 5, 8, 15, every 4 weeks **Control** PLD (40 mg/m^2) IVI, every 4 weeks Methylprednisolone 20 mg was given as premedication to the PLD arm.
Outcomes	**Primary outcome** Time to progression **Secondary outcomes** OS ORR SAE QoL (QLQ-C30)
Notes	Trial used a lower (40 mg/m^2) dose of PLD to minimise SAEs. Post-progression treatment was only documented in 36 participants so OS data difficult to interpret. Median TTP was 20 weeks versus 16 weeks in favour of GEM. Median time to death was 51 weeks versus 56 weeks in favour of PLD. HR for OS and PFS not given but requested from Dr Ferrandina on 3 December 2012.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central randomisation.

MITO-3 *(Continued)*

Allocation concealment (selection bias)	Low risk	Random assignment by central telephone service.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and physicians not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	Primary outcome was TTP. PFS/OS were not reported clearly with HRs, but we were able to obtain these from the investigators in January 2013. 79% of participants completed the QoL questionnaire.
Other bias	Low risk	Treatment groups were well-balanced for baseline characteristics.

Monk 2017

Study characteristics	
Methods	Phase II, randomised controlled trial, double-blinded, multicentre in the USA.
Participants	297 participants (148 in experimental Arm; PLD + VTX-2337, 149 in control Arm; PLD + placebo) **Inclusion criteria** Recurrent or persistent epithelial ovarian, primary peritoneal or fallopian tube carcinoma. Serous adenocarcinoma, endometrioid adenocarcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial adenocarcinoma, transitional cell carcinoma, malignant Brenner's tumour or adenocarcinoma not otherwise specified. Measurable disease by RECIST Eastern Cooperative Oncology Group (ECOG) performance status 0-1 No more than one cytotoxic regimen for management of recurrent or persistent disease or one biologic/targeted therapy Received a platinum-based chemotherapeutic regimen for management of primary disease containing carboplatin, cisplatin or another organoplatinum compound Adequate bone marrow and organ function Recovered from effects of recent surgery, radiotherapy or chemotherapy Free of active infection Informed consent Effective form of contraception Any prior radiation therapy must be completed at least four weeks prior to registration **Exclusion criteria**

Monk 2017 *(Continued)*

	Other malignancy within the last 3 years, except for non-melanoma skin cancer Radiotherapy or chemotherapy within the last 3 years other than for ovarian, fallopian tube or primary peritoneal cancer Chemotherapy, biologic/targeted agents and immunologic agents, within 3 weeks Hormonal therapy within the last 1 week Investigational agent within the last 4 weeks Prior treatment with VTX-2337, doxorubicin, PLD, or any other anthracycline. Clinically significant cardiovascular disease Gastrointestinal obstruction Requiring parenteral hydration or nutrition Brain metastases or primary brain tumour, seizures not controlled with standard medical therapy, cerebrovascular accident, transient ischaemic attack or subarachnoid haemorrhage within six months Current or use in last 2 weeks of corticosteroids or requiring systemic immunosuppressive therapy Active autoimmune disease Pregnant or breastfeeding
Interventions	Randomisation 1:1 **Intervention** PLD 40 mg/m^2 plus VTX-2337 - PLD on Day 1 plus VTX-2337 on Day 3, Day 10, and Day 17 for the first 4 cycles. Starting with cycle 5, the dose regimen will be PLD on Day 1 plus VTX-2337 on Day 3 only, without additional doses of VTX-2337 on Days 10 and Day 17. **Control** PLD 40 mg/m^2 plus placebo. The starting dose schedule is PLD on Day 1 plus placebo on Day 3, Day 10, and Day 17 for the first 4 cycles. Starting with cycle 5, the dose regimen will be PLD on Day 1 plus placebo on Day 3 only.
Outcomes	**Primary outcome** OS **Secondary outcomes** PFS AE- frequency and severity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified how sequence was generated.
Allocation concealment (selection bias)	Unclear risk	Not specified how allocation was done.

Monk 2017 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of both participants and personnel, use of placebo.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participant flow data provided in clinicaltrials.gov does not suggest high risk of bias.
Selective reporting (reporting bias)	Low risk	Outcomes on study protocol on clinicaltrials.gov similar to those reported in the results paper.
Other bias	Unclear risk	Study sponsored by VentiRx Pharmaceuticals. Principal Investigators are not employed by the organisation sponsoring the study. There is not an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

Monk 2020

Study characteristics	
Methods	Open-label, randomised, active-controlled phase 3 study International, multicentre
Participants	n = 576 **Inclusion criteria** Histologically confirmed epithelial ovarian cancer, primary peritoneal or fallopian tube cancer ≥ 18 years of age Measurable disease by RECIST Eastern Cooperative Oncology Group (ECOG) performance status 0-1 Received no more than 2 lines of systemic therapy Second-line treatment with a platinum-based regimen, with progression of disease after attaining a complete or partial response Progression of disease based on imaging after the second-line platinum-based regimen Adequate bone marrow, organ function and echocardiogram Side effects of prior treatment resolved to at least Grade 1 Effective form of contraception and negative pregnancy test at screening **Exclusion criteria** Mucinous histology Other malignancy within the last 3 years, except for non-metastatic basal cell or squamous cell skin cancer, or non-invasive malignancy requiring ongoing therapy

Monk 2020 *(Continued)*

	Radiation therapy, experimental therapy, hormonal therapy, prior chemotherapy or biological therapy within the last 3 weeks Prior treatment with more than 2 lines of systemic therapy Prior treatment with doxorubicin or other anthracycline at cumulative doses greater than 300 mg/m^2 Currently enrolled in an investigational study Known allergies, hypersensitivity, or intolerance to PLD, dexamethasone, or their excipients Myocardial infarction within 6 months, unstable angina, NYHA class II or greater heart failure, severe uncontrolled ventricular arrhythmias, clinically significant pericardial disease, ECG evidence of acute ischaemic or conductive system abnormalities Uncontrolled seizures Active systemic infection likely to interfere with study Significant chronic liver disease Uncontrolled diabetes Newly diagnosed DVT Psychiatric disorder, including dementia, that prevents compliance with protocol Pregnant or breastfeeding
Interventions	**Intervention** PLD 30 mg/m^2 for 1.5 hrs followed by trabectedin 1.1 mg/ m^2 for 3 hrs every 3 weeks **Control** PLD 50 mg/m^2 for 1.5 hrs every 4 weeks
Outcomes	**Primary outcome** OS **Secondary outcomes** PFS ORR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants randomly assigned in 1:1 ratio to treatment groups based on a computer-generated randomisation schedule prepared before the study by or under the supervision of the sponsor.
Allocation concealment (selection bias)	Low risk	The interactive voice response system (IVRS) and/or interactive web response system (IWRS) assigned a unique treatment code, which dictated the treatment assignment and matching study drug kit for the subject.

Monk 2020 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study - the requirement of a central venous catheter, limited to the combination trabectedin+DOXIL arm, precludes blinded treatment in this study.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding not possible due to drug delivery method.
Incomplete outcome data (attrition bias) All outcomes	Low risk	14% attrition due to loss to follow-up/withdrawal from study 289 enrolled in experimental arm, and 286 received treatment. 287 enrolled in standard arm, and 282 received treatment.
Selective reporting (reporting bias)	Low risk	Study protocol outcomes and results paper outcome match.
Other bias	Unclear risk	Study sponsored by Janssen, manufacturers of Caelyx

Mutch 2007

Study characteristics	
Methods	Phase III open-label multicentre RCT; accrual from July 2002 to May 2004 at 44 sites in the USA.
Participants	195 women with PR ROC who had received 1 to 2 prior platinum-based chemotherapy regimens with measurable (RECIST) or assessable disease (Zubrod performance status of 0 to 2 and adequate bone marrow, hepatic and neurological function.
Interventions	**Intervention** GEM (1000 mg/m^2) IV day 1 and day 8, every 3 weeks **Control** PLD (50 mg/m^2) IV every 4 weeks
Outcomes	**Primary outcome** PFS **Secondary outcomes** OS SAE (NCI-CTCAE v 2.0) QoL (FACT-O)
Notes	If participants experienced disease progression, unacceptable toxicity or if cumulative PLD dose exceeded 500 mg/m^2, they crossed over to the alternative drug. Median follow-up was 29.2 months. 99% of women had received prior taxane. Median TTP was 15.4 weeks versus 13.3 weeks in favour of the GEM arm. Median time to death was 54.4 versus 57.9 weeks in favour of the PLD arm.

Mutch 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation.
Allocation concealment (selection bias)	Low risk	Central allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Independent assessment/blinding not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of events/(total number evaluated) and censoring was not described for the primary outcome (PFS) or OS. Attrition for QoL outcomes not reported. Additional data requested from authors 4 December 2012.
Selective reporting (reporting bias)	High risk	HRs, number of events, and censoring was not described for the primary outcome (PFS) or OS. Limited (non-comparative) QoL data reported. Additional data requested from authors 4 December 2012.
Other bias	Unclear risk	Study funded by drug manufacturers

NCT00653952

Study characteristics

Methods	Phase 3, randomised, open-label study
Participants	The study was halted to new recruits in 1999 due to low accrual after 50% of planned participants were recruited (216 participants). **Inclusion criteria** • ≥ 18 years • Histologically proven (i.e. not borderline) epithelial ovarian carcinoma • Measurable disease • Recurrence of disease or disease progression indicative of failure of first-line platinum-based chemotherapy (PS or PR but number in each not given) • Disease-free from prior malignancies for > 5 years with the exception of curatively treated basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix • Adequate renal creatinine (< 2.5 mg/dL (< 220 µmol/L)) & liver function (aspartate amino transferase (AST) and alanine amino transferase (ALT) < 2 x upper limit of normal, alkaline phosphatase < 2.0 x upper limit of normal, except if attributed to tumour, and bilirubin < upper limit of normal) **Exclusion criteria** • Pregnant or breast-feeding • Life expectancy of < 3 months

NCT00653952 *(Continued)*

- Prior radiation therapy to more than one-third of haematopoietic sites within 30 days prior to first dose of study drug
- Prior therapy with PLD or paclitaxel
- Prior chemotherapy within 28 days of first dose of study drug (or 42 days if subject has received a nitrosourea or mitomycin)
- Treated with high dose therapy supported by bone marrow or peripheral stem cell transplantation at any time

Interventions	PLD (50 mg/m^2) every 28 days for up to 1 year versus Paclitaxel (175 mg/m^2) Day 1 every 3 weeks
Outcomes	**Primary outcome** Time to progression (TTP) **Secondary outcomes** Response rates Time to response Duration of response Quality of life assessment Survival
Notes	Terminated in 2010 due to poor accrual. Results released online. https://yoda.yale.edu/sites/default/files/nct00653952.pdf https://clinicaltrials.gov/ct2/show/NCT00653952?term=nct00653952&draw=2&rank=1 Previous abstract (O'Byrne 2002 in previous review) stated "This study is listed as 'Terminated' on the NCT registry after enrolling 220 women." The only published report is an ASCO 2002 abstract which had no data that could be included in our meta-analyses. Results were reported as follows: "A preliminary analysis indicates that the overall progression-free survival rates are similar between the two arms (PLD: 21.7 versus paclitaxel: 22.4 weeks; P = 0.15). The overall response rates for PLD and paclitaxel are 17.8% and 22.4%, respectively (P = 0.34). Median overall survival times are 45.7 weeks for PLD and 56.1 weeks for paclitaxel (P = 0.44). No significant difference was seen in median progression-free or overall survival for platinum sensitive or refractory patients in either treatment arm. The overall number of adverse events was equivalent in either arm. Nausea and vomiting, stomatitis and plantar-palmar erythrodysesthesia were seen more frequently with PLD whereas alopecia, myalgia, arthralgia and paraesthesiae occurred more commonly with paclitaxel. These findings clearly indicate that PLD has comparable efficacy to paclitaxel in taxane naive patients with ROC. PLD may be particularly suitable for those patients with musculoskeletal disorders or for whom the prospect of alopecia has a significant adverse psychological effect."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not provided.
Allocation concealment (selection bias)	Unclear risk	Details not provided.

NCT00653952 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details not provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	AE data reported for all 216, although initial abstract stated 220 recruited.
Selective reporting (reporting bias)	High risk	The study was terminated due to poor accrual after approximately 50% of the planned subjects had been entered. Therefore, efficacy analyses were limited to overall survival only, pursuant to an agreement with the Oncology Division.
Other bias	High risk	Study terminated early due to poor accrual. Data available online but not published in peer-reviewed journal, as far as we have been able to ascertain. Study sponsored by Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

NCT01840943

Study characteristics	
Methods	Phase III randomised control trial Multicentre - China
Participants	n = 32 **Inclusion criteria** Histologically confirmed epithelial ovarian cancer Measurable disease Received no more than one platinum based chemotherapy Demonstrate adequate organ function and echocardiogram Effective form of contraception Other invasive malignancy within the past 5 years except curatively treated basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix **Exclusion criteria** Chemotherapy within 4 weeks Prior therapy with PLD or topotecan Myocardial infarct within 6 months, class II or greater heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, clinically significant pericardial disease Uncontrolled systemic infection that requires systemic treatment

NCT01840943 *(Continued)*

	Pregnant or breastfeeding or planning to become pregnant while enrolled in this study or within 1 year after the last dose of study medication
Interventions	**Intervention** IV PLD 50 mg/m^2 Day 1 of each cycle as: 60 to 90-minute infusion to the participants not undergoing pharmacokinetic (PK) evaluation and 90-minute infusion to the participants undergoing PK evaluation **Outcome** IV topotecan (TOP) 1.25 mg/m^2 per day administered for 30 minutes duration, on Day 1 to Day 5 of each cycle.
Outcomes	**Primary outcome** PFS **Secondary outcomes** OS Duration of PFS Number of participants With response Time to response Duration of response Health-related quality of life assessment (HQL) Maximum plasma concentration of PLD Time to reach the maximum plasma concentration of PLD Area under the plasma concentration of PLD Apparent terminal elimination half-life of plasma concentration of PLD Apparent terminal elimination rate constant of plasma concentration of PLD Systemic clearance of plasma concentration of PLD Apparent volume of distribution of plasma concentration of PLD Number of participants with adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not specified.
Allocation concealment (selection bias)	Unclear risk	Allocation methods not specified.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unblinded trial.

NCT01840943 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of assessors.
Incomplete outcome data (attrition bias) All outcomes	High risk	PLD 14: withdrawal 5; physician decision 4; lost to follow-up 4. Topotecan 12: withdrawal 6; physician decision 2; lost to follow-up 4.
Selective reporting (reporting bias)	High risk	Extremely low numbers and incomplete compared to planned protocol.
Other bias	High risk	Study overall at extremely high risk of bias. Study funded by Xian-Janssen Pharmaceutical Ltd.

OVA-301

Study characteristics	
Methods	Phase III multicentre RCT (21 countries); recruited from April 2005 to May 2007. Participants were followed up every 8 weeks.
Participants	672 women with PR ROC (PFI < 6 months) and women with PS ROC (PFI ≥ 6 months), excluding platinum refractory patients. Planned enrolment was 650 women. Included if measurable disease was present (defined by RECIST); only 1 prior platinum-based regimen received; ECOG PS 0,1 or 2; PFI based on radiological evaluation; no other major medical conditions.
Interventions	**Intervention** PLD (30 mg/m^2) IVI for 90 min + trabectedin (TBD) (1.1 mg/m^2) IVI for 3-hours, every 21 days **Control** PLD (50 mg/m^2) IVI for 90 min, every 28 days
Outcomes	**Primary outcome** PFS **Secondary outcomes** OS ORR Duration of response SAE (NCI-CTCAE v3.0) **Tertiary outcome** QoL
Notes	Growth factor was necessary in 42% arm 1 versus 17% arm 2 to treat neutropenia (precise figures were not given). There were more withdrawals in the TBD arm than the PLD alone arm due to patient choice or adverse events (126 versus 89 participants). Dexamethasone was given to the TBD group only to reduce hepatic toxicity (personal communication).

OVA-301 *(Continued)*

When results were subgrouped by platinum sensitivity, only women in the PS ROC group experienced significantly longer PFS with arm 1; i.e. TBD + PLD offered no significant additional benefit over PLD alone for women with PR ROC. Similarly, for OS, only the PPS ROC subgroup of arm 1 had a statistically significantly longer OS than the arm 2 subgroup (HR 0.59; 95% CI 0.42 to 0.82; P value 0.0015).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central block randomisation (1:1) with stratification by platinum sensitivity and ECOG PS.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Independent radiological assessment and oncologist review.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All expected outcomes were reported, although missing data was > 20% for QoL outcomes.
Selective reporting (reporting bias)	Unclear risk	The reduced rate of PLD toxicity reported in the combination arm could have been due to dexamethasone premedication, or the lower dose of PLD used.
Other bias	Unclear risk	Women in arm 2 had a significantly longer PFI than arm 1 (P value 0.009) which may have biased the survival data in the direction of PLD alone. When the investigators adjusted OS results for the PFI and other prognostic factors in ad hoc exploratory analyses, the adjusted OS produced a statistically significant result in favour of arm 1 (HR = 0.82; 95% CI 0.69 to 0.98; P value 0.0285). Conflict of interest: Employment or Leadership Position: Stanley B. Kaye, PharmaMar Board of Directors (C); Youn Choi Park, Johnson & Johnson Pharmaceutical Research & Development (C); Claudia A. Lebedinsky, PharmaMar (C) Consultant or Advisory Role: Thomas J. Herzog, Genentech (C), GlaxoSmithKline (C), Johnson & Johnson/OrthoBiotech (C); Carolyn N. Krasner, Johnson & Johnson (U); Jan B. Vermorken, Johnson & Johnson (C), PharmaMar (C); Franco M. Muggia, Johnson & Johnson (C); Andrés M. Poveda, PharmaMar (C) Stock Ownership: Youn Choi Park, Johnson & Johnson; Claudia A. Lebedinsky, Grupo Zeltia Honoraria: Thomas J. Herzog, GlaxoSmithKline, Johnson & Johnson/OrthoBiotech, PTI, Eli Lilly; Carolyn N. Krasner, Johnson & Johnson; Jan B. Vermorken, PharmaMar; Franco M. Muggia, Ortho Biotech; Eric Pujade-Lauraine, Schering Plough, Pharmamar Research Funding: Bradley J. Monk, Johnson & Johnson; Hextan Yuen-Sheung Ngan, Johnson & Johnson Pharmaceutical Research & Development Expert Testimony:Bradley J. Monk, Johnson & Johnson–Oncologic Drugs Advisory Committee (C) Other Remuneration: None

Pfisterer 2020

Study characteristics

Pfisterer 2020 *(Continued)*

Methods	International multicentre open-label, randomised, phase 3 trial
Participants	n = 682 **Inclusion criteria** Histologically confirmed epithelial ovarian, primary peritoneal or fallopian tube cancer ≥ 18 years of age Measurable or non-measurable disease by RECIST or CA 125 assessable disease (GCIG criteria) or histological proven diagnosis of relapse Eastern Cooperative Oncology Group (ECOG) performance status 0-2 Adequate bone marrow and organ function. Normal blood pressure or adequately treated and controlled hypertension (either systolic BP ≤ 140 mmHg and/or diastolic BP ≤ 90 mmHg) Patients commencing cytotoxic chemo-therapy after cytoreductive surgery must be able to do so within 8 weeks Effective form of contraception **Exclusion criteria** Ovarian tumours of low malignant potential Other malignancy within the last 5 years Administration of other simultaneous chemotherapy drugs, any other anticancer therapy or antineoplastic hormonal therapy, or simultaneous radiotherapy during the trial treatment period Prior radiotherapy to the abdomen or pelvis Surgery (including open biopsy) within 4 weeks prior to anticipated first dose of bevacizumab Known hypersensitivity to trial chemotherapeutic agents, bevacizumab, Chinese hamster ovary cell products or other recombinant human or humanised antibodies Significant heart disease, e.g. congestive heart failure Grade 3 or 4, myocardial infarction or unstable angina within ≤ 6 months, poorly controlled cardiac arrhythmia despite medication; peripheral vascular disease grade ≤ 3. Prior history of hypertensive crisis or hypertensive encephalopathy Current, clinically relevant bowel obstruction, including sub-occlusive disease, related to underlying disease. Patients with evidence of abdominal free air not explained by paracentesis or recent surgical procedure. History of VEGF therapy related abdominal fistula or gastrointestinal perforation. Brain metastases or spinal cord compression. Previous cerebrovascular accident, transient ischaemic attack or subarachnoid haemorrhage Non-healing wound, active ulcer or bone fracture Current or recent chronic use of aspirin > 325 mg/day History of thrombotic or haemorrhagic disorders within 6 months. Evidence of bleeding diathesis or significant coagulopathy or requirement of therapeutic anticoagulation using marcumar, warfarin or PTT-prolonging heparin Significant traumatic injury during 4 weeks prior to randomisation Pregnant or breastfeeding
Interventions	**Intervention**

Pfisterer 2020 *(Continued)*

	n = 345: bevacizumab (BEV) 10mg/kg day 1 and 15, plus PLD 30mg/m2 day1, plus carboplatin AUC4 day 1; every 4 weeks up to 6 cycles, followed by BEV 15mg/kg every 3 weeks until progression/toxicity **Control** n= 337: BEV 15 mg/kg day 1 plus gemcitabine 1000 mg/m^2 day 1 + 8 plus carboplatin AUC4 day 1; every 3 weeks up to 6 cycles, followed by BEV 15 mg/kg every 3 weeks until progression/toxicity
Outcomes	**Primary outcomes** PFS by RECIST Median progression-free survival was 13·3 months (95% CI 11·7 to 14·2) in the PLD/carbo/BEV group versus 11·6 months (11·0 to 12·7) in the GEM/Carbo/BEV group (HR 0·81, 95% CI 0·68 to 0·96; P = 0·012). **Secondary outcomes** PFS by CA125 Health related quality of life Overall survival
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned centrally 1:1.
Allocation concealment (selection bias)	Low risk	Randomly assigned centrally by authorised personnel from the Coordinating Center for Clinical Trials at Philipps-University of Marburg, Germany.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label, no blinding of outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participant data presented on flow diagram.
Selective reporting (reporting bias)	Low risk	Same outcomes on study protocol and clinical trials.gov and results paper.
Other bias	Unclear risk	Funding: Hoffmann-La Roche. The funder of the study had no role in study design, data collection, data analysis, or data interpretation.

PRECEDENT

Study characteristics

PRECEDENT *(Continued)*

Methods	Phase II open-label multicentre RCT; randomisation ratio EC145 (Vintafolide) + PLD to PLD was 2:1; recruitment between September 2008 and June 2010 in the USA, Canada and Poland.
Participants	162 women with PR ROC (149 had measurable disease); ≥ 18 years; ECOG performance status of 0-2; measurable disease; ≤ 2 prior systemic cytotoxic regimens and adequate organ function. Excluded if prior exposure to PLD, folate-receptor (FR) targeted therapy or vinca-containing compounds; recent surgery; serious comorbidities; concurrent malignancy.
Interventions	**Intervention** (100 women): EC145 (2.5 mg IV days 1,3 and 5, weeks 1 and 3, every 4 weeks) + PLD (50 mg/m^2), every 4 weeks **Control** (49 women): PLD (50 mg/m^2) IV, every 4 weeks EC145 is a folate-linked vinca alkaloid. Premedication was optional, but considered not necessary for EC145 administration.
Outcomes	**Primary outcome** PFS assessed within 12 months following completion of accrual using RECIST and clinical findings. **Secondary outcomes** OS assessed within 18 months after PFS analysis; ORR; safety and tolerability; correlation between therapeutic response and 99mTc-EC20 levels.
Notes	We contacted the investigators, who gave us access to their unpublished manuscript and provided us with additional unpublished data. The independent radiologic committee (IRC) assessment in women with more than one CT scan correlation was 74%. PFS was not significantly different between the treatment groups for the IRC assessment except for the subgroup of folate-receptor positive women. One woman in each group required growth factor support (unpublished data). Median OS was unusually long in the PLD only arm (16.8 months)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation 2:1 EC145/PLD:PLD. Stratified according to primary or secondary platinum resistance, treatment centre, and baseline CA-125 (< 200 versus ≥ 200 U/ml).
Allocation concealment (selection bias)	Low risk	Central randomisation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessment was based upon investigator assessment using RECIST criteria; however, blinded assessment was performed by an IRC to check for investigator bias.

PRECEDENT *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Censoring due to clinical progression was 12% and 10% for treatment arms respectively. Eight women in the EC145 arm were withdrawn from EC145 due to treatment related AEs (7.5%) but were included in ITT analyses. Women with non-measurable disease (13) were included in the safety analyses but excluded from the survival analyses.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported. Sensitivity analysis performed for primary outcome.
Other bias	Unclear risk	Baseline characteristics were similar between the arms except for the number of tumour lesions, which was greater in the EC145 arm, however this was not a prognostic factor for shorter PFS. Conflict of interest: Supported by Endocyte who developed the study drug. Employment or Leadership Position: Chandra D. Lovejoy, Endocyte (C); Christopher P. Leamon, Endocyte (C) Consultant or Advisory Role: Robert L. Coleman, Endocyte (C); Robert A. Burger, Endocyte (C); Richard T. Penson, Endocyte (C); James T. Symanowski, Endocyte (C); Chandra D. Lovejoy, Endocyte (C) Stock Ownership: Chandra D. Lovejoy, Endocyte; Christopher P. Leamon, Endocyte; David E. Morgenstern, Endocyte Honoraria: Robert L. Coleman, Endocyte; Richard T. Penson, Endocyte Research Funding: R. Wendel Naumann, Endocyte; Robert L. Coleman, Endocyte; Robert A. Burger, Endocyte; Edward A. Sausville, Endocyte; Sharad A. Ghamande, Endocyte; Nashat Y. Gabrail, Endocyte; Stephen E. DePasquale, Endocyte; Lucy Gilbert, Endocyte; Michael G. Teneriello, Endocyte; Wael A. Harb, Endocyte; Panagiotis A. Konstantinopoulos, Endocyte; Richard T. Penson, Endocyte Expert Testimony: None Patents: None Other Remuneration: None

PROCEED 2014

Study characteristics	
Methods	Multicentre international randomised double-blind phase III trial The primary analysis was conducted in FR (100%) patients as determined by ^{99m}Tc-etarfolatide scan
Participants	182 participants ≥ 18 years old PR Pathology confirmed epithelial ovarian, fallopian tube, or primary peritoneal carcinoma ECOG 0-2 Measurable disease by RECIST Adequate bone marrow, hepatic, and renal function
Interventions	Vintafolide 2.5 mg IV injection three times a week, weeks 1 and 3 of a 4-week cycle AND PLD 50 mg/m^2 every 4 weeks versus Placebo

PROCEED 2014 *(Continued)*

	AND
	PLD 50 mg/m^2 every 4 weeks
Outcomes	**Primary outcome**
	PFS
	Secondary outcomes
	OS
	Disease control rate
	Duration of disease control
	ORR
	Duration of response
	QoL
	CA125 response rate
	CA125 PFS
	Pharmacokinetics
	Archived tumour specimen biomarker analysis
	AE
	SAE
	Death
Notes	Initial recruitment delayed due to PLD availability.
	At interim futility analysis the Data and Safety Monitoring Board (DSMB) recommended the trial stop because it did not meet the efficacy hurdle specified in the statistical analysis plan.
	Interim analysis data only.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally randomised.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	RECIST criteria, unclear if blinded assessors .

PROCEED 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Interim analysis data only.
Selective reporting (reporting bias)	High risk	Short duration of follow-up and high censoring rates.
Other bias	Unclear risk	At interim futility analysis the DSMB recommended the trial stop because it did not meet the efficacy hurdle specified in the statistical analysis plan. 321 of planned 350 patients randomised. Sponsored by Endocyte, who developed the study drug.

SWOG S0200

Study characteristics	
Methods	Phase III multicentre RCT. Accrual from August 2002 to December 2004. (ID:NCT00043082)
Participants	61 women with PS ROC or peritoneal cancer; a progression-free and platinum-free interval of 6 to 24 months according to RECIST or GCIG CA-125 criteria; progression following first-line platinum-based chemotherapy and up to 12 courses of non-platinum containing consolidation treatment; Zubrod performance status 0-1.
Interventions	**Intervention** PLD (30 mg/m^2) IV plus carbo IV (AUC = 5 mg/mL/min), every 4 weeks **Control** Carboplatin IV (AUC = 5 mg/mL/min), every 4 weeks Patients could receive a premed of intravenous dexamethasone (20 mg) plus IV granisetron before carboplatin dose, and further dexamethasone on days 2,3, and 4. G-CSF was allowed to treat G3 to 4 neutropenia when it occurred, and then subsequently to prevent it.
Outcomes	**Primary** OS **Secondary** PFS, ORR, toxicity
Notes	The accrual goal was 900, but study was discontinued due to slow accrual. Unpublished final survival data related to the 2010 publication was received from investigators on 13 December 2012. PFS was significantly improved by the addition of PLD to carboplatin. The final OS was not statistically significantly different between treatment arms, in contrast to the earlier report of 2008 where OS was significantly longer in the PLD/carboplatin arm. Despite using a lower dose of PLD, this trial had a relatively high rate of haematological SAEs (G3 to 4) in the PLD/carboplatin arm compared with the carboplatin alone arm (neutropenia 48% versus 3%; anaemia 16% versus 0%; thrombocytopenia 39% versus 10%). Eight women in the carboplatin arm had allergic reactions (any grade) compared with 0 in the PLD/carbo arm. The HFS rate was 3/31 (10%) in the PLD/carbo arm. The proportion of women in each group who received a dexamethasone premed was not described.

SWOG S0200 *(Continued)*

	Investigators concluded that PLD/carboplatin dosing interval was more convenient than the PAC/carboplatin and GEM/carboplatin alternatives; that PLD was well tolerated with no significant HFS problems; and that "administering PLD with carboplatin appears to substantially reduce the incidence of platinum-associated hypersensitivity reactions."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation.
Allocation concealment (selection bias)	Low risk	Central allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition.
Selective reporting (reporting bias)	Low risk	Final HRs for survival were not published; however, the investigators provided us with these unpublished data.
Other bias	Unclear risk	This study closed early due to insufficient accrual and the final sample size was not powered to detect a survival difference. Conflict of interest: this investigation was supported in part by Ortho Biotech Products, L.P.

TRINOVA-2

Study characteristics

Methods	Randomised, double-blind, placebo-controlled phase 3 study from April 2011 to October 2013 in 69 sites in 16 countries (USA, Australia, Austria, Belgium, Canada, Denmark, France, Germany, Hong Kong, Hungary, Italy, New Zealand, Poland, Singapore, Slovakia, Switzerland, Taiwan, UK)
Participants	223 women with PR ROC **Inclusion criteria** Histologically or cytologically confirmed epithelial ovarian, primary peritoneal, or fallopian tube cancer ≥ 18 years of age One prior platinum-based chemotherapeutic regimen for primary disease containing carboplatin, cisplatin, or another organoplatinum compound Radiographically documented disease progression

TRINOVA-2 *(Continued)*

	Adequate bone marrow and organ function **Exclusion criteria** Platinum-free interval > 12 months from their last platinum based therapy Major surgery within the last 4 weeks or still recovering from prior surgery Prior treatment with more than 3 regimens of anti-cancer therapy for epithelial ovarian, primary peritoneal or fallopian tube cancer Prior treatment with PLD or any anthracycline-based or mitoxantrone-based chemotherapy CNS metastases
Interventions	**Intervention** IV PLD 50 mg/m^2 once every 4 weeks plus weekly IV trebananib 15 mg/kg **Control** IV PLD 50 mg/m^2 once every 4 weeks plus weekly IV placebo
Outcomes	**Primary outcome** PFS **Secondary outcomes** OS ORR DoR
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants randomised, however method not specified
Allocation concealment (selection bias)	Unclear risk	Allocation concealment for mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind, placebo controlled study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned. Outcomes were assessed using the RECIST criteria.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Patient flow chart included and all patients accounted for.

TRINOVA-2 *(Continued)*

Selective reporting (reporting bias)	High risk	No study protocol available. Clinical trials.gov has only overall survival (OS) as secondary outcome. Overall response rate (ORR) and duration of response (DOR) are added as outcomes in results.
Other bias	Unclear risk	Sponsored by Amgen, the maker of the study drug

AE: adverse event; ALT: alanine amino transferase; ASCO: American Society of Clinical Oncology; AST: aspartate amino transferase; AUC: area under the curve; bd: twice daily; BEV: bevacizumab; BRCA: breast cancer antgen; CA125: cancer antigen 125; CAN: canfosfomide; CRs: complete responses; DCR: disease control rate; DoR: duration of response; DSMB: Data and Safety Monitoring Board; EC145: vintafolide; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; FR: folate receptor; GCIG: Gynecologic Cancer Intergroup; G-CSF: granulocyte colony stimulating factor; GEM: gemcitabine; HQL: Health-related quality of life assessment; HR: hazard ratio; IV: intravenous; IVI:intravenous infusion; M200: volociximab; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; NYHA: New York Heart Association; OLA: olaparib; ORR: objective (or overall) response rate; OS; overall survival; PAC: paclitaxel; PARP: Poly(ADP-ribose) polymerase; PD: programmed death receptor; PDGF: platelet-derived growth factor; PDGF-R; platelet-derived growth factor receptor; PD-L: programmed death ligand; PFI: platinum-free interval; PFS: progression-free survival; PK: pharmacokinetic; PLD: peglyated liposomal doxorubicin; PPS; partially platinum-sensitive; PR: platinum resistant (or refractory); PRs: partial responses; PS: platinum sensitive; PTT: prothrombin time; QoL: quality of life; RCT: randomised control trial; RECIST: Response Evaluation Criteria in Solid Tumours; ROC: recurrent/relpased ovarian cancer; SAE: serious adverse events; TBD: trabectedin; Tc: technetium; TOP: topotecan; TTP: time-to-progression; VTX-2337: motolimod.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
A'hern 1995	Ineligible intervention - review of previous studies focusing on addtion of doxorubicin to chemotherapy regimes.
AGOG06-001	Phase III RCT of maintenance pegylated liposomal doxorubicin (PLD)/carboplatin versus without in patients with advanced ovarian cancer after first-line treatmetn. Patients therefore did not have relpasoed EOC. (ANZCTR reg. ID: ACTRN12607000329460)
Aracil 2013	Ineligible study design - not an RCT.
Bakrin 2018	Study protocol of a Phase III trial comparing progression-free survival between cisplatin + PLD as Pressurized Intraperitoneal Chemotherapy (PIPAC) and chemotherapy alone. Results not available at time of review update.
Basu 2011	Ineligible study design - prospective study, not an RCT.
Basu 2013	Ineligible study design, not an RCT.
Bhowmik 2018	Ineligible intervention - compares generic with branded PLD.
Bookman 2002	Ineligible study design - review of developmental chemotherapy in advanced OC and description of Phase III trial protocol.
Cherchi 2003	Ineligible study design - not an RCT.
Colombo 2014	Ineligible intervention.
Colombo 2014a	Ineligible study design - exploratory analysis of results.
GOG0182/ICON 5	Ineligible study group - use of PLD as first line agent, not in ROC.
Graybill 2014	Ineligible study design - abstract describing other studies only.

Study	Reason for exclusion
Herzog 2014	Prediction model taking data from other study already included in review.
INOVATYON	Ineligible comparison as PLD in both arms, combined with different chemo agents in each arm, therefore not PLD randomisation. Phase III international, randomised study of trabectedin plus pegylated liposomal doxorubicin (PLD) versus carboplatin plus PLD in patients with ovarian cancer progressing within 6 to 12 months of last platinum (ID: NCT01379989).
Kavanagh 2004	Ineligible study design - not an RCT.
Khokhlova 2012	Ineligible study design - cis+trabectedin versus PLD+trabectadin
Lai 2018	Ineligible intervention - compares chemotherapy to observation only.
Lindemann 2017	Ineligible comparison - chemotherapy versus hormonal treatment
Lorusso 2014	Ineligible intervention - doxorubicin not PLD
Marme 2019	Ineligible intervention - studies efficacy and safety of atezolizumab v placebo.
MILO ENGOT-ov11	Participants had low grade serous ovarian cancer.
MITO-2 2011	Ineligible study cohort - use of PLD as first line treatment, not for patients with ROC.
Monk 2016	Ineligible intervention - comparing use of bevacizumab with CA4p v bevacizumab with placebo.
Nagao 2016	Ineligible intervention- pilot study of addition of low-dose paclitaxel to carboplatin-based combination chemotherapy
NCT02641639 2015	Ineligible intervention - does not study use of PLD.
NCT02891824 2016	Ineligible intervention - does not study use of PLD.
NCT03632798 2018	Ineligible intervention - PCC v ChemoID-guided treatment.
NCT03639246 2018	Ineligible study design - phase 1b/2 - no randomisation.
NCT03699449 2018	Ineligible intervention - compares durvalumab with other agents. Wrong primary outcome - ORR.
NCT03949283 2019	Ineligible intervention - PCC v ChemoID-guided treatment. Ineligible outcomes - primary outcome ORR.
Palaia 2006	Ineligible study design - not an RCT.
PiSARRO 2016	Not an RCT - phase 1b study of APR-246 with carboplatin and PLD.
Scarfone 2006	Not an RCT.
Shoji 2018	Ineligible intervention - compares chemo +/- bevacizumab.
Trillsch 2016	Subanalysis of aurelia - compares PPR v SPR. Does not meet intervention.
Wydra 2014	Ineligible intervention - patients who discontinued PLD and continued on vintafolide only.
Yabuno 2019	Does not meet intervention criteria - comparing dosage regimens.

Abbreviations: AE = adverse effect; EOC: epithelial ovarian cancer; GEM = gemcitabine; HRQoL = health related quality of life; OC = ovarian cancer; ORR = objective response rate; PCC = physician choice chemotherapy; PLD = pegylated liposomal doxorubicin; PR ROC = platinum refractory relapsed ovarian cancer; RCT = randomised controlled trial; ROC = relapsed ovarian cancer; TOP = topotecan;

Characteristics of studies awaiting classification *[ordered by study ID]*

ASSIST-1 2009

Methods	International, multicentre randomised active control trial The choice of PLD or TOPO for patients randomised to the active control arm was based on the prior failed second-line therapy
Participants	461 participants PR **Inclusion criteria** ≥ 18 years of age Eastern Cooperative Oncology Group (ECOG) performance status 0-2 Histologically or cytologically proven advanced epithelial ovarian, fallopian tube or peritoneal carcinoma Failed one second line therapy with TOPO or PLD Adequate haematopoietic, hepatic and renal function **Exclusion criteria** Bone marrow transplant Prior malignancy except curative treatment of cervical carcinoma in situ, BCC or SCC skin Significant cardiac disease Hypercalcaemia Systemic infection
Interventions	Canfosfamide 1000mg/m^2 3 weekly versus PLD 50mg/m^2 4 weekly or TOPO at 1.5mg/m^2 3 weekly
Outcomes	Primary Outcome OS Secondary Outcomes Safety PFS ORR
Notes	

AURELIA 2012

Methods	Multicentre, open-label, randomised, two-arm phase III trial
Participants	361
Interventions	**Intervention** Chemotherapy of choice plus bevacizumab 10mg/kg every 2 weeks **Control** Chemotherapy of choice alone (paclitaxel 80mg/m^2 days 1, 8, 15, 22 every 4 weeks; PLD 40mg/m^2 day 1 every 4 weeks; topotecan 4mg/m^2 days 1, 8, 15 every 4 weeks or 1.25mg/m^2 on days 1 to 5 every 3 weeks)
Outcomes	**Primary outcome** Percentage of participants with disease progression or death, progression free survival. **Secondary outcomes** Percentage of participants with best overall confirmed objective response of complete response (CR) or partial response (PR) per modified RECIST Duration of objective response Percentage of participatns who died Overall survival Quality of life (EORTC OV 28).
Notes	Median PFS was 3.4 months (95% CI 2.2 to 3.7) for the chemotherapy alone arm and 6.7 months (95% CI 5.7 to 7.9) in the chemotherapy with bevacizumab arm. There was no statistically significant difference in overall survival. The results are presented as chemotherapy of choice and have not been separated into individual results (PLD/paclitaxel/topotecan). We have emailed the researchers for individual response. Until then, we have moved this study into awaiting classification.

FORWARD I

Methods	Open-label phase 3 randomised control trial; international multicentre (131 study locations in the USA, Belgium, Bosnia, Canada, Czech Republic, France, Ireland, Italy, Russia, Serbia, Spain, Switzerland, UK). Randomised 2:1 intervention versus control.
Participants	366 patients with relapsed platinum-resistant tubo-ovarian/primary peritoneal cancer. At least 1 and no more than 3 previous lines of chemotherapy. Females >18 years of age. Folate receptor-alpha receptor positive tumour expression. Clear cell and low grade histology types excluded.
Interventions	Mirvetuximab soravtansine 6 mg/kg IV on D1 of 3-weekly cycles versus chemotherapy of physician's choice (paclitaxel; topotecan; PLD). Study drug continued until progressive disease as per RESIST criteria or unacceptable toxicity or withdrawal of consent or termination of study.
Outcomes	OS PFS ORR
Notes	Unable to extract data specific for PLD group. Data not able to be included in meta-analysis.

HECTOR

Methods	Phase III multicentre RCT
Participants	550 women with PS ROC.
Interventions	Arm 1:TC Arm 2: GC or PC or PLDC
Outcomes	Primary: PFS Secondary: toxicity
Notes	Interim data of the first 200 women was presented at ASCO 2012.

MITO-16 MANGO OV2b

Methods	Open-label, multicentre, phase III, randomised trial; NCT01802749
Participants	406 participants with recurrent EOC
Interventions	Combination chemotherapy with ONE of the following regimens: • PLD-Carboplatin: Pegylated liposomal doxorubicin 30 mg/m^2 + Carboplatin AUC (area under curve) 5 on day 1 every 4 weeks; • GEM-C: Gemcitabine 1000 mg/m^2 on day 1, 8 every 21 + Carboplatin AUC of 4 on day 1 every 21 days; • PAC-C: Paclitaxel 175 mg/m^2 on day 1, every 21 + Carboplatin AUC of 5 on day 1 every 21 days. versus Combination chemotherapy AND bevacizumab with ONE of the following regimens: • PLD-C: Pegylated liposomal doxorubicin 30 mg/m^2 + Carboplatin AUC 5 on day 1 every 4 weeks and bevacizumab 10 mg/kg i.v. on Day 1 every 2 weeks; • GEM-C: Gemcitabine 1000 mg/m^2 on day 1, 8 every 21 + Carboplatin AUC of 4 on day 1 every 21 days AND bevacizumab 15 mg/kg i.v. on Day 1 every 3 weeks; • PAC-C: Paclitaxel 175 mg/m^2 on day 1, every 21 + Carboplatin AUC of 5 on day 1 every 21 days AND bevacizumab 15 mg/kg i.v. on Day 1 every 3 weeks
Outcomes	**Primary outcome** Progression free survival (12 months) assessed by local Investigator **Secondary outcomes** Overall survival (12 months) Number of complete or partial responses (6 months) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 Worst grade toxicity per patient (evaluated every 3 weeks up to 12 months) according to Common Toxicity Criteria for Adverse Events v. 4.03 Number of patients taking oral antidiabetic therapy (at baseline) Number of patients taking antithrombotic therapy (at baseline) Progression-free survival (12 months) as measured by independent central review Other outcomes

MITO-16 MANGO OV2b *(Continued)*

	Predictive clinical factors for efficacy of bevacizumab (12 months) Correlation of baseline plasma biomarker expression and clinical outcome (12 months)
Notes	For carboplatin with PLD, median PFS was 9.0 months (7.8 to 10.0) without bevacizumab and 12.5 months (10.9 to 15.2) with bevacizumab. Contact authors for PLD-only data from each arm.

MITO-23

Methods	Open-label, prospective, multicentre, randomised phase III. Patients will be randomly assigned in a 1:1 ratio to treatment arms.
Participants	242 participants **Inclusion Criteria** Female of age 18 years or older Histologically or cytologically documented invasive epithelial ovarian cancer, primary peritoneal carcinoma, or fallopian tube cancer Platinum resistant or sensitive patients with either: 1. *BRCA*-mutated patients 2. BRCAness phenotype patients: patients who have received and responded (subsequent PFI > 6 months) to at least 2 previous platinum based chemotherapy lines 3. Platinum sensitive patients who are not able to receive or not willing to receive other platinum treatments 4. Measurable and evaluable disease per RECIST 1.1 5. ECOG performance status 0 or 1 6. No limits in the number of previous chemotherapy lines, previous treatment with PARP inhibitors is allowed 7. Left Ventricular Ejection Fraction (LVEF) ≥ institutional lower limit normal 8. Life expectancy of at least 3 months Adequate organ functions: 1. Haematopoietic: absolute neutrophil count ≥ 1500/mm^3; platelet count ≥ 100,000/mm^3; haemoglobin ≥ 9 g/dl 2. Hepatic: AST and ALT ≤ 1.5 times upper limit of normal (ULN)* ; alkaline phosphatase ≤ 2.5 times ULN*; Bilirubin ≤ 1.5 times ULN. (NOTE: * ≤ 3 times ULN if liver metastases are present) 3. Renal: creatinine clearance ≥ 45 ml/min or serum creatinine ≤ 1.5 x ULN 4. Serum albumin >2.5 g/dl 5. No other invasive malignancy within the past 3 years except non-melanoma skin cancer or in situ cervical cancer (patients with previous cancers may be enrolled providing that no recurrences have be reported in the last 3 years) 6. Written informed consent 7. Adequately recovered from the acute toxicity of any prior treatment 8. For agents in the standard arm, also refer to the local prescribing information with regard to warnings, precautions, and contraindications **Exclusion Criteria** 1. Prior exposure to trabectedin 2. Known hypersensitivity to any of the components of the trabectedin IV formulation or dexamethasone

MITO-23 *(Continued)*

	3. People with borderline ovarian cancer, i.e. people with low malignant potential tumours are excluded 4. Less than 2 reported responses to platinum (i.e. subsequent recurrences at least 6 months after the first and the second platinum based treatment), unless BRCA mutation is documented. 5. Less than 4 weeks from last dose of therapy with any investigational agent, or chemotherapy 6. History of another neoplastic disease (except basal cell carcinoma or cervical carcinoma in situ adequately treated) unless in remission for 3 years or longer 7. Known clinically relevant CNS metastases, unless treated and asymptomatic Other serious illnesses, such as: 1. Congestive heart failure or angina pectoris; myocardial infarction within 1 year before enrolment; uncontrolled arterial hypertension or arrhythmias. 2. Psychiatric disorder that prevents compliance with protocol. 3. Active viral hepatitis; or chronic liver disease. 4. Active infection. 5. Any other unstable medical conditions.
Interventions	Trabectedin 1.3 mg/m^2 on day 1 3-weekly versus Chemotherapy of physician's choice (PLD 40 mg/m^2 every 28 days *or* topotecan 4 mg/m^2 days 1, 8, 15 every 28 days *or* gemcitabine 1000 mg/m^2 days 1, 8, 15 every 28 days, *or* weekly paclitaxel 80 mg/m^2 days 1, 8, 15 every 28 days *or* carboplatin AUC 5-6 3-weekly or 4-weekly)
Outcomes	**Primary outcome** Overall survival (OS) (4 years) **Secondary Outcomes** Progression-free survival (PFS) (4 years) assessed by radiological criteria; CA 125 increases alone (GCIG criteria of progression) will not be considered as progression of disease without a radiological confirmation of progression. Duration of Response (4 years) Adverse events (4 years) Incidence of adverse events, according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4.0.
Notes	Estimated 4-year follow up https://clinicaltrials.gov/ct2/show/NCT02903004 November 2022: Abstracts for conferences published but full data not yet published. Will request data for PLD-only once further data available.

MITO-8 2017

Methods	International, multicentre, randomised, open-label, superiority trial (Belgium, Germany, Italy)
Participants	215 participants with PS ROC with disease recurrence between 6 and 12 months after a first-line platinum based therapy, but no more than 2 previous lines of previous therapy and a life expectancy of more than 3 months.
Interventions	**Intervention**

MITO-8 2017 *(Continued)*

	n = 107 PLD 40 mg/m^2 day 1 every 28 days OR topotecan as per institutional guidelines OR gemcitabine 1000 mg/m^2 on days 1, 8, 15 every 28 days **Control** n = 108 carboplatin AUC 5 day 1 every 28 days plus either paclitaxel 175 mg/m^2 day 1 every 21 days OR gemcitabine 1000 mg/m^2 on days 1, 8, 15 every 28 days
Outcomes	**Primary outcome** OS **Secondary outcome** PFS QOL OR Worst grade toxicity for each patient
Notes	**Inclusion criteria** Histological or cytologically confirmed ovarian cancer Received no more than two lines of chemotherapy Life expectancy ≥ 12 weeks Informed consent **Exclusion criteria** Other malignancy, previous or current, except adequately treated basal cell carcinoma or squamous cell carcinoma of the skin or carcinoma in situ of the cervix Prior therapy with stealth liposomal doxorubicin Grade ≤ 3 residual peripheral neuropathy Heart disease (congestive heart failure, myocardial infarction within 6 months from study entry, atrioventricular block of any grade, severe arrhythmias) Present or suspected hemorrhagic syndromes

MORAb-003

Methods	Randomised phase II placebo control trial
Participants	211 participants Low CA125 Platinum sensitive first relapse
Interventions	Carboplatin with paclitaxel or carboplatin with PLD AND Farletuzumab (weekly 10 mg/kg first 2 weeks followed by 5 mg/kg)

MORAb-003 *(Continued)*

	OR placebo
Outcomes	**Primary outcome** PFS **Secondary outcomes** OS Best Overall Response Time to Tumour Response Duration of Response Percentage of Participants Achieving Each Second Platinum-Free Interval Stratified by First Platinum-Free Interval
Notes	

NCT03690739

Methods	Open-label, prospective, randomised, controlled, parallel group, multicentre phase III
Participants	330 patients randomised in a 1:1 ratio. **Inclusion criteria** • Adult females. • Histologically proven diagnosis of cancer of the ovary, the fallopian tube or primary peritoneal cancer. • Measurable or non-measurable disease (according RECIST v1.1) or CA-125 assessable disease (according GCIG criteria) or histologically proven diagnosis of relapse. • Platinum-treatment free interval > 6 months. • Disease stabilisation according to RECIST or GCIG criteria after three cycles of platinum-based chemotherapy for recurrent disease. • Symptomatic disease (abdominal/GI symptom scale score > 15 (EORTC QLQ-OV28)). • Previous taxane treatment. • ECOG performance status ≤ 2. • Life expectancy of at least 12 weeks. • Adequate bone marrow, renal and hepatic function. • Non-pregnant and on contraception of risk of pregnancy. **Exclusion criteria** • Borderline tumours. • Non-epithelial ovarian or mixed epithelial/non-epithelial tumours. • Radiotherapy for ovarian cancer. • Heart disease (heart failure; myocardial infarction; atrial or ventricular arrhythmia). • Pregnancy or breastfeeding.
Interventions	Arm A - platinum-based chemotherapy according to investigator's discretion Arm B - pegylated liposomal doxorubicin 30 mg/m² + trabectedin 1.1 mg/m² every 3 weeks

NCT03690739 *(Continued)*

Outcomes	**Primary outcome** Symptom benefit rate **Secondary outcomes** Deterioration in quality of life outcomes Progression-free survival Response rate (RECIST v1.1) Quality of life (EORTC QLQ-C30 and EORTC QLQ-OV 28) Overall survival
Notes	AGO-OVAR 2.32 Closed early due to lack of recruitment.

Oza 2019

Methods	Multicentre, randomised, open-label phase II trial conducted at 20 centres in the USA, UK, and Canada
Participants	103 participants (51 in experimental arm, 49 in chemotherapy of choice arm)
Interventions	Intervention: guadicitabine 30mg/m2 s.c. OD on days 1-5, + carboplatin IV AUC 4 on day 8 (51 patients) Control: treatment choice of tocotecan IV 3.5 to 4.0mg/m^2/week on day 1/8/15 (20 patients), PLD IV 40 to 50mg/m^2 on day 1 (15 patients), paclitaxel IV 60 to 80mg/m^2/week on day 1/8/15/22 (11 patients) or gemcitabine IV 800 to 100mg/m^2 on day 1/8/15 (3 patients)
Outcomes	**Primary outcome** Progression free survival (PFS) **Secondary outcomes** Objective response rate (ORR), defined as complete response (CR) and partial response (PR) based on both measurable and evaluable disease PFS at 6 months Clinical benefit rate (CBR: defined as CR+PR+SD for at least 3 months) Proportion of patients with CA- 125 reduction of at least 50%, duration of response (DOR) Overall survival (OS); in participants crossing over from the TC to the G+C arm, ORR was measured. Response was assessed using RECIST v1.1 for patients with measurable disease (20), and modified Rustin criteria for patients with detectable disease according to CA-125 criteria (21, 22). Tumour measurements were obtained by CT or MRI at screening, after every two cycles for the first six cycles, and every 3 months until progression.
Notes	E-mailed author for separated results - awaiting response. Until then study included in the awaiting classification studies.

PROVE 2011

Methods	Open-label randomised phase II Trial
Participants	Platinum sensitive 102 randomised, 96 participants **Inclusion criteria** Epithelial ovarian/ fallopian/ peritoneal cancer No more than 2 prior treatment lines Measurable disease or elevated CA125 KRAS wild type
Interventions	Investigators choice of gemcitabine 1000 mg/m^2 days 1/8 and carboplatin (AUC 4) 3 weekly or PLD 30 mg/m^2 3 weekly and carboplatin (AUC 5) 4 weekly with or without panitumumab 6 mg/kg days 1/15 4 weekly
Outcomes	**Primary outcome** PFS **Secondary outcomes** Duration of tumour response PFS OS Toxicity Tumour response rate
Notes	

SOLO3

Methods	Randomised, controlled, open-label, phase III trial conducted in 13 countries
Participants	266 participants underwent random assignment. 178 participants were randomly assigned to olaparib and 88 to chemotherapy (PLD, n = 47; paclitaxel, n = 20; gemcitabine, n = 13; topotecan, n = 8; intent-to-treat population).
Interventions	Participants were randomly assigned 2:1 to olaparib tablets 300 mg twice a day or to physician's choice of single-agent chemotherapy: PLD 50 mg/m^2 on day 1 every 4 weeks; paclitaxel 80 mg/m^2 on days 1, 8, 15, and 22 every 4 weeks; gemcitabine 1000 mg/m^2 on days 1, 8, and 15 every 4 weeks; or topotecan 4 mg/m^2 on days 1, 8, and 15 every 4 weeks. The investigator made his/her chemotherapy choice before random assignment.
Outcomes	**Primary outcome**

SOLO3 *(Continued)*

	ORR as assessed by blinded independent central review (BICR) in the measurable disease analysis set (MDAS) using RECIST version 1.1. **Secondary outcomes** PFS as assessed by BICR Investigator-assessed PFS Time from random assignment to second progression or death (PFS2) Overall survival (OS) Time from random assignment to first subsequent therapy or death (TFST) Time to earliest progression by RECIST or cancer antigen-125 (CA-125) or death Time from random assignment to study treatment discontinuation or death (TDT).
Notes	We emailed the authors in November 2020, but they were not able to provide us with separated data for PLD only. Therefore, this study has been placed in th awaiting classification group.

Volasertib Trial

Methods	International, open-label, controlled, randomised, phase II trial conducted at 31 centres in five countries (Belgium, France, Slovakia, Spain, and Sweden)
Participants	A total of 122 patients were screened between 23 April 2010, and 21 April 2011, and 110 participants (volasertib, n = 55; chemotherapy, n = 55) were randomly assigned. Of these participants, 109 (volasertib, n = 54; chemotherapy, n = 55) were treated and included in the analysis.
Interventions	Participants were randomly assigned 1:1 to receive either volasertib 300 mg by intravenous infusion every 3 weeks or an investigator's choice of single-agent nonplatinum cytotoxic chemotherapy. The investigator was free to choose the most appropriate nonplatinum cytotoxic single agent according to patient status (previous chemotherapy, cumulative toxic effects, performance status, and nutritional status), the summary of product characteristics, and the local standard of care. There were no restrictions but the following single agents were recommended: pegylated liposomal doxorubicin, topotecan, paclitaxel, or gemcitabine.
Outcomes	**Primary outcome** 24-week disease control rate (CR, PR or SD; according to RECIST vl.l). **Secondary outcomes** Best overall response (according to RECIST vl.l) OS PFS QoL and symptom control safety Pharmacokinetics of volasertib Biomarker analysis.
Notes	

C = carboplatin; GEM = gemcitabine; PAC = paclitaxel; PLD = pegylated liposomal doxorubicin

Characteristics of ongoing studies *[ordered by study ID]*

ABT-888/NCT01113957

Study name	A trial of ABT-888 in combination with temozolomide versus pegylated liposomal doxorubicin alone in ovarian cancer

ABT-888/NCT01113957 *(Continued)*

Methods	Phase II open-label multicentre RCT
Participants	150 women with recurrent high grade serous OC; must be PR or unable to tolerate platinum-based therapy
Interventions	ABT-888 + temozolomide versus PLD
Outcomes	**Primary outcome** ORR based on tumour measurements and CA125 levels (assessed every 3 months for 3 years) **Secondary outcomes** PFS, OS, 12-month survival rate, 6-month PFS rate, duration of response, safety and tolerability, QoL
Starting date	March 2010
Contact information	Yan Luo (Abbott): yan.luo@abbott.com
Notes	End date: Mar 2013. No results available, checked 23 November 2022

ATI0918/NCT01715168

Study name	A cross-over bioequivalence study of intravenously administered ATI0918 and DOXIL/CAELYX in patients with ovarian cancer
Methods	Phase I single-blind RCT
Participants	40 women with ROC
Interventions	PLD (50 mg/m^2) versus ATI-0918
Outcomes	Pharmaco-equivalence outcomes
Starting date	Oct 2012
Contact information	Karen Kuhn: kkuhn@ockham.com
Notes	May 2013 Nov 2022 - looks to be completed, no results

EPIK-O/ENGOT-OV61

Study name	EPIK-O/ENGOT-OV61: a phase 3, randomised study of alpelisib + olaparib in patients with no germline BRCA mutation detected, platinum-resistant or-refractory, high-grade serous ovarian cancer
Methods	Phase 3, randomised, open-label, controlled trial
Participants	358 PR
Interventions	**Intervention**: alpelisib and olaparib

EPIK-O/ENGOT-OV61 *(Continued)*

	Control: paclitaxel or PLD
Outcomes	**Primary outcome** PFS **Secondary outcomes** OS Overall response rate Clinical benefit rate Safety Quality of life
Starting date	
Contact information	
Notes	

MIRASOL

Study name	MIRASOL
Methods	Phase III randomised open-label trial
Participants	Estimated enrolment 430 PR
Interventions	**Intervention**: mirvetuximab soravtansine **Control**: paclitaxel or PLD or topotecan
Outcomes	**Primary outcome** PFS **Secondary outcomes** Safety and tolerability ORR OS Patient-reported outcomes (QLQ-OV28) Duration of response CA-125 response
Starting date	31 December 2019
Contact information	ImmunoGen, Inc. 781-895-0600 medicalaffairs@immunogen.com
Notes	

MIROVA

Study name	Mirvetuximab Soravtansine (IMGN853), in Folate Receptor Alpha (FRα) High Recurrent Ovarian Cancer (MIROVA) NCT04274426
Methods	Phase II randomised open-label
Participants	Estimated enrolment 136 participants
Interventions	Intervention: carboplatin and mirvetuximab soravtansine Control: carboplatin and PLD or gemcitabine or paclitaxel
Outcomes	**Primary outcome** PFS **Secondary outcomes** OS Objective response rate PFS OS ORR Time to serological progressive disease Time to first subsequent treatment Time to second subsequent treatment Patient-reported outcomes Safety and tolerability
Starting date	13 October 2021
Contact information	Michaela Fredrich +49 611 880467 ext 42 mfredrich@ago-ovar.de
Notes	

MITO-27

Study name	MITO 27; NCT03539328
Methods	Multicentre, randomised, open-label trial,
Participants	138 participants **Inclusion Criteria** Platinum resistant (platinum free interval 1 to 6 months from last platinum dose) ovarian, Fallopian tube or primary peritoneal cancer

MITO-27 *(Continued)*

	≥ 18 years of age Measurable disease or evaluable based on RECIST 1.1 (patients with only CA 125 increase without evidence of disease are not included) Willing to provide tissue from a newly obtained core or excisional biopsy of a tumour lesion Performance status of 0 or 1 on the ECOG Performance Scale Adequate organ function Negative pregnancy test/on contraception, if required **Exclusion criteria** Received > 2 previous lines of chemotherapy Pregnant or breastfeeding Immunodeficiency, including HIV 1/2 Active infection
Interventions	Physician's choice chemotherapy (PLD 40 mg/m^2 IV every 4 weeks, or weekly paclitaxel 80 mg/m^2 days 1, 8, 15 every 4 weeks, or gemcitabine 1000 mg/m^2 days 1 and 8 every 3 weeks) versus Physician's choice chemotherapy (PLD 40 mg/m^2 IV every 4 weeks, or weekly paclitaxel 80 mg/m^2 days 1, 8, 15 every 4 weeks, or gemcitabine 1000 mg/m^2 days 1 and 8 every 3 weeks) plus pembrolizumab 200 mg d1 every 3 weeks via IV infusion. Participants will receive treatments until disease progression, unacceptable toxicity or patient choice to withdraw. At least 6 to 8 cycles of chemotherapy at physician's discretion. In the experimental arm patients who stop chemotherapy for toxicity reasons and whose disease is at least in stabilisation, may continue treatment with pembrolizumab as single agent.
Outcomes	**Primary outcome** Overall survival (OS) (from randomisation to the date of death, assessed up to 44 months) **Secondary outcomes** Progression free survival (PFS) (from randomisation to the date of radiological/clinical progression of disease or death, assessed up to 44 months) Response rate (44 months) Adverse events (44 months) Incidence of adverse events, according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 5.0 Quality of life (44 months) Physical subscale of the National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy FACT-Ovarian Symptom Index 18 (FOSI-18) Changes. The time to an event in PRO (patient-reported outcome) of worsening of disease symptoms will be defined as the time from randomisation to a 4-point reduction in the FACT-O questionnaire to assess PRO of patients receiving chemotherapy plus pembrolizumab with respect to patients receiving chemotherapy alone using Euro-Quality of Life 5D tool, indicating which statements best describe the patient health state regarding: mobility, self-care, usual activities, pain/discomfort, anxiety/depression.

MITO-27 *(Continued)*

Starting date	June 2018
Contact information	domenica.lorusso@istitutotumori.mi.it
Notes	https://clinicaltrials.gov/ct2/show/NCT03539328?term=NCT03539328&draw=2&rank=1

MITO-29/NCT03467178

Study name	MITO29/NCT03467178
Methods	Open-label, prospective, multicentre, randomised phase II
Participants	119 participants Age ≥ 18 years **Inclusion criteria** Cytologic/histologic diagnosis of FIGO stage 1 to 4 epithelial, fallopian tube and primary peritoneal cancer (carcinosarcomas are included) 1-2 prior lines of treatment Relapsed within 6 months after platinum containing regimen Disease measurable or evaluable by RECIST version 1.1 or Ca 125 GCIG criteria (Gynaecologic Cancer Intergroup). No residual peripheral neurotoxicity > Grade 1 from previous chemotherapy treatment Performance Status (PS) 0 to 1 Life expectancy of at least 3 months Adequate organ functions **Exclusion criteria** Pregnant or breast-feeding. Serious heart disease. Active infection requiring antibiotics. History of cerebrovascular accident, pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months History of human immunodeficiency virus (HIV) infection or chronic hepatitis B or C. Patients with evidence of interstitial lung disease.
Interventions	Carboplatin AUC (Area Under Curve) 5 day 8 every 4 weeks plus decitabine 10 mg/m^2 IV days 1 to 5 every 4 weeks versus PLD 40 mg/m^2 every 4 weeks or gemcitabine 1000 mg/m^2 days 1, 8, 15 every 4 weeks or weekly paclitaxel 80 mg/m^2 days 1, 8, 15 every 4 weeks
Outcomes	**Primary outcome**

MITO-29/NCT03467178 *(Continued)*

	PFS (from randomisation to the date of radiological/clinical progression of disease or death, assessed up to 3 years) **Secondary outcomes** Overall survival (OS) (from randomisation to the date of death, assessed up to 3 years) Radiological response rate (in patients with measurable disease) Duration of response Cancer-Antigen 125 (CA-125) response rate Toxicity profile Patient Reported Outcome: physical well-being (3 years) Patient Reported Outcome: social/family well-being (3 years) Patient Reported Outcome: functional well-being (3 years) Patient Reported Outcome: emotional well-being (3 years) Functional Assessment of Cancer Therapy (FACT-O) and FACT-O Ovarian Cancer-specific Subscale (OCS) questionnaire
Starting date	30 July 2018
Contact information	domenica.lorusso@istitutotumori.mi.it
Notes	https://clinicaltrials.gov/ct2/show/NCT03467178?term=NCT03467178&draw=2&rank=1

NCT01100372

Study name	NCT01100372
Methods	Randomised phase II trial
Participants	154 participants **Disease characteristics** Histologically confirmed ovarian epithelial, fallopian tube, or primary peritoneal cavity cancer Recurrent platinum-refractory disease OR platinum-resistant disease Meets ≥ 1 of the following criteria: • Measurable metastatic disease on CT or MRI scan, ultrasound, or chest x-ray • Evaluable disease on CT/MRI scan (e.g., ascites or pleural effusion) or chest x-ray (e.g., pleural effusion) Tumour marker progression (CA-125) according to Rustin criteria, meeting 1 of the following criteria: • CA-125 > 2 times upper limit of normal (UNL) • CA-125 > 2 times nadir value on two occasions • No ovarian carcinosarcoma (malignant mixed Müllerian tumour) or pure sarcoma **Participant characteristics** Karnofsky performance status 70 to 100% Life expectancy ≥ 3 months

NCT01100372 *(Continued)*

	Platelet count ≥ 100,000/mm^3 Haemoglobin ≥ 10 g/dL Neutrophil count ≥ 1.5 x 10^3/mm^3 Serum creatinine < 1.5 times ULN Bilirubin < 1.5 times ULN (< 2.5 times ULN if liver metastases are present) AST/ALT < 2.5 times ULN (unless caused by parenchymal liver metastases) No childbearing capacity LVEF ≥ 50% by ECHO or MUGA scan No significant comorbidity (e.g. uncontrolled infection, clinical signs of cardiac insufficiency, history of myocardial infarction, or cardiac rhythmic disorders (NYHA class III-IV disease)) No known hypersensitivity to study drugs No active secondary malignant tumour within the past 5 years (e.g. metastases from primary breast cancer) No condition (medical, social, or psychological), that would prevent adequate follow-up **Prior concurrent therapy** No prior chemotherapy with PLD, other anthracyclines, or gemcitabine hydrochloride No other concurrent tumour-specific therapy for ovarian cancer
Interventions	PLD on day 1 and gemcitabine on days 1 and 8 every 3 weeks for 6 courses. versus PLD on day 1 every 3 weeks for 6 courses.
Outcomes	**Primary outcome** Remission rates (complete response and partial response) **Secondary outcomes** Quality of life as measured by EORTC-QLQ30 and QLQ-OV28 questionnaires Progression-free survival Overall survival Toxicity
Starting date	8 April 2010
Contact information	Alain Zeimet, Medical University Innsbruck Alain.zeimet@i-med.ac.at
Notes	https://clinicaltrials.gov/ct2/show/NCT01100372?cond=nct01100372&draw=2&rank=1

NCT03353831

Study name	NTC03353831
Methods	Randomised phase III trial
Participants	Platinum resistant **Inclusion criteria** Epithelial ovarian, fallopian tube, or primary peritoneal cancer Up to three prior therapies Biopsy for PDL1 status
Interventions	Paclitaxel or PLD

NCT03353831 *(Continued)*

	AND Bevacizumab AND Atezolizumab or placebo
Outcomes	**Primary outcomes** OS PFS
Starting date	September 2018
Contact information	AGO Research GmbH
Notes	

NCT04739800

Study name	Comparison of Standard of Care Treatment With a Triplet Combination of Targeted Immunotherapeutic Agents
Methods	Randomised Phase II Trial
Participants	Estimated enrolment 164 participants PR
Interventions	**Intervention** MEDI4736 (durvalumab) and olaparib and cediranib or Durvalumab and cediranib or Olaparib and cediranib **Control** Standard of care chemotherapy
Outcomes	**Primary outcome** PFS **Secondary outcomes** Objective response rate Duration of response Overall survival Incidence of adverse events
Starting date	28 April 2021

NCT04739800 *(Continued)*

Contact information	
Notes	

NCT05092360

Study name	Phase 3 Study of Nemvaleukin Alfa in Combination With Pembrolizumab (ARTISTRY-7)
Methods	Phase 3, multicentre, open-label, randomised study
Participants	Estimated enrolment 376 participants PR
Interventions	**Intervention**: nemvaleukin and pembrolizumab combination **Control**: PLD or topotecan or paclitaxel or gemcitabine
Outcomes	**Primary outcome** PFS **Secondary outcomes** Objective response rate Overall Survival Rate Disease Control Rate Duration of Response Time to Response CA-125 Treatment-emergent adverse events
Starting date	10 February 2022
Contact information	
Notes	

PROVE/NCT01388621

Study name	
Methods	Phase II open-label RCT
Participants	140 women with ROC
Interventions	Panitumumab + carbo + PLD or GEM versus carbo + PLD or GEM (physician's choice)
Outcomes	**Primary outcome** PFS

PROVE/NCT01388621 *(Continued)*	**Secondary outcomes** OS Duration of response SAE Translational research
Starting date	
Contact information	
Notes	End Date: July 2015; once available, we will request data by those participants treated with PLD, and will be transferred to 'awaiting classification' until these are made available by the author (requested).

Abbreviations: CR = complete response; DCR = disease control rate; DDC = duration of disease control; GEM = gemcitabine; IV: intravenous; OC = ovarian cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PLD = pegylated liposomal doxorubicin; PR = partial response; PR ROC = platinum refractory relapsed ovarian cancer; QoL = quality of life; ROC = relapsed ovarian cancer; RCT = randomised controlled trial; SAE = serious adverse event; TOP = topotecan

DATA AND ANALYSES

Comparison 1. Platinum-sensitive recurrent EOC: PLD with chemotherapy versus alternative combination chemotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Overall survival	5	2006	Hazard Ratio (IV, Fixed, 95% CI)	0.93 [0.83, 1.04]
1.1.1 PLD with carboplatin versus carboplatin alone	1	61	Hazard Ratio (IV, Fixed, 95% CI)	0.69 [0.40, 1.21]
1.1.2 PLD with carboplatin versus paclitaxel with carboplatin	2	1164	Hazard Ratio (IV, Fixed, 95% CI)	1.01 [0.88, 1.17]
1.1.3 PLD with carboplatin versus gemcitabine with carboplatin	1	99	Hazard Ratio (IV, Fixed, 95% CI)	1.04 [0.61, 1.78]
1.1.4 PLD with carboplatin and bevacizumab versus gemcitabine with carboplatin and bevacizumab	1	682	Hazard Ratio (IV, Fixed, 95% CI)	0.81 [0.67, 0.98]
1.2 Progression-free survival	5	2006	Hazard Ratio (IV, Fixed, 95% CI)	0.81 [0.74, 0.89]
1.2.1 PLD with carboplatin versus carboplatin alone	1	61	Hazard Ratio (IV, Fixed, 95% CI)	0.52 [0.31, 0.88]
1.2.2 PLD with carboplatin versus paclitaxel with carboplatin	2	1164	Hazard Ratio (IV, Fixed, 95% CI)	0.84 [0.75, 0.95]
1.2.3 PLD with carboplatin versus gemcitabine with carboplatin	1	99	Hazard Ratio (IV, Fixed, 95% CI)	0.69 [0.45, 1.05]

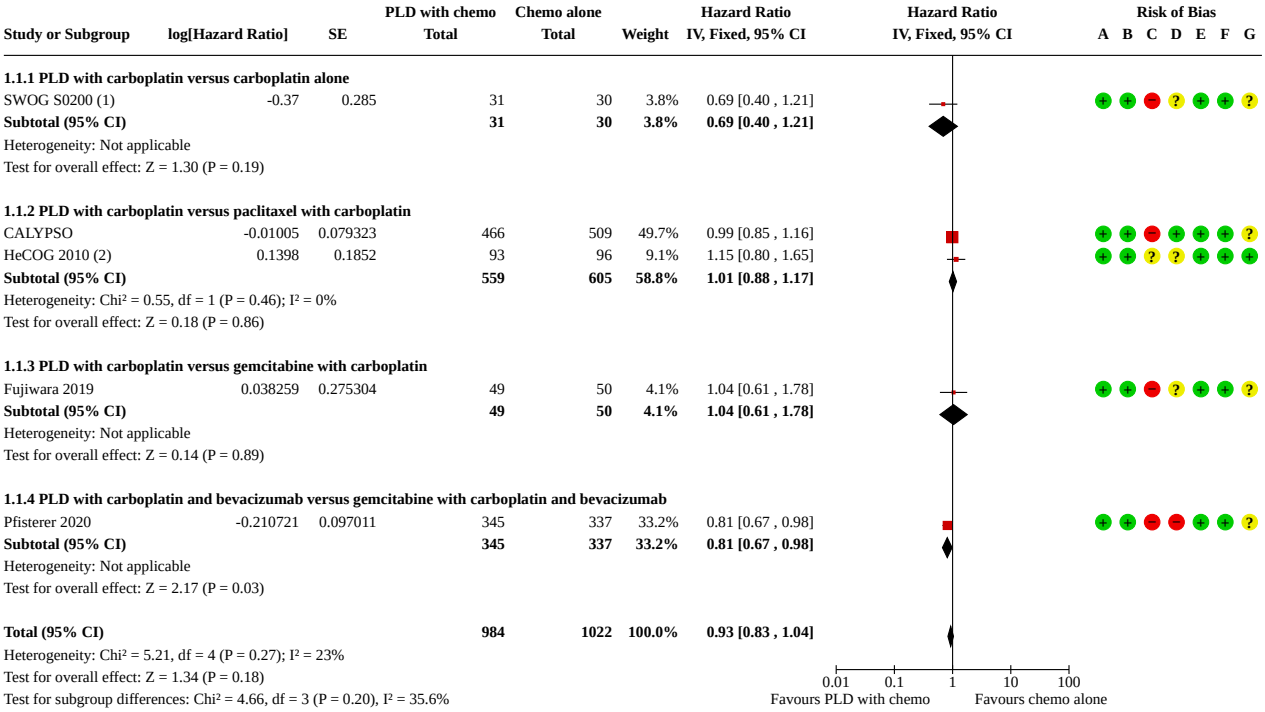
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.4 PLD with carboplatin and bevacizumab versus gemcitabine with carboplatin and bevacizumab	1	682	Hazard Ratio (IV, Fixed, 95% CI)	0.81 [0.68, 0.96]
1.3 Quality of life	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.3.1 PLD with carboplatin versus paclitaxel with carboplatin	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.4 Overall Severe Adverse Events (grade ≥ 3)	2	834	Risk Ratio (IV, Fixed, 95% CI)	1.11 [0.95, 1.30]
1.4.1 PLD with carboplatin versus paclitaxel with carboplatin	1	173	Risk Ratio (IV, Fixed, 95% CI)	1.11 [0.94, 1.31]
1.4.2 PLD with carboplatin and bevacizumab versus gemcitabine with carboplatin and bevacizumab	1	661	Risk Ratio (IV, Fixed, 95% CI)	1.17 [0.72, 1.89]
1.5 SevAE: Anaemia (grade ≥ 3)	5	1961	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.02, 1.85]
1.5.1 PLD with carboplatin versus carboplatin alone	1	61	Risk Ratio (M-H, Fixed, 95% CI)	10.66 [0.61, 184.70]
1.5.2 PLD with carboplatin versus paclitaxel with carboplatin	2	1140	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [1.03, 2.52]
1.5.3 PLD with carboplatin versus gemcitabine with carboplatin	1	99	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.60, 3.52]
1.5.4 PLD with carboplatin and bevacizumab versus gemcitabine with carboplatin and bevacizumab	1	661	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.62, 1.58]
1.6 SevAE: Hand-foot syndrome (grade ≥ 3)	5	1961	Risk Ratio (M-H, Fixed, 95% CI)	4.01 [1.00, 16.01]
1.6.1 PLD with carboplatin versus carboplatin alone	1	61	Risk Ratio (M-H, Fixed, 95% CI)	2.91 [0.12, 68.66]
1.6.2 PLD with carboplatin versus paclitaxel with carboplatin	2	1140	Risk Ratio (M-H, Fixed, 95% CI)	4.30 [0.92, 20.15]
1.6.3 PLD with carboplatin versus gemcitabine with carboplatin	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.6.4 PLD with carboplatin and bevacizumab versus gemcitabine with carboplatin and bevacizumab	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.7 SevAE: Neurological (grade ≥ 3)	4	1900	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.20, 0.74]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7.1 PLD with carboplatin versus paclitaxel with carboplatin	2	1140	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.08, 0.48]
1.7.2 PLD with carboplatin versus gemcitabine with carboplatin	1	99	Risk Ratio (M-H, Fixed, 95% CI)	3.06 [0.13, 73.34]
1.7.3 PLD with carboplatin and bevacizumab versus gemcitabine with carboplatin and bevacizumab	1	661	Risk Ratio (M-H, Fixed, 95% CI)	2.48 [0.48, 12.68]
1.8 SevAE: Neutropenia (grade ≥ 3)	5	1961	Risk Ratio (IV, Fixed, 95% CI)	0.78 [0.70, 0.88]
1.8.1 PLD with carboplatin versus carboplatin alone	1	61	Risk Ratio (IV, Fixed, 95% CI)	14.52 [2.04, 103.16]
1.8.2 PLD with carboplatin versus paclitaxel with carboplatin	2	1140	Risk Ratio (IV, Fixed, 95% CI)	0.81 [0.70, 0.94]
1.8.3 PLD with carboplatin versus gemcitabine with carboplatin	1	99	Risk Ratio (IV, Fixed, 95% CI)	0.80 [0.64, 1.01]
1.8.4 PLD with carboplatin and bevacizumab versus gemcitabine with carboplatin and bevacizumab	1	661	Risk Ratio (IV, Fixed, 95% CI)	0.54 [0.38, 0.77]
1.9 SevAE: Thrombocytopenia (grade ≥ 3)	5	1961	Risk Ratio (IV, Fixed, 95% CI)	1.14 [0.90, 1.44]
1.9.1 PLD with carboplatin versus carboplatin alone	1	61	Risk Ratio (IV, Fixed, 95% CI)	3.87 [1.21, 12.36]
1.9.2 PLD with carboplatin versus paclitaxel with carboplatin	2	1140	Risk Ratio (IV, Fixed, 95% CI)	2.69 [1.83, 3.96]
1.9.3 PLD with carboplatin versus gemcitabine with carboplatin	1	99	Risk Ratio (IV, Fixed, 95% CI)	0.75 [0.46, 1.23]
1.9.4 PLD with carboplatin and bevacizumab versus gemcitabine with carboplatin and bevacizumab	1	661	Risk Ratio (IV, Fixed, 95% CI)	0.53 [0.36, 0.78]
1.10 SevAE: Stomatitis (grade ≥ 3)	4	1900	Risk Ratio (M-H, Fixed, 95% CI)	2.52 [1.01, 6.28]
1.10.1 PLD with carboplatin versus paclitaxel with carboplatin	2	1140	Risk Ratio (M-H, Fixed, 95% CI)	2.44 [0.90, 6.61]
1.10.2 PLD with carboplatin versus gemcitabine with carboplatin	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.10.3 PLD with carboplatin and bevacizumab versus gemcitabine with carboplatin and bevacizumab	1	661	Risk Ratio (M-H, Fixed, 95% CI)	2.97 [0.31, 28.43]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.11 SevAE: Vomiting (grade ≥ 3)	5	1961	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.78, 2.02]
1.11.1 PLD with carboplatin versus carboplatin alone	1	61	Risk Ratio (M-H, Fixed, 95% CI)	2.91 [0.12, 68.66]
1.11.2 PLD with carboplatin versus paclitaxel with carboplatin	2	1140	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.68, 2.00]
1.11.3 PLD with carboplatin versus gemcitabine with carboplatin	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.11.4 PLD with carboplatin and bevacizumab versus gemcitabine with carboplatin and bevacizumab	1	661	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.54, 4.13]
1.12 SevAE: Fatigue (grade ≥ 3)	5	1961	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.67, 1.50]
1.12.1 PLD with carboplatin versus carboplatin alone	1	61	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.26, 8.09]
1.12.2 PLD with carboplatin versus paclitaxel with carboplatin	2	1140	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.63, 1.62]
1.12.3 PLD with carboplatin versus gemcitabine with carboplatin	1	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.12.4 PLD with carboplatin and bevacizumab versus gemcitabine with carboplatin and bevacizumab	1	661	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.39, 2.09]
1.13 SevAE: Arthralgia/myalgia (grade ≥ 3)	4	1862	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.04, 0.85]
1.13.1 PLD with carboplatin versus carboplatin alone	1	61	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.63]
1.13.2 PLD with carboplatin versus paclitaxel with carboplatin	2	1140	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.02, 1.48]
1.13.3 PLD with carboplatin and bevacizumab versus gemcitabine with carboplatin and bevacizumab	1	661	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.78]
1.14 SevAE: Hypersensitivity reactions (grade ≥ 3)	5	1961	Risk Ratio (IV, Fixed, 95% CI)	0.27 [0.15, 0.48]
1.14.1 PLD with carboplatin versus carboplatin alone	1	61	Risk Ratio (IV, Fixed, 95% CI)	0.09 [0.01, 1.53]
1.14.2 PLD with carboplatin versus paclitaxel with carboplatin	2	1140	Risk Ratio (IV, Fixed, 95% CI)	0.29 [0.15, 0.54]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.14.3 PLD with carboplatin versus gemcitabine with carboplatin	1	99	Risk Ratio (IV, Fixed, 95% CI)	0.20 [0.01, 4.14]
1.14.4 PLD with carboplatin and bevacizumab versus gemcitabine with carboplatin and bevacizumab	1	661	Risk Ratio (IV, Fixed, 95% CI)	0.20 [0.01, 4.11]
1.15 Serious AE: Treatment-related death	3	1801	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.29, 7.15]
1.15.1 PLD with carboplatin versus paclitaxel with carboplatin	2	1140	Risk Ratio (M-H, Fixed, 95% CI)	5.37 [0.26, 111.66]
1.15.2 PLD with carboplatin and bevacizumab versus gemcitabine with carboplatin and bevacizumab	1	661	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.05, 5.44]
1.16 Discontinuation due to toxicity	3	1811	Risk Ratio (IV, Fixed, 95% CI)	0.93 [0.75, 1.15]
1.16.1 PLD with carboplatin versus paclitaxel with carboplatin	2	1150	Risk Ratio (IV, Fixed, 95% CI)	0.38 [0.26, 0.57]
1.16.2 PLD with carboplatin and bevacizumab versus gemcitabine with carboplatin and bevacizumab	1	661	Risk Ratio (IV, Fixed, 95% CI)	1.32 [1.03, 1.70]
1.17 Antibiotics required	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.17.1 PLD with carboplatin versus paclitaxel with carboplatin	2	1144	Risk Ratio (IV, Random, 95% CI)	1.12 [0.57, 2.21]
1.18 Granulocyte colony stimulating factor (G-CSF) required	2	838	Risk Ratio (IV, Fixed, 95% CI)	1.14 [0.85, 1.54]
1.18.1 PLD with carboplatin versus paclitaxel with carboplatin	1	177	Risk Ratio (IV, Fixed, 95% CI)	1.14 [0.84, 1.54]
1.18.2 PLD with carboplatin and bevacizumab versus gemcitabine with carboplatin and bevacizumab	1	661	Risk Ratio (IV, Fixed, 95% CI)	1.49 [0.25, 8.84]

Analysis 1.1. Comparison 1: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus alternative combination chemotherapy, Outcome 1: Overall survival



Footnotes

(1) Final unpublished data

(2) Unpublished data

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

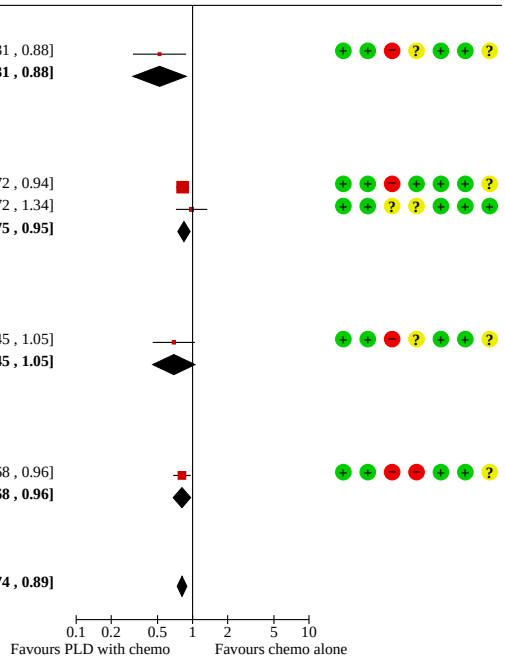
(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Analysis 1.2. Comparison 1: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus alternative combination chemotherapy, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	PLD with chemo Total	Chemo alone Total	Weight	Hazard Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G
1.2.1 PLD with carboplatin versus carboplatin alone							
SWOG S0200 (1)	-0.653	0.268	31	30	3.3%	0.52 [0.31 , 0.88]	+ + − ? + + ?
Subtotal (95% CI)			**31**	**30**	**3.3%**	**0.52 [0.31 , 0.88]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.44 (P = 0.01)							
1.2.2 PLD with carboplatin versus paclitaxel with carboplatin							
CALYPSO	-0.198	0.067	466	509	52.0%	0.82 [0.72 , 0.94]	+ + − + + + ?
HeCOG 2010 (1)	-0.02	0.158	93	96	9.4%	0.98 [0.72 , 1.34]	+ + ? ? + + +
Subtotal (95% CI)			**559**	**605**	**61.4%**	**0.84 [0.75 , 0.95]**	
Heterogeneity: Chi² = 1.08, df = 1 (P = 0.30); I² = 7%							
Test for overall effect: Z = 2.77 (P = 0.006)							
1.2.3 PLD with carboplatin versus gemcitabine with carboplatin							
Fujiwara 2019	-0.371064	0.212603	49	50	5.2%	0.69 [0.45 , 1.05]	+ + − ? + + ?
Subtotal (95% CI)			**49**	**50**	**5.2%**	**0.69 [0.45 , 1.05]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.75 (P = 0.08)							
1.2.4 PLD with carboplatin and bevacizumab versus gemcitabine with carboplatin and bevacizumab							
Pfisterer 2020	-0.210721	0.087971	345	337	30.2%	0.81 [0.68 , 0.96]	+ + − − + + ?
Subtotal (95% CI)			**345**	**337**	**30.2%**	**0.81 [0.68 , 0.96]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.40 (P = 0.02)							
Total (95% CI)			**984**	**1022**	**100.0%**	**0.81 [0.74 , 0.89]**	
Heterogeneity: Chi² = 4.78, df = 4 (P = 0.31); I² = 16%							
Test for overall effect: Z = 4.32 (P < 0.0001)							
Test for subgroup differences: Chi² = 3.71, df = 3 (P = 0.29), I² = 19.1%							

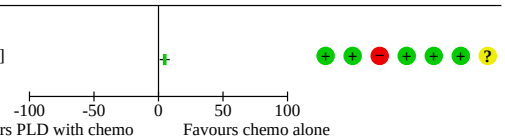


Footnotes
(1) Unpublished data

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.3. Comparison 1: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus alternative combination chemotherapy, Outcome 3: Quality of life

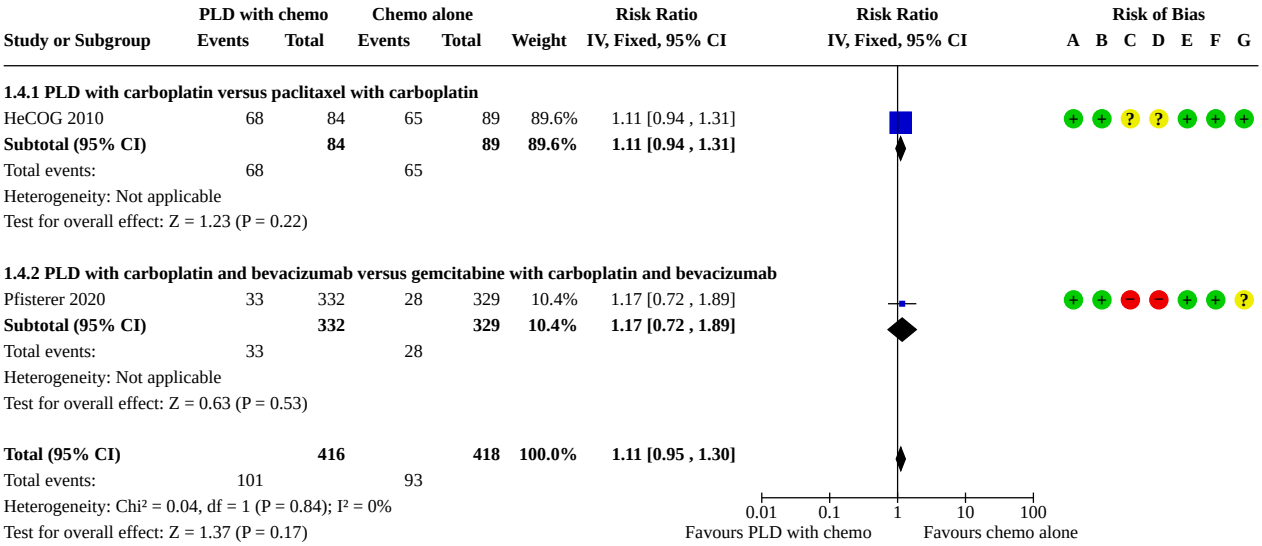
Study or Subgroup	PLD with chemo Mean	SD	Total	Chemo alone Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F G
1.3.1 PLD with carboplatin versus paclitaxel with carboplatin								
CALYPSO (1)	2.6	26	301	-2.2	22.7	307	4.80 [0.92 , 8.68]	+ + − + + + ?



Footnotes
(1) mean change at 3 months post-randomisation measured using by European Organisation for Research andTreatment of Cancer Quality of Life Questionnaire C30

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

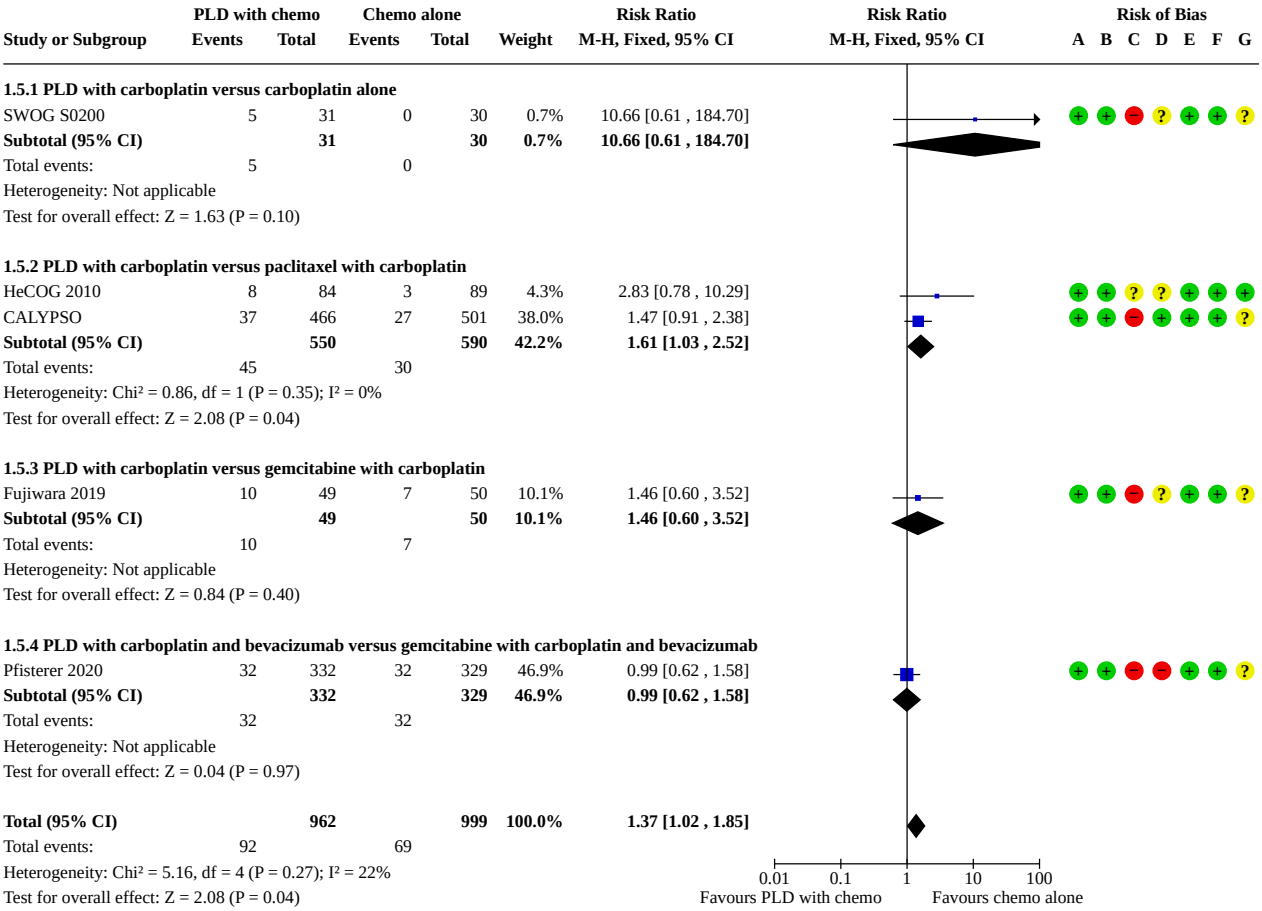
Analysis 1.4. Comparison 1: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus alternative combination chemotherapy, Outcome 4: Overall Severe Adverse Events (grade ≥ 3)



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.5. Comparison 1: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus alternative combination chemotherapy, Outcome 5: SevAE: Anaemia (grade ≥ 3)

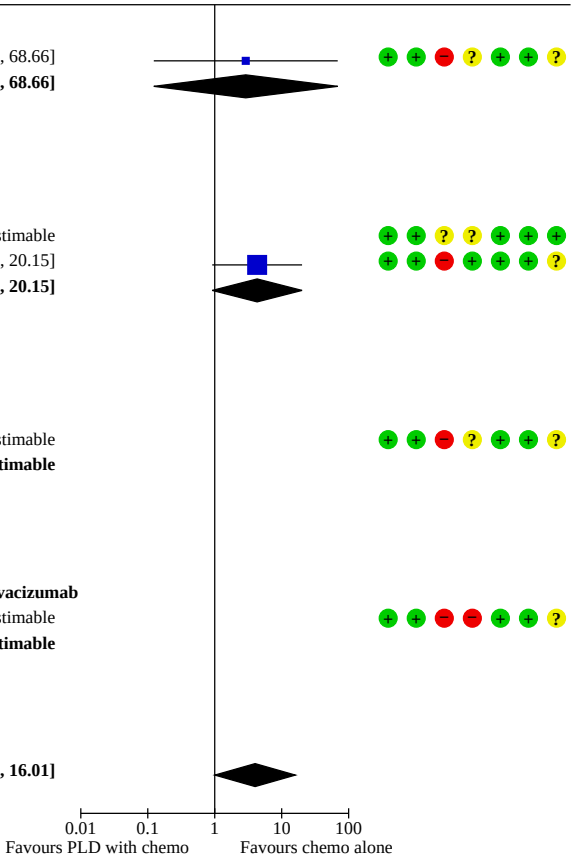


Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.6. Comparison 1: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus alternative combination chemotherapy, Outcome 6: SevAE: Hand-foot syndrome (grade ≥ 3)

Study or Subgroup	PLD with chemo Events	PLD with chemo Total	Chemo alone Events	Chemo alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 PLD with carboplatin versus carboplatin alone						
SWOG S0200	1	31	0	30	20.9%	2.91 [0.12 , 68.66]
Subtotal (95% CI)		**31**		**30**	**20.9%**	**2.91 [0.12 , 68.66]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
1.6.2 PLD with carboplatin versus paclitaxel with carboplatin						
HeCOG 2010	0	84	0	89		Not estimable
CALYPSO (1)	8	466	2	501	79.1%	4.30 [0.92 , 20.15]
Subtotal (95% CI)		**550**		**590**	**79.1%**	**4.30 [0.92 , 20.15]**
Total events:	8		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.85 (P = 0.06)						
1.6.3 PLD with carboplatin versus gemcitabine with carboplatin						
Fujiwara 2019	0	49	0	50		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.6.4 PLD with carboplatin and bevacizumab versus gemcitabine with carboplatin and bevacizumab						
Pfisterer 2020	0	332	0	329		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**962**		**999**	**100.0%**	**4.01 [1.00 , 16.01]**
Total events:	9		2			
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.83); I² = 0%						
Test for overall effect: Z = 1.97 (P = 0.05)						
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.83), I² = 0%						



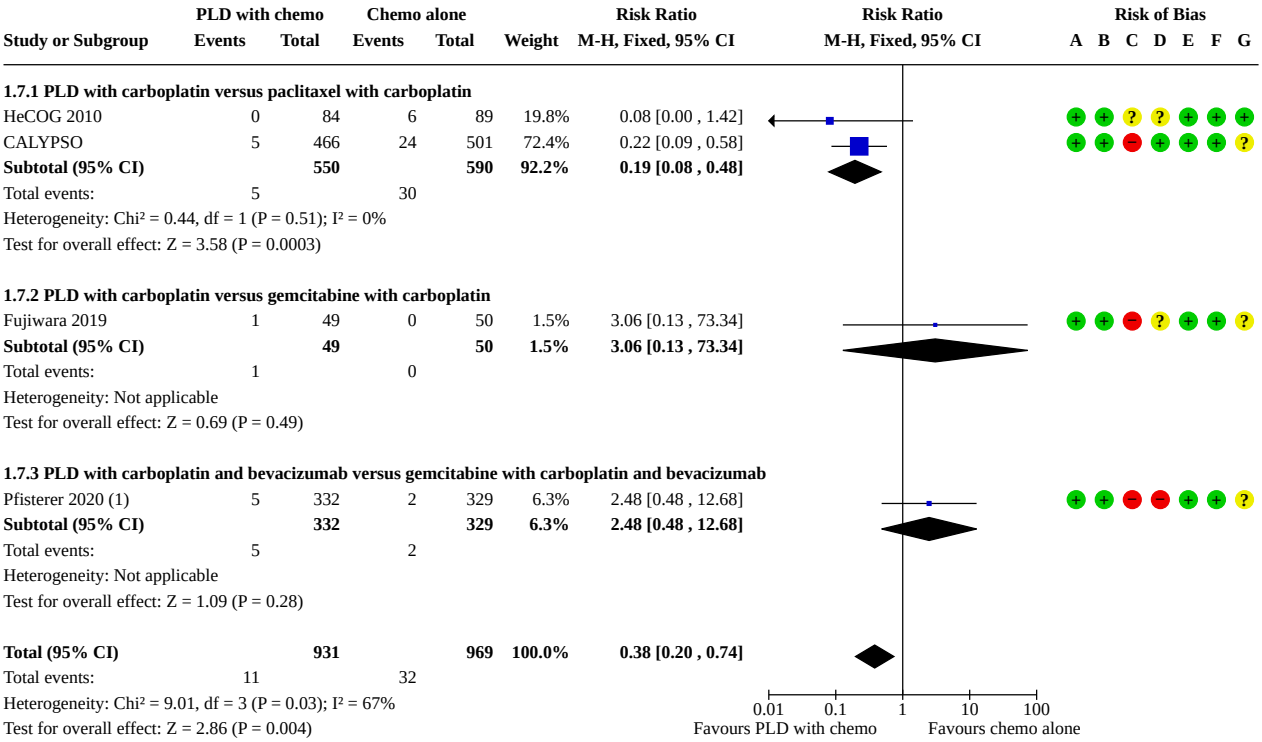
Footnotes

(1) Grade 3 only. No women experienced grade 4 events.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.7. Comparison 1: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus alternative combination chemotherapy, Outcome 7: SevAE: Neurological (grade ≥ 3)



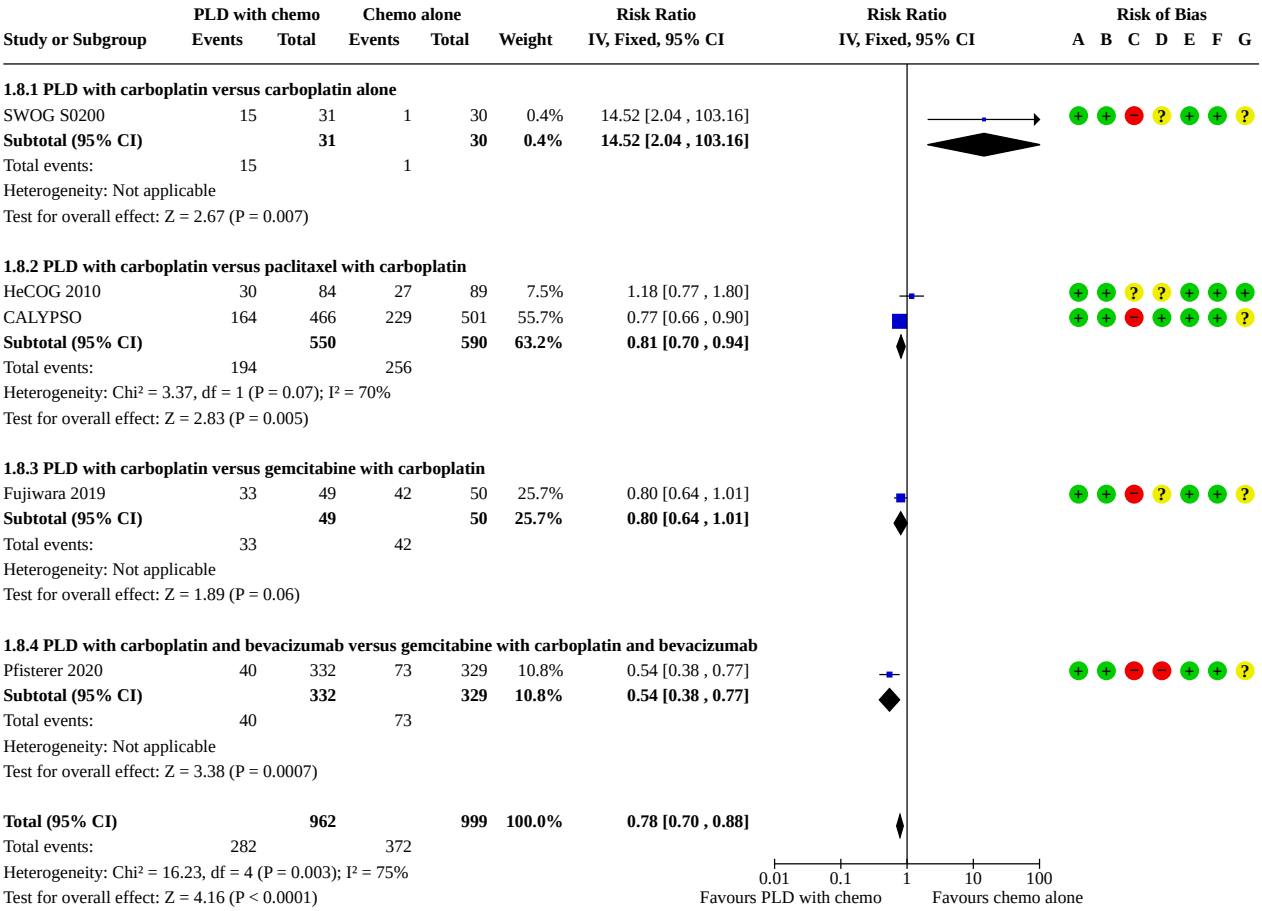
Footnotes

(1) Peripheral Sensory Neuropathy Only

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

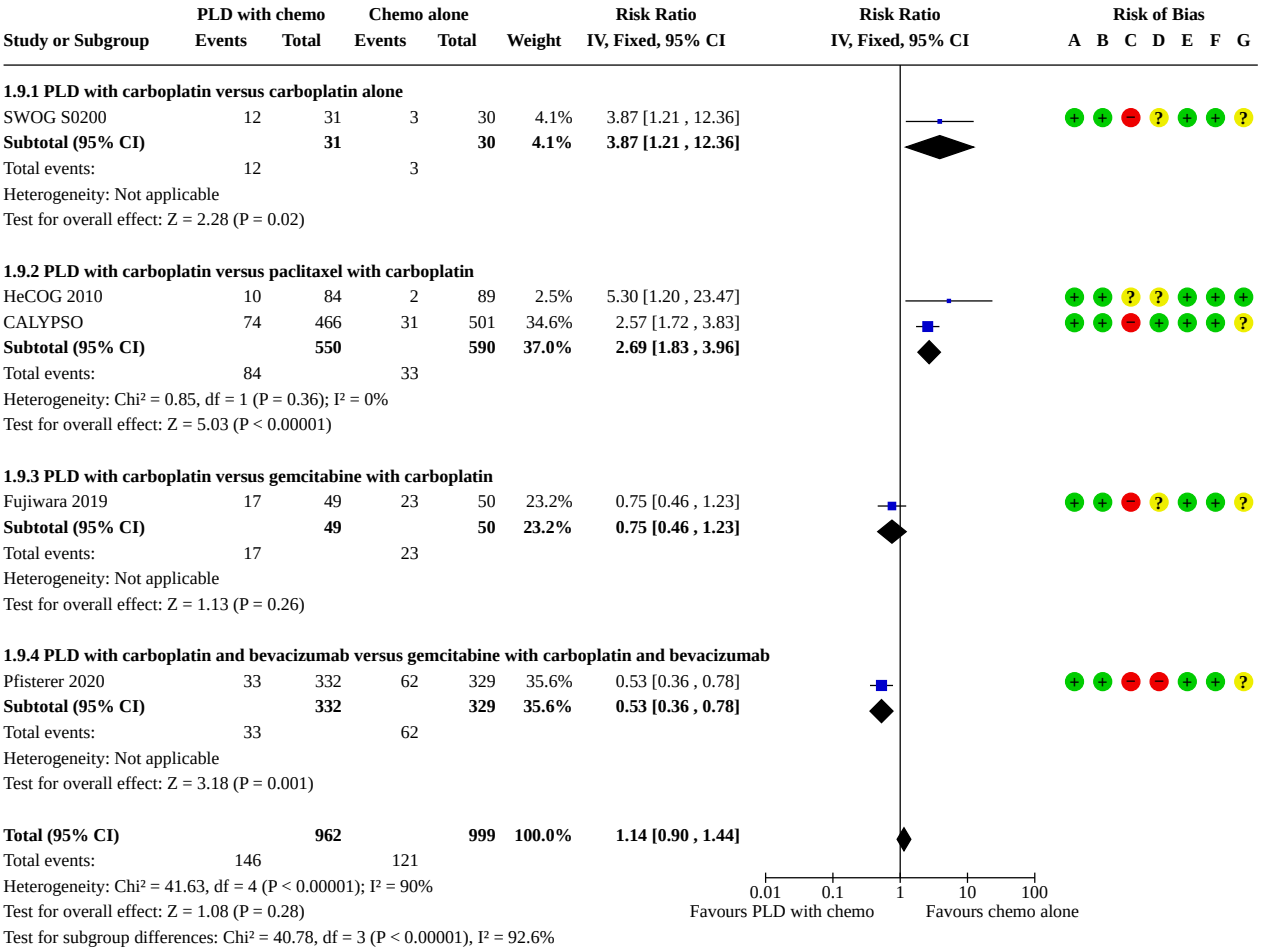
Analysis 1.8. Comparison 1: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus alternative combination chemotherapy, Outcome 8: SevAE: Neutropenia (grade ≥ 3)



Study or Subgroup	PLD with chemo Events	PLD with chemo Total	Chemo alone Events	Chemo alone Total	Weight	Risk Ratio IV, Fixed, 95% CI
1.8.1 PLD with carboplatin versus carboplatin alone						
SWOG S0200	15	31	1	30	0.4%	14.52 [2.04 , 103.16]
Subtotal (95% CI)		**31**		**30**	**0.4%**	**14.52 [2.04 , 103.16]**
Total events:	15		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.67 (P = 0.007)						
1.8.2 PLD with carboplatin versus paclitaxel with carboplatin						
HeCOG 2010	30	84	27	89	7.5%	1.18 [0.77 , 1.80]
CALYPSO	164	466	229	501	55.7%	0.77 [0.66 , 0.90]
Subtotal (95% CI)		**550**		**590**	**63.2%**	**0.81 [0.70 , 0.94]**
Total events:	194		256			
Heterogeneity: Chi² = 3.37, df = 1 (P = 0.07); I² = 70%						
Test for overall effect: Z = 2.83 (P = 0.005)						
1.8.3 PLD with carboplatin versus gemcitabine with carboplatin						
Fujiwara 2019	33	49	42	50	25.7%	0.80 [0.64 , 1.01]
Subtotal (95% CI)		**49**		**50**	**25.7%**	**0.80 [0.64 , 1.01]**
Total events:	33		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.89 (P = 0.06)						
1.8.4 PLD with carboplatin and bevacizumab versus gemcitabine with carboplatin and bevacizumab						
Pfisterer 2020	40	332	73	329	10.8%	0.54 [0.38 , 0.77]
Subtotal (95% CI)		**332**		**329**	**10.8%**	**0.54 [0.38 , 0.77]**
Total events:	40		73			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.38 (P = 0.0007)						
Total (95% CI)		**962**		**999**	**100.0%**	**0.78 [0.70 , 0.88]**
Total events:	282		372			
Heterogeneity: Chi² = 16.23, df = 4 (P = 0.003); I² = 75%						
Test for overall effect: Z = 4.16 (P < 0.0001)						
Test for subgroup differences: Chi² = 12.86, df = 3 (P = 0.005), I² = 76.7%						

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

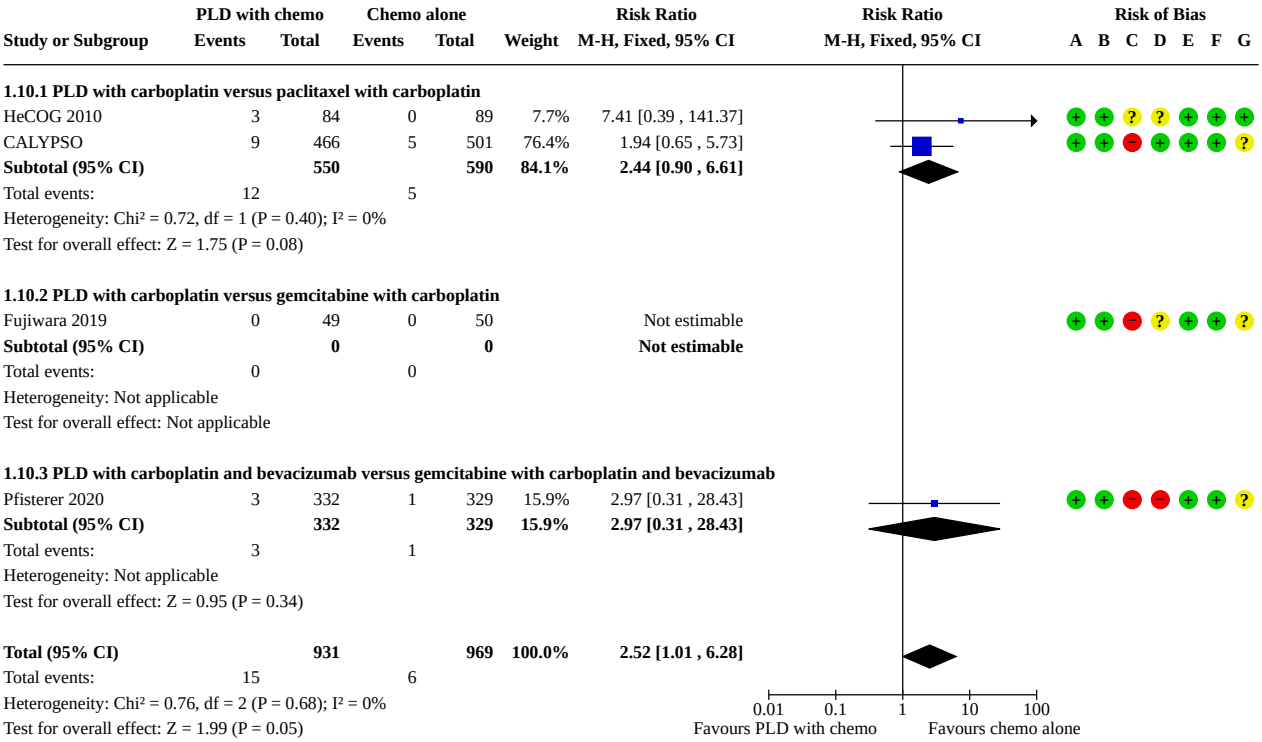
Analysis 1.9. Comparison 1: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus alternative combination chemotherapy, Outcome 9: SevAE: Thrombocytopenia (grade ≥ 3)



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

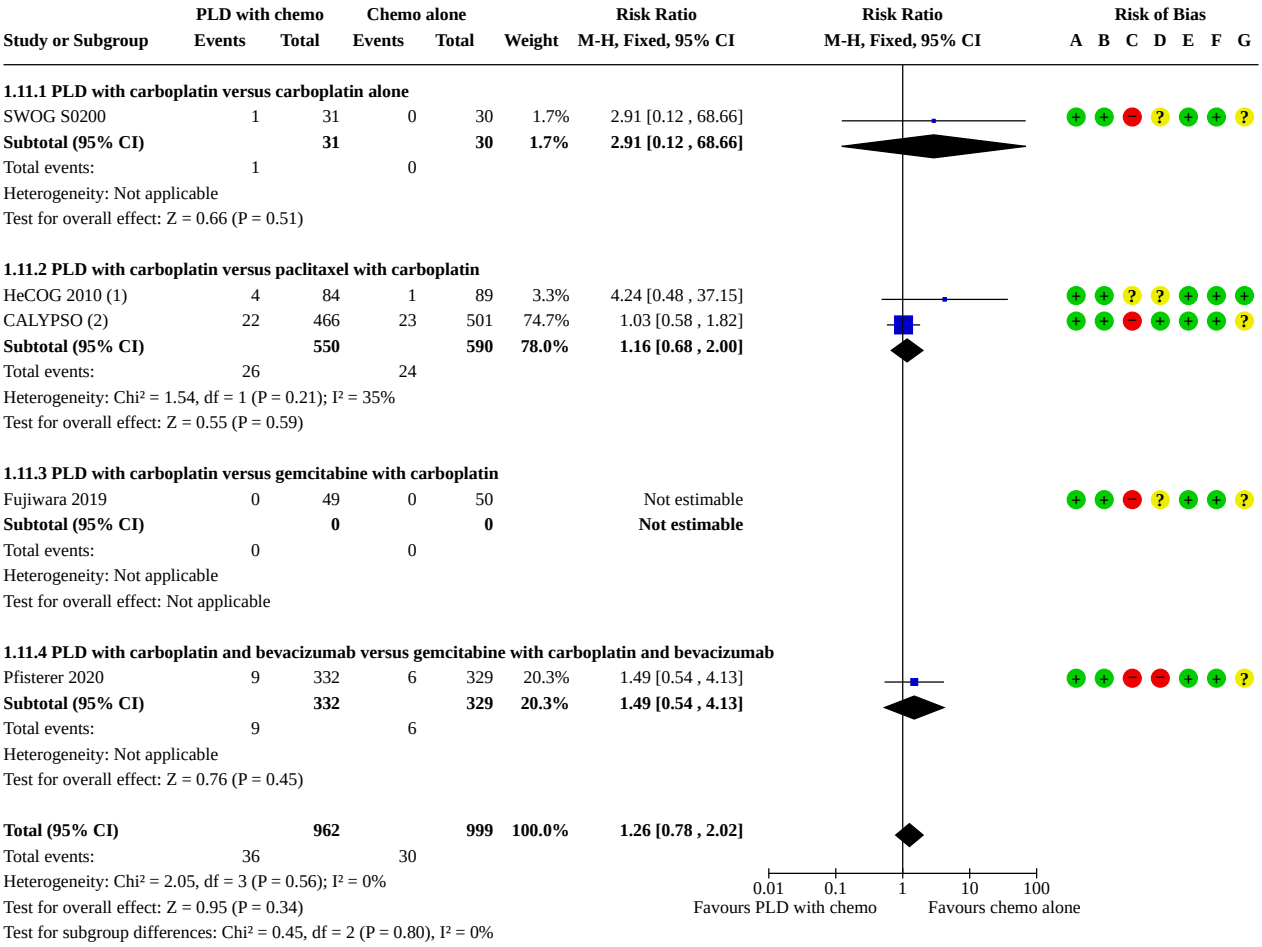
Analysis 1.10. Comparison 1: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus alternative combination chemotherapy, Outcome 10: SevAE: Stomatitis (grade ≥ 3)



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.11. Comparison 1: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus alternative combination chemotherapy, Outcome 11: SevAE: Vomiting (grade ≥ 3)



Footnotes

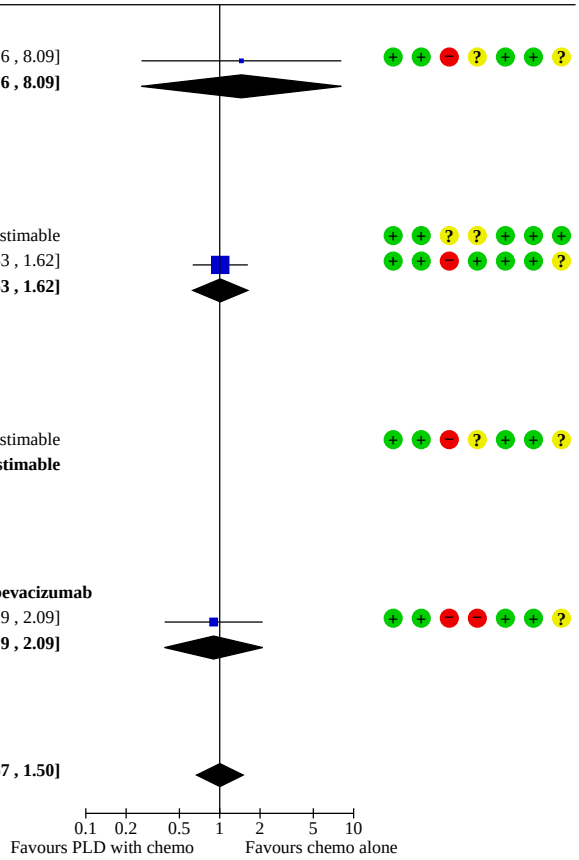
(1) Nausea/vomiting
(2) Vomiting only.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.12. Comparison 1: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus alternative combination chemotherapy, Outcome 12: SevAE: Fatigue (grade ≥ 3)

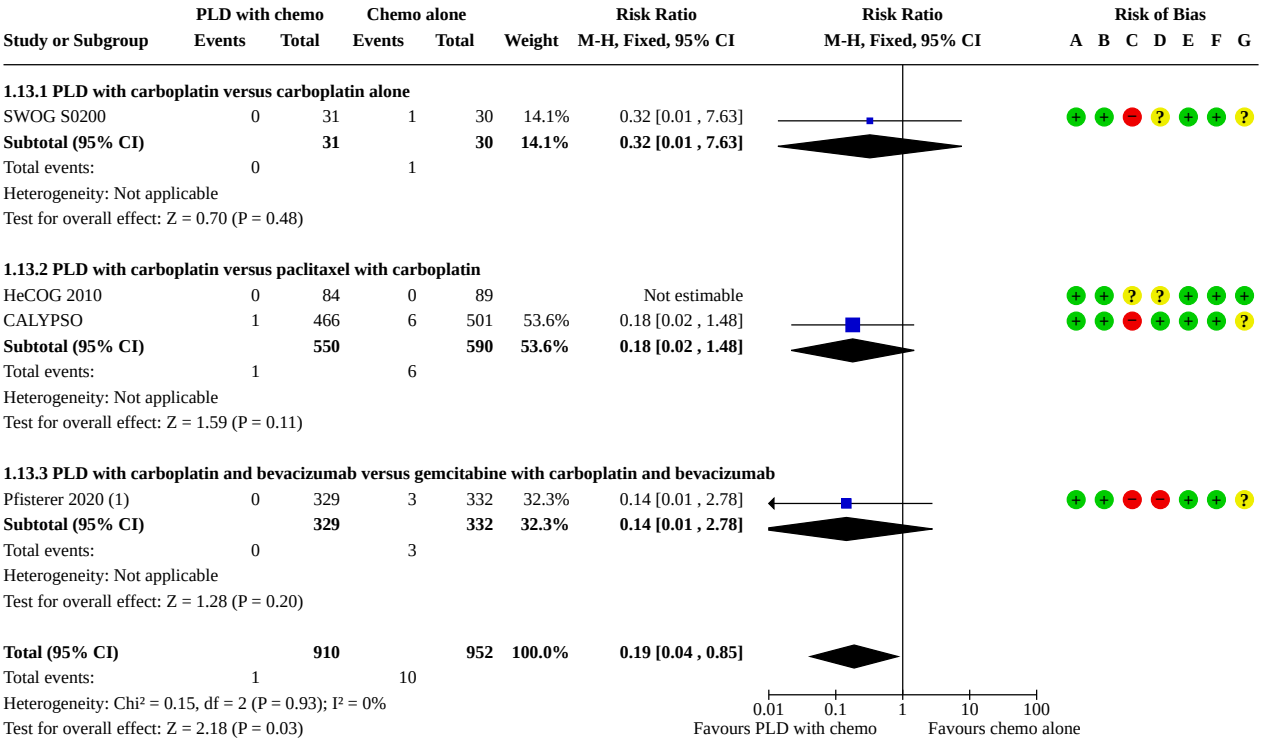
Study or Subgroup	PLD with chemo Events	PLD with chemo Total	Chemo alone Events	Chemo alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.12.1 PLD with carboplatin versus carboplatin alone						
SWOG S0200	3	31	2	30	4.5%	1.45 [0.26 , 8.09]
Subtotal (95% CI)		**31**		**30**	**4.5%**	**1.45 [0.26 , 8.09]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.43 (P = 0.67)						
1.12.2 PLD with carboplatin versus paclitaxel with carboplatin						
HeCOG 2010	0	84	0	89		Not estimable
CALYPSO	31	466	33	501	70.9%	1.01 [0.63 , 1.62]
Subtotal (95% CI)		**550**		**590**	**70.9%**	**1.01 [0.63 , 1.62]**
Total events:	31		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.04 (P = 0.97)						
1.12.3 PLD with carboplatin versus gemcitabine with carboplatin						
Fujiwara 2019	0	49	0	50		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.12.4 PLD with carboplatin and bevacizumab versus gemcitabine with carboplatin and bevacizumab						
Pfisterer 2020	10	332	11	329	24.6%	0.90 [0.39 , 2.09]
Subtotal (95% CI)		**332**		**329**	**24.6%**	**0.90 [0.39 , 2.09]**
Total events:	10		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.24 (P = 0.81)						
Total (95% CI)		**962**		**999**	**100.0%**	**1.00 [0.67 , 1.50]**
Total events:	44		46			
Heterogeneity: Chi² = 0.24, df = 2 (P = 0.89); I² = 0%						
Test for overall effect: Z = 0.02 (P = 0.99)						
Test for subgroup differences: Chi² = 0.24, df = 2 (P = 0.89), I² = 0%						



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.13. Comparison 1: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus alternative combination chemotherapy, Outcome 13: SevAE: Arthralgia/myalgia (grade ≥ 3)



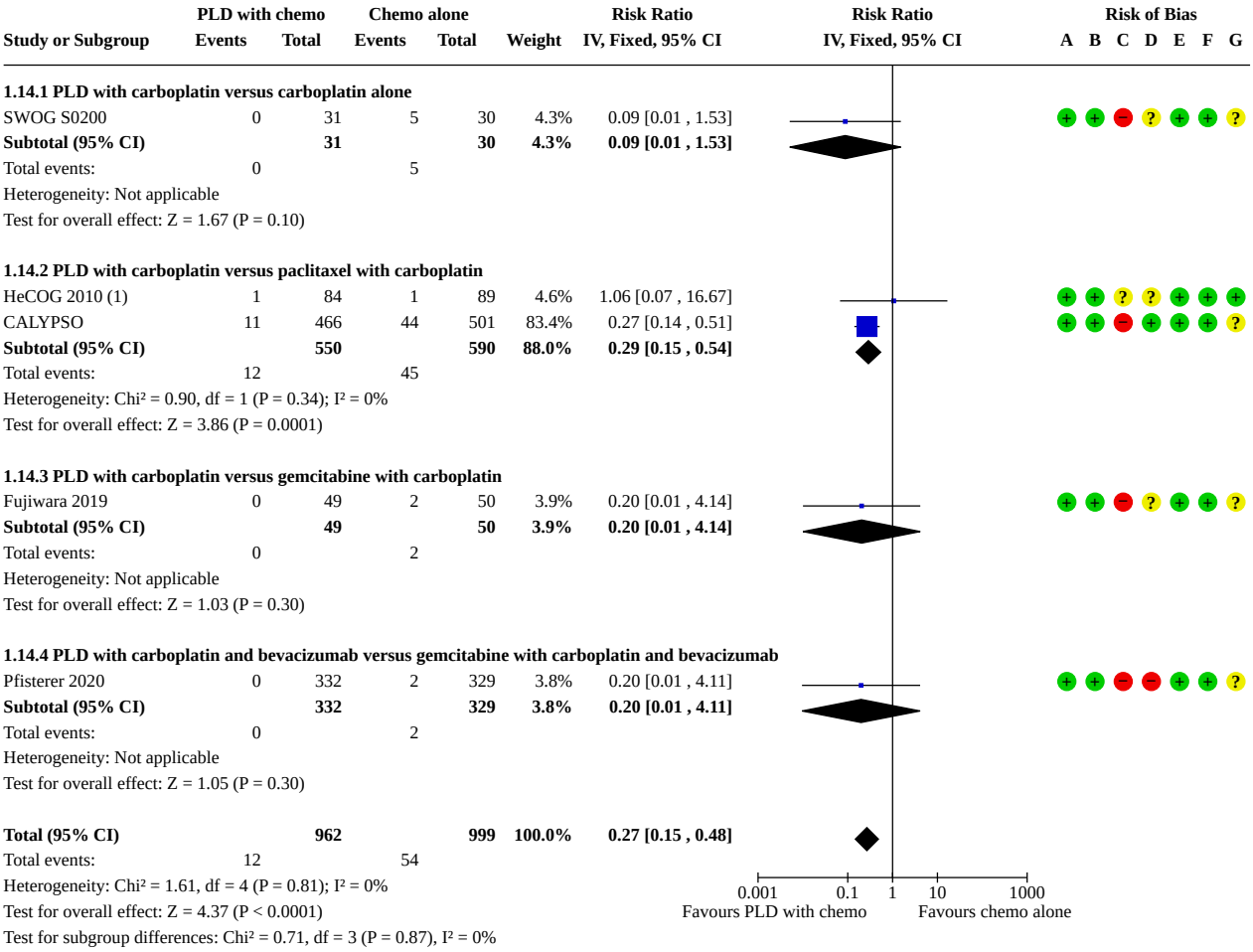
Footnotes

(1) Arthralgia Only

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.14. Comparison 1: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus alternative combination chemotherapy, Outcome 14: SevAE: Hypersensitivity reactions (grade ≥ 3)



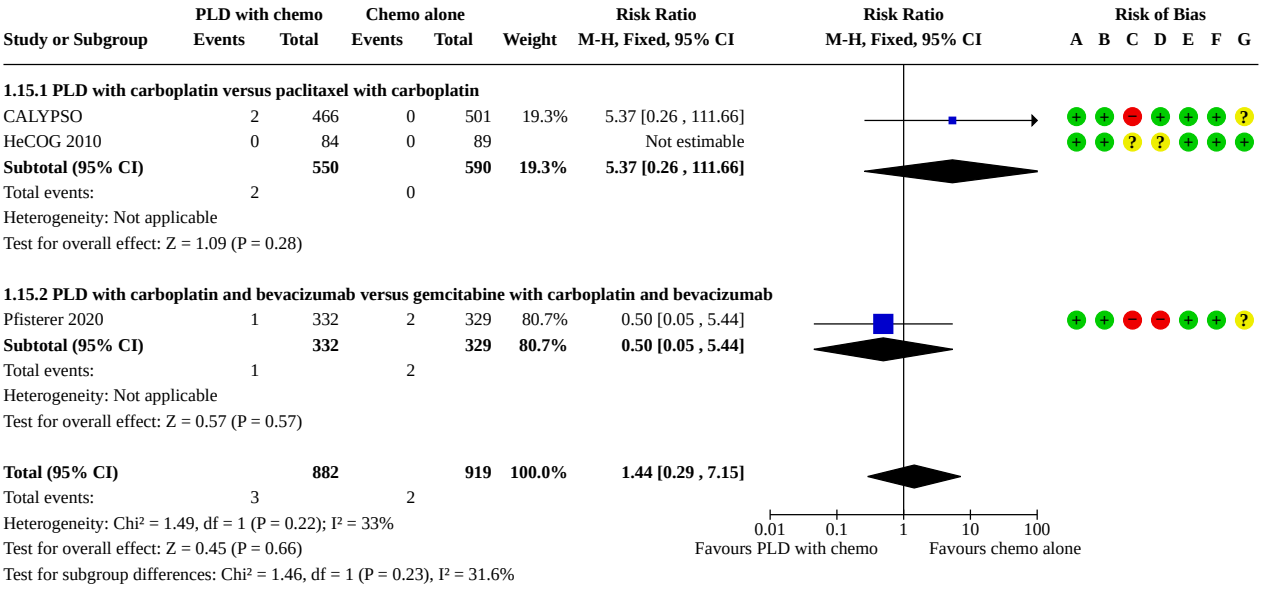
Footnotes

(1) Grade 1/2 HSRs occurred in 7% versus 31% in PLD vs non-PLD arms, respectively.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.15. Comparison 1: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus alternative combination chemotherapy, Outcome 15: Serious AE: Treatment-related death

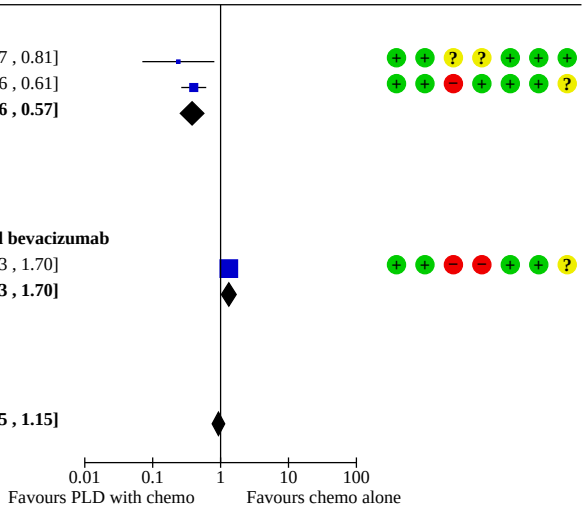


Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.16. Comparison 1: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus alternative combination chemotherapy, Outcome 16: Discontinuation due to toxicity

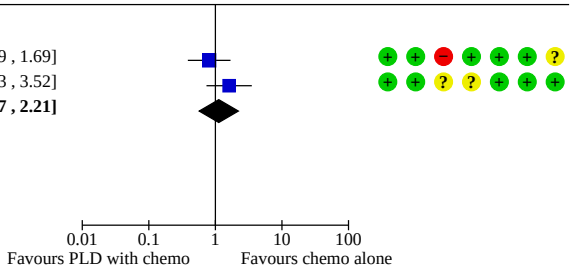
Study or Subgroup	PLD with chemo Events	Total	Chemo alone Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
1.16.1 PLD with carboplatin versus paclitaxel with carboplatin						
HeCOG 2010	3	87	13	90	3.0%	0.24 [0.07 , 0.81]
CALYPSO	27	466	73	507	25.2%	0.40 [0.26 , 0.61]
Subtotal (95% CI)		**553**		**597**	**28.3%**	**0.38 [0.26 , 0.57]**
Total events:	30		86			
Heterogeneity: Chi² = 0.63, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 4.74 (P < 0.00001)						
1.16.2 PLD with carboplatin and bevacizumab versus gemcitabine with carboplatin and bevacizumab						
Pfisterer 2020	104	332	78	329	71.7%	1.32 [1.03 , 1.70]
Subtotal (95% CI)		**332**		**329**	**71.7%**	**1.32 [1.03 , 1.70]**
Total events:	104		78			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.18 (P = 0.03)						
Total (95% CI)		**885**		**926**	**100.0%**	**0.93 [0.75 , 1.15]**
Total events:	134		164			
Heterogeneity: Chi² = 27.35, df = 2 (P < 0.00001); I² = 93%						
Test for overall effect: Z = 0.67 (P = 0.50)						
Test for subgroup differences: Chi² = 26.72, df = 1 (P < 0.00001), I² = 96.3%						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.17. Comparison 1: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus alternative combination chemotherapy, Outcome 17: Antibiotics required

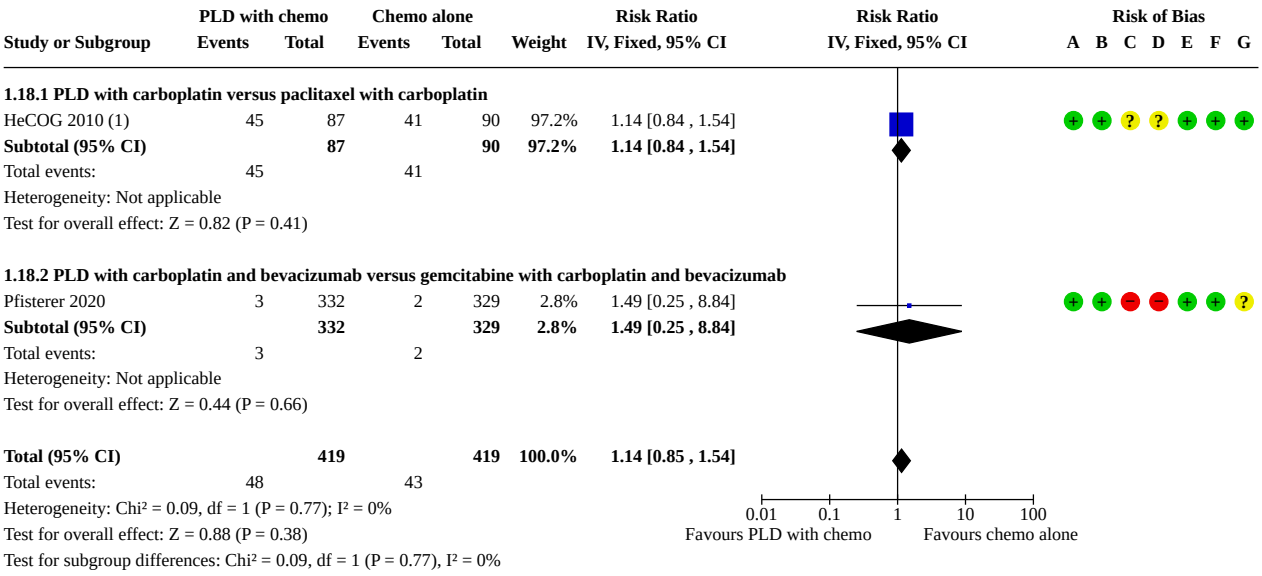
Study or Subgroup	PLD with chemo Events	Total	Chemo alone Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.17.1 PLD with carboplatin versus paclitaxel with carboplatin						
CALYPSO (1)	12	466	16	501	51.9%	0.81 [0.39 , 1.69]
HeCOG 2010 (2)	14	87	9	90	48.1%	1.61 [0.73 , 3.52]
Subtotal (95% CI)		**553**		**591**	**100.0%**	**1.12 [0.57 , 2.21]**
Total events:	26		25			
Heterogeneity: Tau² = 0.09; Chi² = 1.58, df = 1 (P = 0.21); I² = 37%						
Test for overall effect: Z = 0.34 (P = 0.73)						
Test for subgroup differences: Not applicable						



Footnotes
(1) 30mg/m2 PLD dose
(2) 45mg/m2 PLD dose

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.18. Comparison 1: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus alternative combination chemotherapy, Outcome 18: Granulocyte colony stimulating factor (G-CSF) required



Footnotes

(1) 45mg/m2 PLD dose

Risk of bias legend

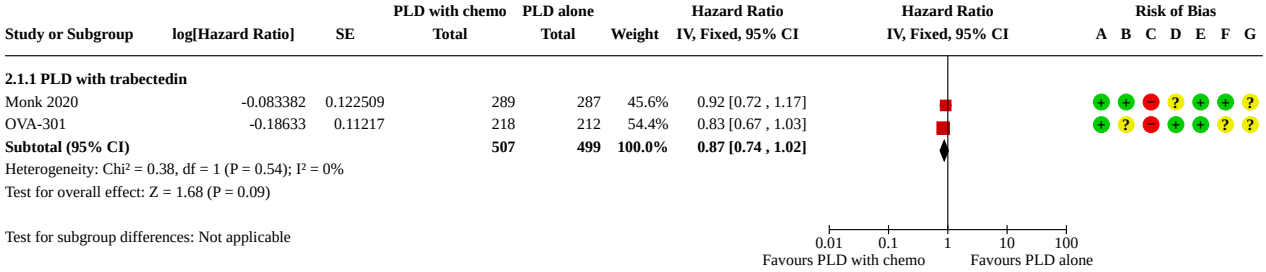
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 2. Platinum-sensitive recurrent EOC: PLD with chemotherapy versus PLD alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Overall survival	2		Hazard Ratio (IV, Fixed, 95% CI)	Subtotals only
2.1.1 PLD with trabectedin	2	1006	Hazard Ratio (IV, Fixed, 95% CI)	0.87 [0.74, 1.02]
2.2 Progression-free survival	2		Hazard Ratio (IV, Fixed, 95% CI)	Subtotals only
2.2.1 PLD with trabectedin	2	732	Hazard Ratio (IV, Fixed, 95% CI)	0.85 [0.72, 1.00]
2.3 Overall Severe Adverse Events (grade ≥3)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2.3.1 PLD with trabectedin	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2.4 SevAE: Anaemia (grade ≥3)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2.4.1 PLD with trabectedin	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.5 SevAE: Hand-foot syndrome (grade ≥ 3)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2.5.1 PLD with trabectedin	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2.6 SevAE: Neutropenia (grade ≥ 3)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2.6.1 PLD with trabectedin	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2.7 SevAE: Thrombocytopenia (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.7.1 PLD with trabectedin	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.8 SevAE: Stomatitis (grade ≥ 3)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2.8.1 PLD with trabectedin	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2.9 SevAE: Vomiting (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.9.1 PLD with trabectedin	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.10 SevAE: Fatigue (grade ≥ 3)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2.10.1 PLD with trabectedin	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus PLD alone, Outcome 1: Overall survival



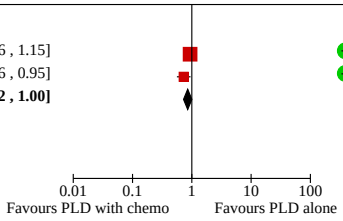
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.2. Comparison 2: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus PLD alone, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	PLD with chemo Total	PLD alone Total	Weight	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G
2.2.1 PLD with trabectedin								
Monk 2020	-0.067209	0.104328	28	287	62.5%	0.93 [0.76 , 1.15]		+ + − ? + + ?
OVA-301	-0.314711	0.13483	202	215	37.5%	0.73 [0.56 , 0.95]		+ ? − + + ? ?
Subtotal (95% CI)			**230**	**502**	**100.0%**	**0.85 [0.72 , 1.00]**		

Heterogeneity: Chi² = 2.11, df = 1 (P = 0.15); I² = 53%
Test for overall effect: Z = 1.94 (P = 0.05)

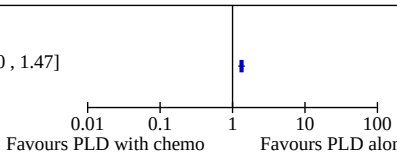
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.3. Comparison 2: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus PLD alone, Outcome 3: Overall Severe Adverse Events (grade ≥3)

Study or Subgroup	PLD with chemo Events	PLD with chemo Total	PLD alone Events	PLD alone Total	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G
2.3.1 PLD with trabectedin							
Monk 2020 (1)	243	286	180	282	1.33 [1.20 , 1.47]		+ + − ? + + ?

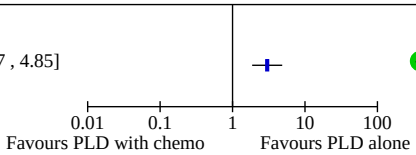


Footnotes
(1) treatment-emergent AEs

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.4. Comparison 2: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus PLD alone, Outcome 4: SevAE: Anaemia (grade ≥3)

Study or Subgroup	PLD with chemo Events	Total	PLD alone Events	Total	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G
2.4.1 PLD with trabectedin							
Monk 2020 (1)	61	286	20	282	3.01 [1.87 , 4.85]		+ + − ? + + ?

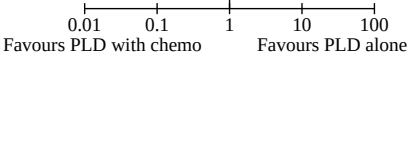


Footnotes
(1) treatment-emergent AEs

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.5. Comparison 2: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus PLD alone, Outcome 5: SevAE: Hand-foot syndrome (grade ≥ 3)

Study or Subgroup	PLD with chemo Events	Total	PLD alone Events	Total	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G
2.5.1 PLD with trabectedin							
Monk 2020 (1)	10	286	33	282	0.30 [0.15 , 0.59]		+ + − ? + + ?

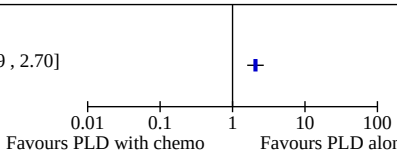


Footnotes
(1) treatment-emergent AEs

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.6. Comparison 2: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus PLD alone, Outcome 6: SevAE: Neutropenia (grade ≥ 3)

Study or Subgroup	PLD with chemo Events	Total	PLD alone Events	Total	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G
2.6.1 PLD with trabectedin							
Monk 2020 (1)	124	286	59	282	2.07 [1.59 , 2.70]		+ + − ? + + ?

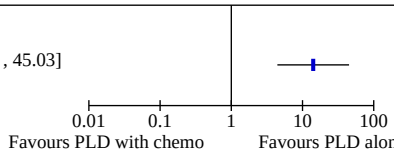


Footnotes
(1) treatment-emergent AEs

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.7. Comparison 2: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus PLD alone, Outcome 7: SevAE: Thrombocytopenia (grade ≥ 3)

Study or Subgroup	PLD with chemo Events	Total	PLD alone Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
2.7.1 PLD with trabectedin							
Monk 2020 (1)	43	286	3	282	14.13 [4.44 , 45.03]		+ + − ? + + ?

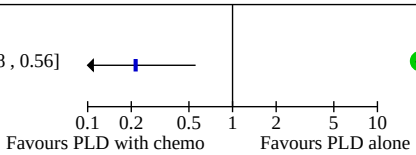


Footnotes
(1) treatment-emergent AEs

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.8. Comparison 2: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus PLD alone, Outcome 8: SevAE: Stomatitis (grade ≥ 3)

Study or Subgroup	PLD with chemo Events	PLD with chemo Total	PLD alone Events	PLD alone Total	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G
2.8.1 PLD with trabectedin							
Monk 2020 (1)	5	286	23	282	0.21 [0.08 , 0.56]		+ + − ? + + ?

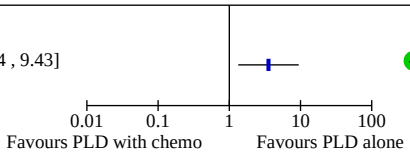


Footnotes
(1) treatment-emergent AEs

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.9. Comparison 2: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus PLD alone, Outcome 9: SevAE: Vomiting (grade ≥ 3)

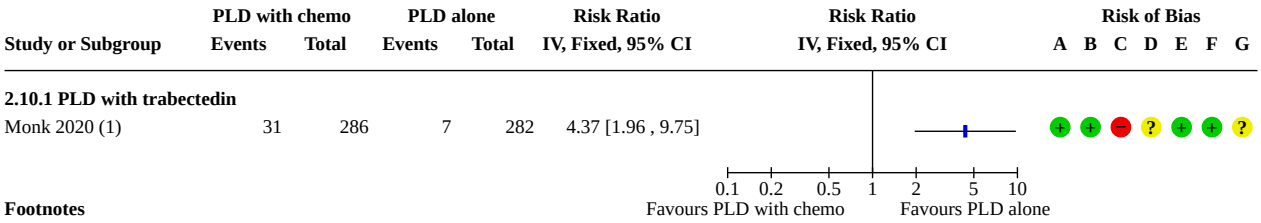
Study or Subgroup	PLD with chemo Events	PLD with chemo Total	PLD alone Events	PLD alone Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
2.9.1 PLD with trabectedin							
Monk 2020 (1)	18	286	5	282	3.55 [1.34 , 9.43]		+ + − ? + + ?



Footnotes
(1) treatment-emergent AEs

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 2.10. Comparison 2: Platinum-sensitive recurrent EOC: PLD with chemotherapy versus PLD alone, Outcome 10: SevAE: Fatigue (grade ≥ 3)



Footnotes
(1) treatment-emergent AEs

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 3. Platinum-resistant recurrent EOC: PLD versus other chemotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Overall survival	6	1995	Hazard Ratio (IV, Random, 95% CI)	0.96 [0.77, 1.19]
3.1.1 PLD versus gemcitabine	2	348	Hazard Ratio (IV, Random, 95% CI)	0.80 [0.52, 1.21]
3.1.2 PLD versus lurbinectedin	1	348	Hazard Ratio (IV, Random, 95% CI)	1.13 [0.88, 1.44]
3.1.3 PLD versus patupilone	1	828	Hazard Ratio (IV, Random, 95% CI)	1.08 [0.92, 1.26]
3.1.4 PLD with topotecan	1	255	Hazard Ratio (IV, Random, 95% CI)	0.94 [0.72, 1.22]
3.1.5 PLD versus paclitaxel	1	216	Hazard Ratio (IV, Random, 95% CI)	1.07 [0.81, 1.42]
3.2 Progression-free survival	4	1803	Hazard Ratio (IV, Random, 95% CI)	0.94 [0.85, 1.04]
3.2.1 PLD versus gemcitabine	1	153	Hazard Ratio (IV, Random, 95% CI)	1.15 [0.78, 1.70]
3.2.2 PLD versus lurbinectedin	1	348	Hazard Ratio (IV, Random, 95% CI)	0.94 [0.73, 1.21]
3.2.3 PLD versus patupilone	1	828	Hazard Ratio (IV, Random, 95% CI)	0.95 [0.81, 1.12]

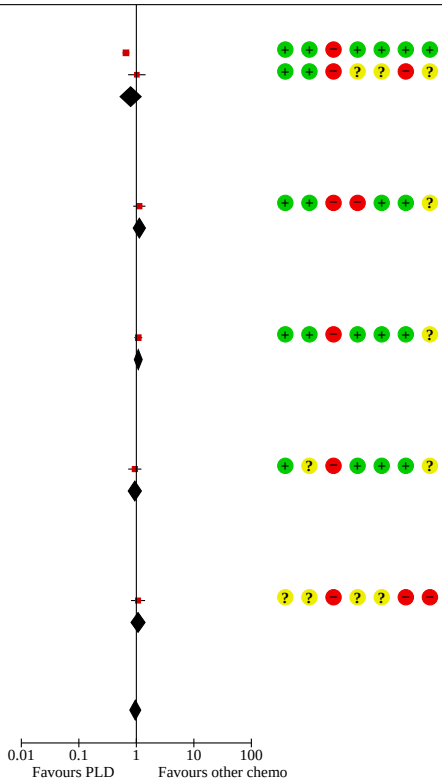
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2.4 PLD versus topotecan	1	474	Hazard Ratio (IV, Random, 95% CI)	0.89 [0.75, 1.06]
3.3 Overall Severe Adverse Events (grade ≥ 3)	2		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
3.3.1 PLD versus gemcitabine	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
3.3.2 PLD versus patupilone	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
3.4 SevAE: Anaemia (grade ≥ 3)	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.4.1 PLD versus gemcitabine	2	338	Risk Ratio (IV, Random, 95% CI)	0.75 [0.27, 2.11]
3.4.2 PLD versus lurbinectedin	1	345	Risk Ratio (IV, Random, 95% CI)	0.68 [0.40, 1.16]
3.4.3 PLD versus patupilone	1	811	Risk Ratio (IV, Random, 95% CI)	0.82 [0.42, 1.60]
3.4.4 PLD versus topotecan	1	474	Risk Ratio (IV, Random, 95% CI)	0.19 [0.11, 0.34]
3.5 SevAE: Hand-foot syndrome (grade ≥ 3)	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.5.1 PLD versus gemcitabine	2	338	Risk Ratio (M-H, Fixed, 95% CI)	15.19 [2.04, 113.27]
3.5.2 PLD versus lurbinectedin	1	345	Risk Ratio (M-H, Fixed, 95% CI)	53.70 [3.24, 889.90]
3.5.3 PLD versus patupilone	1	811	Risk Ratio (M-H, Fixed, 95% CI)	109.10 [6.76, 1760.19]
3.5.4 PLD versus topotecan	1	474	Risk Ratio (M-H, Fixed, 95% CI)	109.15 [6.78, 1756.69]
3.5.5 PLD versus paclitaxel	1	216	Risk Ratio (M-H, Fixed, 95% CI)	35.00 [2.13, 574.74]
3.6 SevAE: Neurological (grade ≥ 3)	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.6.1 PLD versus gemcitabine	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.6.2 PLD versus patupilone	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.6.3 PLD versus paclitaxel	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.7 SevAE: Neutropenia (grade ≥ 3)	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.7.1 PLD versus gemcitabine	2	338	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.28, 0.67]
3.7.2 PLD versus lurbinectedin	1	432	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.38, 1.80]
3.7.3 PLD versus patupilone	1	811	Risk Ratio (M-H, Fixed, 95% CI)	3.36 [1.79, 6.30]
3.7.4 PLD versus topotecan	1	474	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.11, 0.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.8 SevAE: Thrombocytopenia (grade ≥ 3)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.8.1 PLD versus gemcitabine	2	338	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.20, 1.46]
3.8.2 PLD versus lurbinectedin	1	345	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.17, 1.13]
3.8.3 PLD versus topotecan	1	474	Risk Ratio (M-H, Fixed, 95% CI)	0.04 [0.01, 0.12]
3.9 SevAE: Stomatitis (grade ≥ 3)	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.9.1 PLD versus gemcitabine	2	338	Risk Ratio (M-H, Fixed, 95% CI)	2.53 [0.50, 12.82]
3.9.2 PLD versus lurbinectedin	1	345	Risk Ratio (M-H, Fixed, 95% CI)	9.85 [2.94, 32.95]
3.9.3 PLD versus patupilone	1	811	Risk Ratio (M-H, Fixed, 95% CI)	20.15 [4.91, 82.75]
3.9.4 PLD versus topotecan	1	474	Risk Ratio (M-H, Fixed, 95% CI)	19.67 [2.66, 145.35]
3.9.5 PLD versus paclitaxel	1	216	Risk Ratio (M-H, Fixed, 95% CI)	11.00 [1.45, 83.73]
3.10 SevAE: Vomiting (grade ≥ 3)	4		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
3.10.1 PLD versus gemcitabine	2	338	Risk Ratio (IV, Fixed, 95% CI)	0.57 [0.21, 1.50]
3.10.2 PLD versus lurbinectedin	1	345	Risk Ratio (IV, Fixed, 95% CI)	0.14 [0.02, 1.10]
3.10.3 PLD verusus patupilone	1	811	Risk Ratio (IV, Fixed, 95% CI)	0.74 [0.44, 1.23]
3.11 SevAE: Diarrhoea (grade ≥ 3)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.11.1 PLD versus gemcitabine	2	338	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.08, 4.55]
3.11.2 PLD versus lurbinectedin	1	345	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.02, 7.16]
3.11.3 PLD versus patupilone	1	812	Risk Ratio (M-H, Fixed, 95% CI)	0.09 [0.04, 0.17]
3.12 SevAE: Fatigue (grade ≥ 3)	5		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
3.12.1 PLD versus gemcitabine	2	338	Risk Ratio (IV, Fixed, 95% CI)	0.40 [0.14, 1.14]
3.12.2 PLD versus lurbinectedin	1	345	Risk Ratio (IV, Fixed, 95% CI)	0.54 [0.20, 1.45]
3.12.3 PLD versus patupilone	1	811	Risk Ratio (IV, Fixed, 95% CI)	0.80 [0.52, 1.22]
3.12.4 PLD versus paclitaxel	1	216	Risk Ratio (IV, Fixed, 95% CI)	0.80 [0.22, 2.90]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.13 SevAE: Hypersensitivity reactions (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.13.1 PLD versus gemcitabine	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.14 Dose reductions	4	1773	Risk Ratio (IV, Random, 95% CI)	1.04 [0.54, 2.01]
3.14.1 PLD versus gemcitabine	1	143	Risk Ratio (IV, Random, 95% CI)	0.85 [0.30, 2.39]
3.14.2 PLD versus lurbinectedin	1	345	Risk Ratio (IV, Random, 95% CI)	2.96 [1.70, 5.18]
3.14.3 PLD versus patupilone	1	811	Risk Ratio (IV, Random, 95% CI)	0.95 [0.74, 1.23]
3.14.4 PLD versus topotecan	1	474	Risk Ratio (IV, Random, 95% CI)	0.52 [0.41, 0.67]
3.15 Dose delays	3	962	Risk Ratio (IV, Random, 95% CI)	0.97 [0.55, 1.69]
3.15.1 PLD versus gemcitabine	1	143	Risk Ratio (IV, Random, 95% CI)	0.60 [0.31, 1.18]
3.15.2 PLD versus lurbinectedin	1	345	Risk Ratio (IV, Random, 95% CI)	1.81 [1.09, 2.99]
3.15.3 PLD versus topotecan	1	474	Risk Ratio (IV, Random, 95% CI)	0.81 [0.69, 0.94]

Analysis 3.1. Comparison 3: Platinum-resistant recurrent EOC: PLD versus other chemotherapy, Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	PLD Total	Other chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI	Risk of Bias A B C D E F G
3.1.1 PLD versus gemcitabine							
MITO-3 (1)	-0.415515	0.068953	76	77	19.3%	0.66 [0.58 , 0.76]	+ + − + + + +
Mutch 2007 (2)	0.019803	0.178617	96	99	13.6%	1.02 [0.72 , 1.45]	+ + − ? ? − ?
Subtotal (95% CI)			**172**	**176**	**33.0%**	**0.80 [0.52 , 1.21]**	
Heterogeneity: Tau² = 0.08; Chi² = 5.17, df = 1 (P = 0.02); I² = 81%							
Test for overall effect: Z = 1.06 (P = 0.29)							
3.1.2 PLD versus lurbinectedin							
CORAIL (3)	0.118672	0.124878	127	221	16.6%	1.13 [0.88 , 1.44]	+ + − − + + ?
Subtotal (95% CI)			**127**	**221**	**16.6%**	**1.13 [0.88 , 1.44]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.95 (P = 0.34)							
3.1.3 PLD versus patupilone							
Colombo 2012 (4)	0.076961	0.080229	412	416	18.9%	1.08 [0.92 , 1.26]	+ + − + + + ?
Subtotal (95% CI)			**412**	**416**	**18.9%**	**1.08 [0.92 , 1.26]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.96 (P = 0.34)							
3.1.4 PLD with topotecan							
Gordon 2001 (5)	-0.061875	0.134532	130	125	16.0%	0.94 [0.72 , 1.22]	+ ? − + + + ?
Subtotal (95% CI)			**130**	**125**	**16.0%**	**0.94 [0.72 , 1.22]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.46 (P = 0.65)							
3.1.5 PLD versus paclitaxel							
NCT00653952 (6)	0.067659	0.143211	108	108	15.6%	1.07 [0.81 , 1.42]	? ? − ? ? − −
Subtotal (95% CI)			**108**	**108**	**15.6%**	**1.07 [0.81 , 1.42]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.47 (P = 0.64)							
Total (95% CI)			**949**	**1046**	**100.0%**	**0.96 [0.77 , 1.19]**	
Heterogeneity: Tau² = 0.06; Chi² = 30.56, df = 5 (P < 0.0001); I² = 84%							
Test for overall effect: Z = 0.38 (P = 0.70)							
Test for subgroup differences: Chi² = 2.78, df = 4 (P = 0.60), I² = 0%							



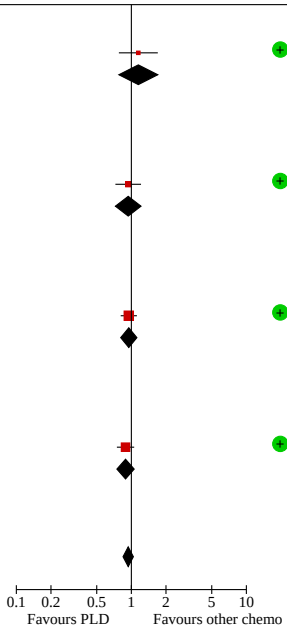
Footnotes

(1) participants regardless of platinum sensitivity status; recalculated HR for gemcitabine arm as a comparator
(2) recalculated HR for gemcitabine arm as a comparator
(3) recalculated HR for lurbinectedin arm as a comparator
(4) recalculated HR for patupilone arm as a comparator
(5) recalculated HR for topotecan arm as a comparator; participants regardless of platinum sensitivity status
(6) participants regardless of platinum sensitivity status

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.2. Comparison 3: Platinum-resistant recurrent EOC: PLD versus other chemotherapy, Outcome 2: Progression-free survival



Study or Subgroup	log[Hazard Ratio]	SE	PLD Total	Other chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI	Risk of Bias A B C D E F G
3.2.1 PLD versus gemcitabine								
MITO-3 (1)	0.139762	0.198751	76	77	7.1%	1.15 [0.78 , 1.70]		+ + − + + + +
Subtotal (95% CI)			**76**	**77**	**7.1%**	**1.15 [0.78 , 1.70]**		
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.70 (P = 0.48)								
3.2.2 PLD versus lurbinectedin								
CORAIL (2)	-0.06294	0.130806	127	221	16.3%	0.94 [0.73 , 1.21]		+ + − − + + ?
Subtotal (95% CI)			**127**	**221**	**16.3%**	**0.94 [0.73 , 1.21]**		
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.48 (P = 0.63)								
3.2.3 PLD versus patupilone								
Colombo 2012 (3)	-0.051293	0.082667	412	416	40.8%	0.95 [0.81 , 1.12]		+ + − + + + ?
Subtotal (95% CI)			**412**	**416**	**40.8%**	**0.95 [0.81 , 1.12]**		
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.62 (P = 0.53)								
3.2.4 PLD versus topotecan								
Gordon 2001 (1)	-0.116534	0.088254	239	235	35.8%	0.89 [0.75 , 1.06]		+ ? − + + + ?
Subtotal (95% CI)			**239**	**235**	**35.8%**	**0.89 [0.75 , 1.06]**		
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.32 (P = 0.19)								
Total (95% CI)			**854**	**949**	**100.0%**	**0.94 [0.85 , 1.04]**		
Heterogeneity: Tau² = 0.00; Chi² = 1.43, df = 3 (P = 0.70); I² = 0%								
Test for overall effect: Z = 1.19 (P = 0.23)								
Test for subgroup differences: Chi² = 1.43, df = 3 (P = 0.70), I² = 0%								

Footnotes

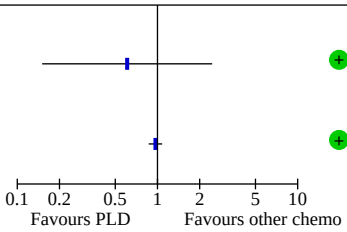
(1) participants regardless of platinum sensitivity status
(2) recalculated HR for lurbinectedin arm as a comparator
(3) recalculated HR for patupilone arm as a comparator

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.3. Comparison 3: Platinum-resistant recurrent EOC: PLD versus other chemotherapy, Outcome 3: Overall Severe Adverse Events (grade ≥ 3)

Study or Subgroup	PLD Events	PLD Total	Other chemotherapy Events	Other chemotherapy Total	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F	G
3.3.1 PLD versus gemcitabine													
MITO-3 (1)	3	76	5	77	0.61 [0.15 , 2.45]		+	+	−	+	+	+	+
3.3.2 PLD versus patupilone													
Colombo 2012 (2)	245	409	249	402	0.97 [0.87 , 1.08]		+	+	−	+	+	+	?



Footnotes

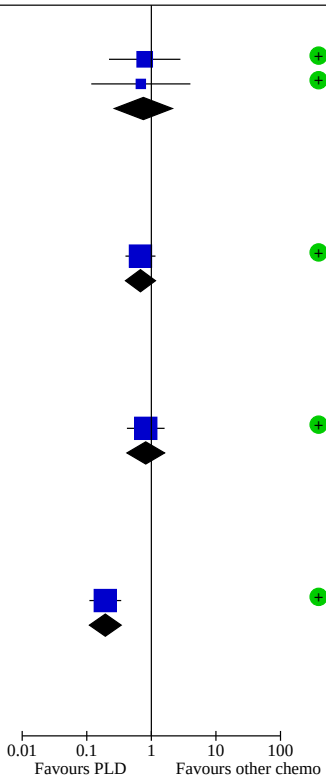
(1) participants regardless of platinum sensitivity status
(2) treatment-emergent AEs

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.4. Comparison 3: Platinum-resistant recurrent EOC: PLD versus other chemotherapy, Outcome 4: SevAE: Anaemia (grade ≥ 3)

Study or Subgroup	PLD Events	PLD Total	Other chemotherapy Events	Other chemotherapy Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias A B C D E F G
3.4.1 PLD versus gemcitabine							
MITO-3 (1)	4	72	5	71	65.8%	0.79 [0.22 , 2.82]	+ + − + + + +
Mutch 2007 (2)	2	96	3	99	34.2%	0.69 [0.12 , 4.02]	+ + − ? ? − ?
Subtotal (95% CI)		**168**		**170**	**100.0%**	**0.75 [0.27 , 2.11]**	
Total events:	6		8				
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.90); I² = 0%							
Test for overall effect: Z = 0.54 (P = 0.59)							
3.4.2 PLD versus lurbinectedin							
CORAIL (3)	16	126	41	219	100.0%	0.68 [0.40 , 1.16]	+ + − − + + ?
Subtotal (95% CI)		**126**		**219**	**100.0%**	**0.68 [0.40 , 1.16]**	
Total events:	16		41				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.42 (P = 0.15)							
3.4.3 PLD versus patupilone							
Colombo 2012 (3)	15	409	18	402	100.0%	0.82 [0.42 , 1.60]	+ + − + + + ?
Subtotal (95% CI)		**409**		**402**	**100.0%**	**0.82 [0.42 , 1.60]**	
Total events:	15		18				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.58 (P = 0.56)							
3.4.4 PLD versus topotecan							
Gordon 2001 (1)	13	239	66	235	100.0%	0.19 [0.11 , 0.34]	+ ? − + + + ?
Subtotal (95% CI)		**239**		**235**	**100.0%**	**0.19 [0.11 , 0.34]**	
Total events:	13		66				
Heterogeneity: Not applicable							
Test for overall effect: Z = 5.68 (P < 0.00001)							
Test for subgroup differences: Chi² = 0.00, df = 3 (P < 0.00001), I² = 0%							



Footnotes

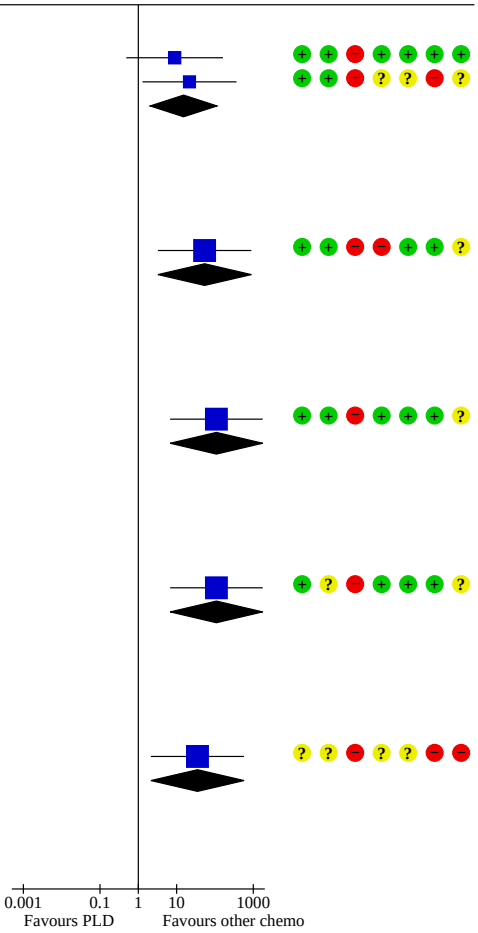
(1) participants regardless of platinum sensitivity status
(2) initial treatment phase
(3) treatment-emergent AEs

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.5. Comparison 3: Platinum-resistant recurrent EOC: PLD versus other chemotherapy, Outcome 5: SevAE: Hand-foot syndrome (grade ≥ 3)

Study or Subgroup	PLD Events	PLD Total	Other chemotherapy Events	Other chemotherapy Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.5.1 PLD versus gemcitabine						
MITO-3 (1)	4	72	0	71	50.6%	8.88 [0.49 , 161.90]
Mutch 2007 (2)	10	96	0	99	49.4%	21.65 [1.29 , 364.39]
Subtotal (95% CI)		**168**		**170**	**100.0%**	**15.19 [2.04 , 113.27]**
Total events:	14		0			
Heterogeneity: Chi² = 0.19, df = 1 (P = 0.66); I² = 0%						
Test for overall effect: Z = 2.65 (P = 0.008)						
3.5.2 PLD versus lurbinectedin						
CORAIL (3)	15	126	0	219	100.0%	53.70 [3.24 , 889.90]
Subtotal (95% CI)		**126**		**219**	**100.0%**	**53.70 [3.24 , 889.90]**
Total events:	15		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.78 (P = 0.005)						
3.5.3 PLD versus patupilone						
Colombo 2012 (3)	55	409	0	402	100.0%	109.10 [6.76 , 1760.19]
Subtotal (95% CI)		**409**		**402**	**100.0%**	**109.10 [6.76 , 1760.19]**
Total events:	55		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.31 (P = 0.0009)						
3.5.4 PLD versus topotecan						
Gordon 2001 (4)	55	239	0	235	100.0%	109.15 [6.78 , 1756.69]
Subtotal (95% CI)		**239**		**235**	**100.0%**	**109.15 [6.78 , 1756.69]**
Total events:	55		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.31 (P = 0.0009)						
3.5.5 PLD versus paclitaxel						
NCT00653952	17	108	0	108	100.0%	35.00 [2.13 , 574.74]
Subtotal (95% CI)		**108**		**108**	**100.0%**	**35.00 [2.13 , 574.74]**
Total events:	17		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.49 (P = 0.01)						
Test for subgroup differences: Chi² = 0.00, df = 4 (P < 0.00001), I² = 0%						



Footnotes

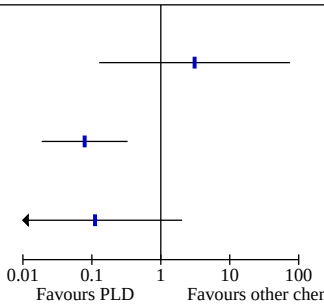
(1) individuals in the PLD arm of this trial received 20 mg methylprednisolone and a lower (40 mg) dose of PLD; participants regardless of platinum sensitivity status
(2) initial treatment phase
(3) treatment-emergent AEs
(4) participants regardless of platinum sensitivity status

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.6. Comparison 3: Platinum-resistant recurrent EOC: PLD versus other chemotherapy, Outcome 6: SevAE: Neurological (grade ≥ 3)

Study or Subgroup	PLD Events	PLD Total	Other chemotherapy Events	Other chemotherapy Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
3.6.1 PLD versus gemcitabine							
Mutch 2007 (1)	1	96	0	99	3.09 [0.13 , 75.00]		+ + − ? ? − ?
3.6.2 PLD versus patupilone							
Colombo 2012 (2)	2	409	25	402	0.08 [0.02 , 0.33]		+ + − + + + ?
3.6.3 PLD versus paclitaxel							
NCT00653952	0	108	4	108	0.11 [0.01 , 2.04]		? ? − ? ? − −



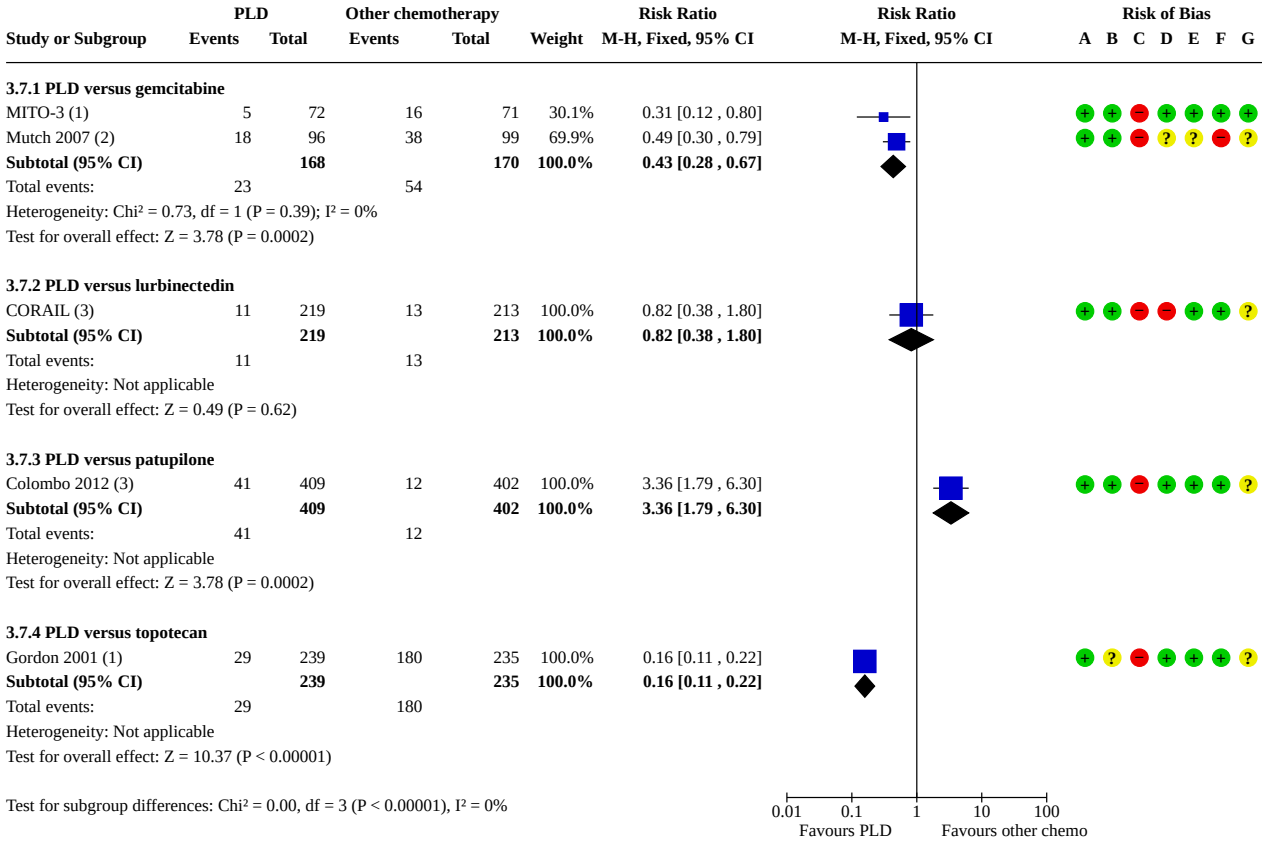
Footnotes

(1) Peripheral neuropathy; initial treatment phase
(2) Peripheral neuropathy; treatment-emergent AEs

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.7. Comparison 3: Platinum-resistant recurrent EOC: PLD versus other chemotherapy, Outcome 7: SevAE: Neutropenia (grade ≥ 3)



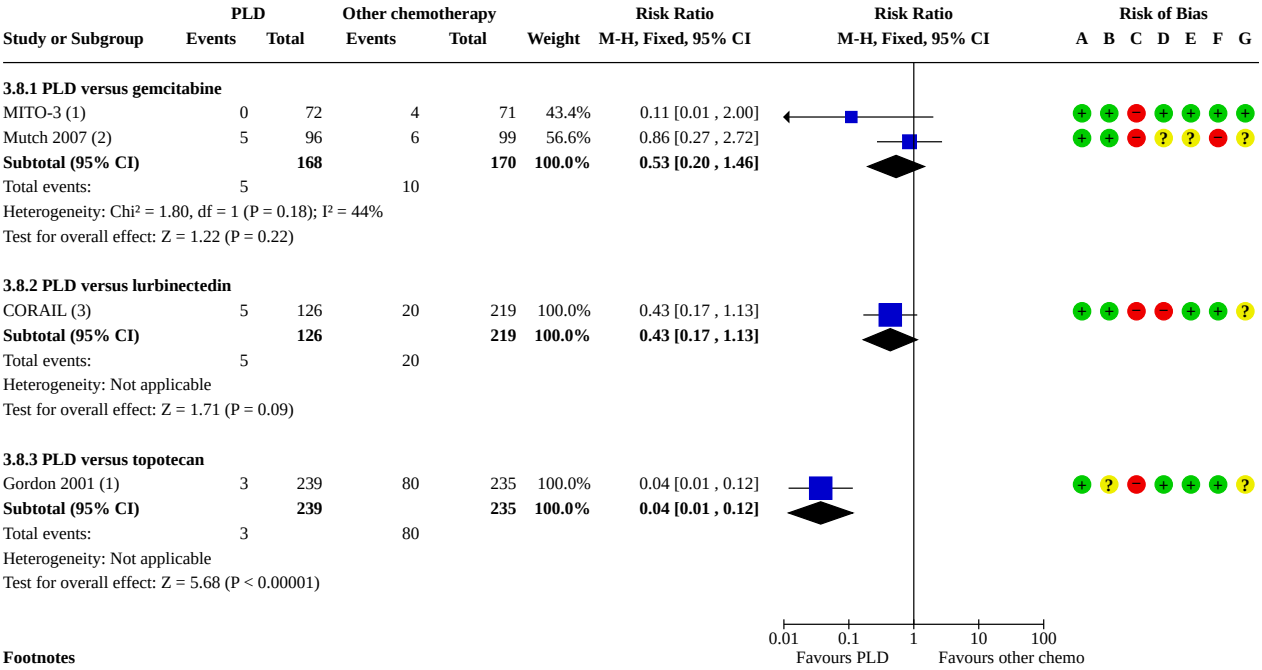
Footnotes

(1) participants regardless of platinum sensitivity status
(2) initial treatment phase
(3) treatment-emergent AEs

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.8. Comparison 3: Platinum-resistant recurrent EOC: PLD versus other chemotherapy, Outcome 8: SevAE: Thrombocytopenia (grade ≥ 3)



Footnotes

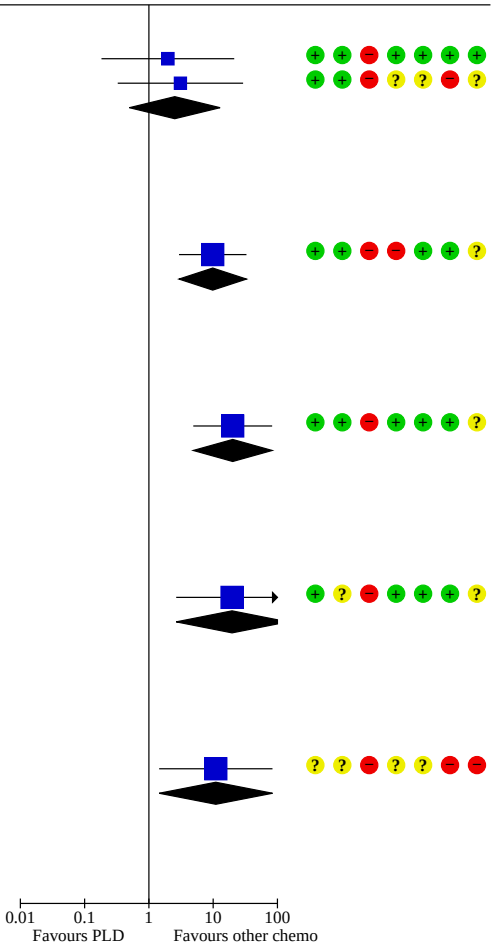
(1) participants regardless of platinum sensitivity status
(2) initial treatment phase
(3) treatment-emergent AEs

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.9. Comparison 3: Platinum-resistant recurrent EOC: PLD versus other chemotherapy, Outcome 9: SevAE: Stomatitis (grade ≥ 3)

Study or Subgroup	PLD Events	PLD Total	Other chemotherapy Events	Other chemotherapy Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.9.1 PLD versus gemcitabine						
MITO-3 (1)	2	72	1	71	50.6%	1.97 [0.18 , 21.27]
Mutch 2007 (2)	3	96	1	99	49.4%	3.09 [0.33 , 29.23]
Subtotal (95% CI)		**168**		**170**	**100.0%**	**2.53 [0.50 , 12.82]**
Total events:	5		2			
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%						
Test for overall effect: Z = 1.12 (P = 0.26)						
3.9.2 PLD versus lurbinectedin						
CORAIL (3)	17	126	3	219	100.0%	9.85 [2.94 , 32.95]
Subtotal (95% CI)		**126**		**219**	**100.0%**	**9.85 [2.94 , 32.95]**
Total events:	17		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.71 (P = 0.0002)						
3.9.3 PLD versus patupilone						
Colombo 2012 (3)	41	409	2	402	100.0%	20.15 [4.91 , 82.75]
Subtotal (95% CI)		**409**		**402**	**100.0%**	**20.15 [4.91 , 82.75]**
Total events:	41		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.17 (P < 0.0001)						
3.9.4 PLD versus topotecan						
Gordon 2001 (4)	20	239	1	235	100.0%	19.67 [2.66 , 145.35]
Subtotal (95% CI)		**239**		**235**	**100.0%**	**19.67 [2.66 , 145.35]**
Total events:	20		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.92 (P = 0.004)						
3.9.5 PLD versus paclitaxel						
NCT00653952	11	108	1	108	100.0%	11.00 [1.45 , 83.73]
Subtotal (95% CI)		**108**		**108**	**100.0%**	**11.00 [1.45 , 83.73]**
Total events:	11		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.32 (P = 0.02)						
Test for subgroup differences: Chi² = 0.00, df = 4 (P < 0.00001), I² = 0%						



Footnotes

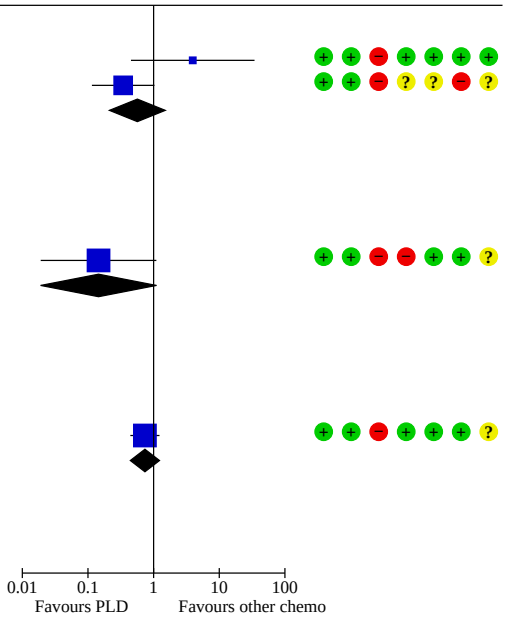
(1) mucositis; participants regardless of platinum sensitivity status
(2) mucositis; initial treatment phase
(3) treatment-emergent AEs
(4) participants regardless of platinum sensitivity status

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.10. Comparison 3: Platinum-resistant recurrent EOC: PLD versus other chemotherapy, Outcome 10: SevAE: Vomiting (grade ≥ 3)

Study or Subgroup	PLD Events	PLD Total	Other chemotherapy Events	Other chemotherapy Total	Weight	Risk Ratio IV, Fixed, 95% CI
3.10.1 PLD versus gemcitabine						
MITO-3 (1)	4	72	1	71	20.4%	3.94 [0.45 , 34.43]
Mutch 2007 (2)	4	96	12	99	79.6%	0.34 [0.11 , 1.03]
Subtotal (95% CI)		**168**		**170**	**100.0%**	**0.57 [0.21 , 1.50]**
Total events:	8		13			
Heterogeneity: Chi² = 3.88, df = 1 (P = 0.05); I² = 74%						
Test for overall effect: Z = 1.14 (P = 0.25)						
3.10.2 PLD versus lurbinectedin						
CORAIL (3)	1	126	12	219	100.0%	0.14 [0.02 , 1.10]
Subtotal (95% CI)		**126**		**219**	**100.0%**	**0.14 [0.02 , 1.10]**
Total events:	1		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.87 (P = 0.06)						
3.10.3 PLD verusus patupilone						
Colombo 2012 (3)	24	409	32	402	100.0%	0.74 [0.44 , 1.23]
Subtotal (95% CI)		**409**		**402**	**100.0%**	**0.74 [0.44 , 1.23]**
Total events:	24		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.17 (P = 0.24)						
Test for subgroup differences: Chi² = 0.00, df = 2 (P < 0.00001), I² = 0%						



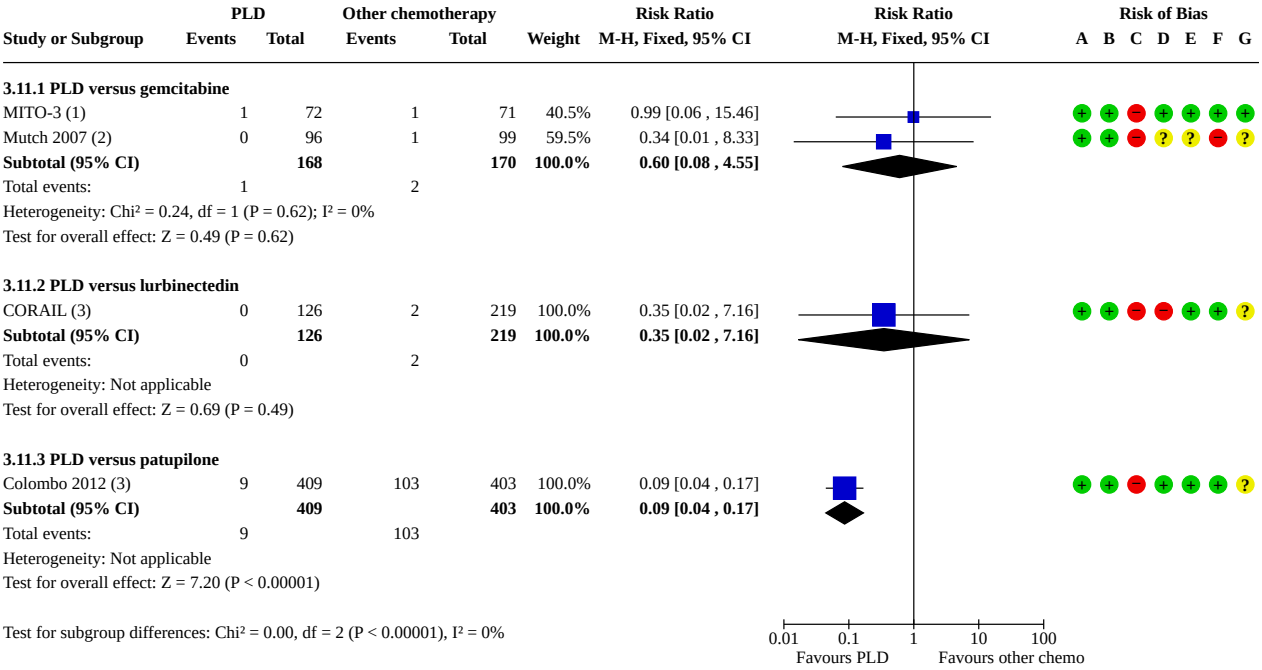
Footnotes

(1) nausea/vomiting; participants regardless of platinum sensitivity status
(2) nausea/vomiting
(3) treatment-emergent AEs

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.11. Comparison 3: Platinum-resistant recurrent EOC: PLD versus other chemotherapy, Outcome 11: SevAE: Diarrhoea (grade ≥ 3)



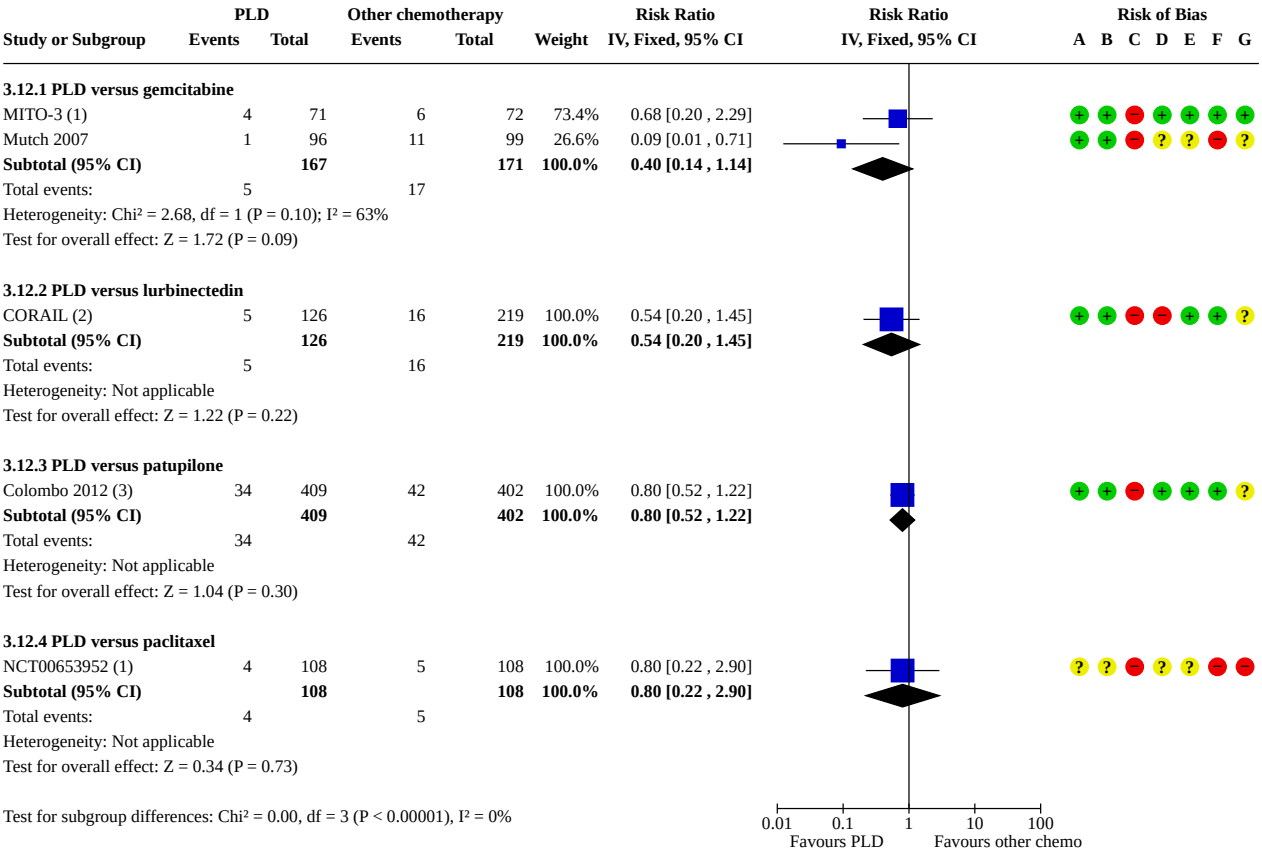
Footnotes

(1) participants regardless of platinum sensitivity status
(2) initial treatment phase
(3) treatment-emergent AEs

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.12. Comparison 3: Platinum-resistant recurrent EOC: PLD versus other chemotherapy, Outcome 12: SevAE: Fatigue (grade ≥ 3)



Study or Subgroup	PLD Events	PLD Total	Other chemotherapy Events	Other chemotherapy Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G
3.12.1 PLD versus gemcitabine							
MITO-3 (1)	4	71	6	72	73.4%	0.68 [0.20 , 2.29]	+ + − + + + +
Mutch 2007	1	96	11	99	26.6%	0.09 [0.01 , 0.71]	+ + − ? ? − ?
Subtotal (95% CI)		**167**		**171**	**100.0%**	**0.40 [0.14 , 1.14]**	
Total events:	5		17				
Heterogeneity: Chi² = 2.68, df = 1 (P = 0.10); I² = 63%							
Test for overall effect: Z = 1.72 (P = 0.09)							
3.12.2 PLD versus lurbinectedin							
CORAIL (2)	5	126	16	219	100.0%	0.54 [0.20 , 1.45]	+ + − − + + ?
Subtotal (95% CI)		**126**		**219**	**100.0%**	**0.54 [0.20 , 1.45]**	
Total events:	5		16				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.22 (P = 0.22)							
3.12.3 PLD versus patupilone							
Colombo 2012 (3)	34	409	42	402	100.0%	0.80 [0.52 , 1.22]	+ + − + + + ?
Subtotal (95% CI)		**409**		**402**	**100.0%**	**0.80 [0.52 , 1.22]**	
Total events:	34		42				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.04 (P = 0.30)							
3.12.4 PLD versus paclitaxel							
NCT00653952 (1)	4	108	5	108	100.0%	0.80 [0.22 , 2.90]	? ? − ? ? − −
Subtotal (95% CI)		**108**		**108**	**100.0%**	**0.80 [0.22 , 2.90]**	
Total events:	4		5				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.34 (P = 0.73)							
Test for subgroup differences: Chi² = 0.00, df = 3 (P < 0.00001), I² = 0%							

Footnotes

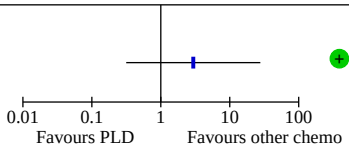
(1) participants regardless of platinum sensitivity status
(2) treatment-emergent AEs
(3) treatment-emergent AEs; includes asthenia and lethargy.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.13. Comparison 3: Platinum-resistant recurrent EOC: PLD versus other chemotherapy, Outcome 13: SevAE: Hypersensitivity reactions (grade ≥ 3)

Study or Subgroup	PLD Events	PLD Total	Other chemotherapy Events	Other chemotherapy Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
3.13.1 PLD versus gemcitabine							
MITO-3 (1)	3	72	1	71	2.96 [0.32 , 27.77]		+ + − + + + +



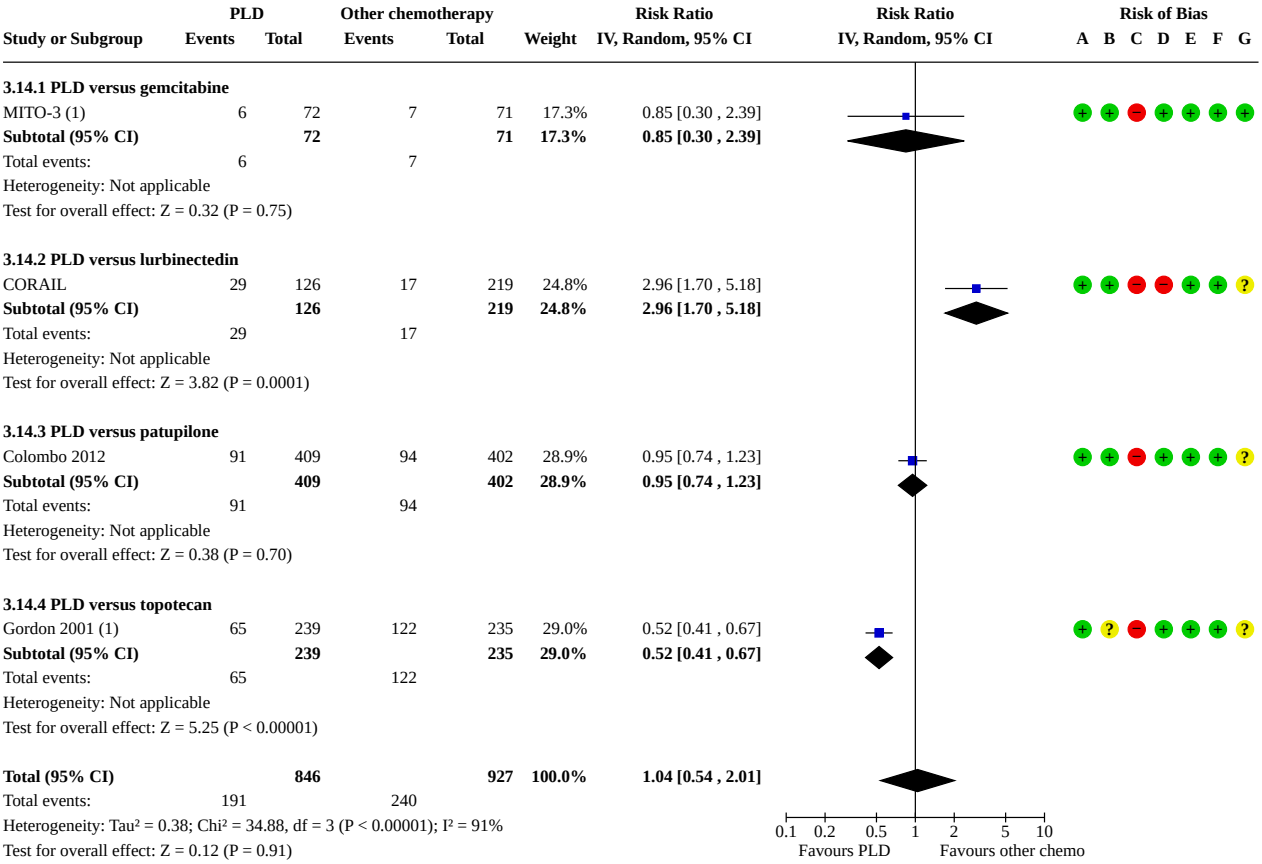
Footnotes

(1) participants regardless of platinum sensitivity status;

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.14. Comparison 3: Platinum-resistant recurrent EOC: PLD versus other chemotherapy, Outcome 14: Dose reductions



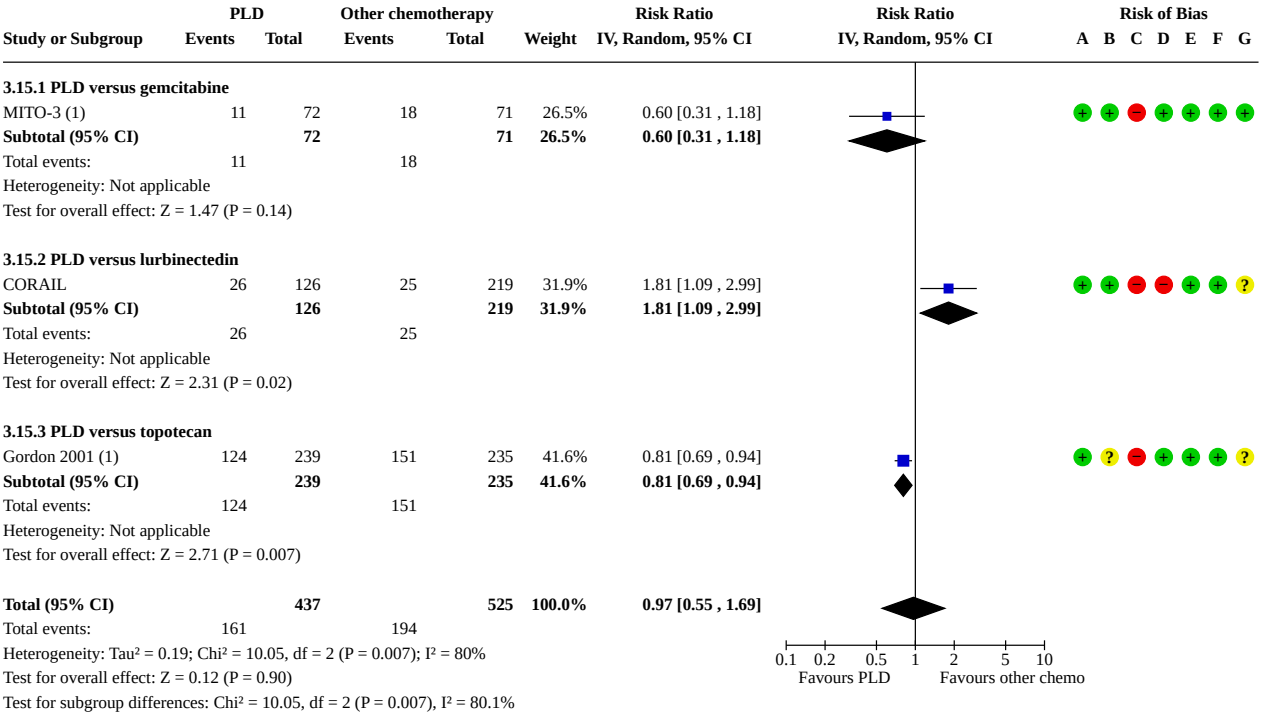
Footnotes

(1) participants regardless of platinum sensitivity status

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.15. Comparison 3: Platinum-resistant recurrent EOC: PLD versus other chemotherapy, Outcome 15: Dose delays



Footnotes

(1) participants regardless of platinum sensitivity status

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

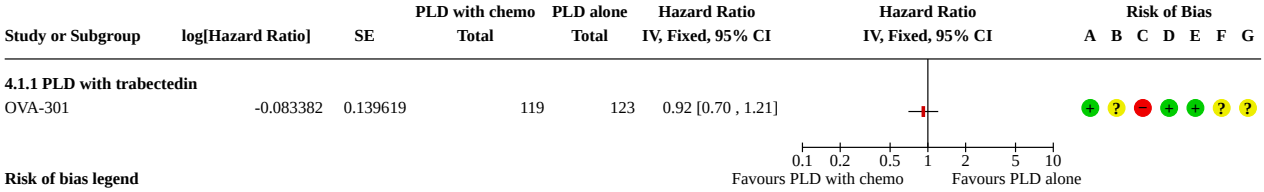
Comparison 4. Platinum-resistant recurrent EOC: PLD with chemotherapy versus PLD alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Overall survival	1		Hazard Ratio (IV, Fixed, 95% CI)	Totals not selected
4.1.1 PLD with trabectedin	1		Hazard Ratio (IV, Fixed, 95% CI)	Totals not selected
4.2 Progression-free survival	2	353	Hazard Ratio (IV, Fixed, 95% CI)	0.94 [0.73, 1.22]
4.2.1 PLD with trabectedin	1	228	Hazard Ratio (IV, Fixed, 95% CI)	0.95 [0.70, 1.29]
4.2.2 PLD with canfosfamide	1	125	Hazard Ratio (IV, Fixed, 95% CI)	0.92 [0.58, 1.46]
4.3 Overall Severe Adverse Events (grade ≥ 3)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
4.3.1 PLD with trabectedin	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.4 SevAE: Anaemia (grade ≥ 3)	2	785	Risk Ratio (IV, Fixed, 95% CI)	2.38 [1.46, 3.87]
4.4.1 PLD with trabectedin	1	663	Risk Ratio (IV, Fixed, 95% CI)	2.54 [1.45, 4.43]
4.4.2 PLD with canfosfamide	1	122	Risk Ratio (IV, Fixed, 95% CI)	1.93 [0.71, 5.22]
4.5 SevAE: Hand-foot syndrome (grade ≥ 3)	2	785	Risk Ratio (IV, Fixed, 95% CI)	0.24 [0.14, 0.40]
4.5.1 PLD with trabectedin	1	663	Risk Ratio (IV, Fixed, 95% CI)	0.20 [0.11, 0.35]
4.5.2 PLD with canfosfamide	1	122	Risk Ratio (IV, Fixed, 95% CI)	0.50 [0.15, 1.62]
4.6 SevAE: Neurological (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.6.1 PLD with trabectedin	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.7 SevAE: Neutropenia (grade ≥ 3)	2	785	Risk Ratio (IV, Fixed, 95% CI)	2.75 [2.23, 3.38]
4.7.1 PLD with trabectedin	1	663	Risk Ratio (IV, Fixed, 95% CI)	2.80 [2.25, 3.48]
4.7.2 PLD with canfosfamide	1	122	Risk Ratio (IV, Fixed, 95% CI)	2.19 [1.05, 4.59]
4.8 SevAE: Thrombocytopenia (grade ≥ 3)	2	785	Risk Ratio (M-H, Fixed, 95% CI)	7.70 [3.90, 15.19]
4.8.1 PLD with trabectedin	1	663	Risk Ratio (M-H, Fixed, 95% CI)	7.56 [3.67, 15.54]
4.8.2 PLD with canfosfamide	1	122	Risk Ratio (M-H, Fixed, 95% CI)	8.77 [1.16, 66.41]
4.9 SevAE: Stomatitis (grade ≥ 3)	2	785	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.13, 0.70]
4.9.1 PLD with trabectedin	1	663	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.05, 0.59]
4.9.2 PLD with canfosfamide	1	122	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.20, 2.49]
4.10 SevAE: Vomiting (grade ≥ 3)	2	785	Risk Ratio (M-H, Fixed, 95% CI)	3.77 [1.91, 7.41]
4.10.1 PLD with trabectedin	1	663	Risk Ratio (M-H, Fixed, 95% CI)	4.81 [2.16, 10.70]
4.10.2 PLD with canfosfamide	1	122	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.37, 5.85]
4.11 SevAE: Fatigue (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.11.1 PLD with trabectedin	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.12 Serious AE: Treatment-related death	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.12.1 trabectedin with PLD vs PLD alone	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

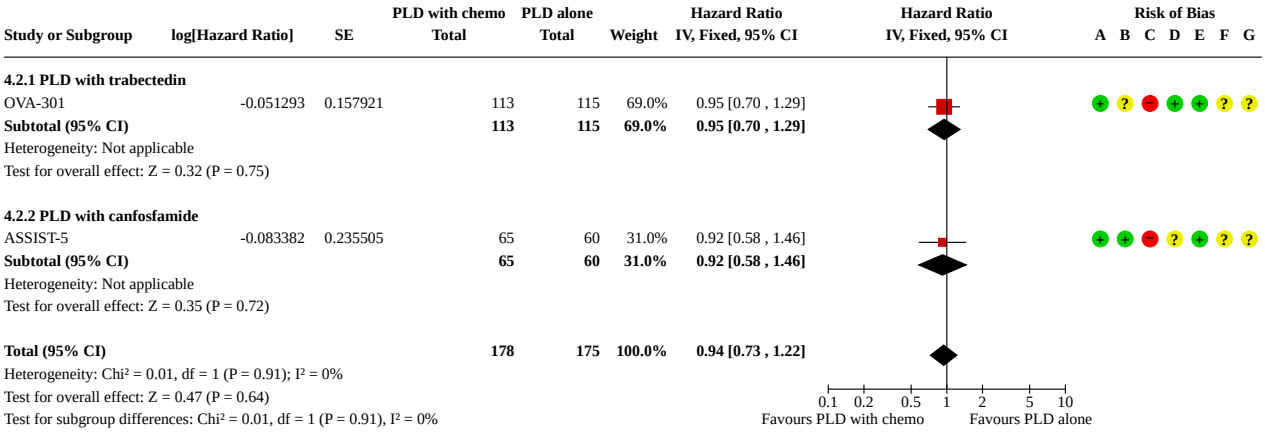
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.13 Dose delays	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
4.13.1 canfosfamide with PLD vs PLD alone	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
4.14 Dose reductions	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.14.1 canfosfamide with PLD vs PLD alone	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4: Platinum-resistant recurrent EOC: PLD with chemotherapy versus PLD alone, Outcome 1: Overall survival



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

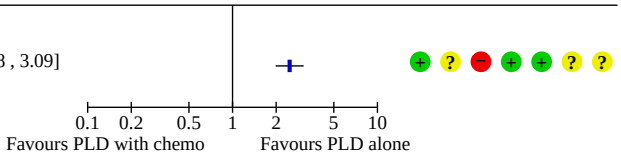
Analysis 4.2. Comparison 4: Platinum-resistant recurrent EOC: PLD with chemotherapy versus PLD alone, Outcome 2: Progression-free survival



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.3. Comparison 4: Platinum-resistant recurrent EOC: PLD with chemotherapy versus PLD alone, Outcome 3: Overall Severe Adverse Events (grade ≥ 3)

Study or Subgroup	PLD with chemo Events	PLD with chemo Total	PLD alone Events	PLD alone Total	Risk Ratio IV, Fixed, 95% CI
4.3.1 PLD with trabectedin					
OVA-301 (1)	185	333	74	330	2.48 [1.98 , 3.09]

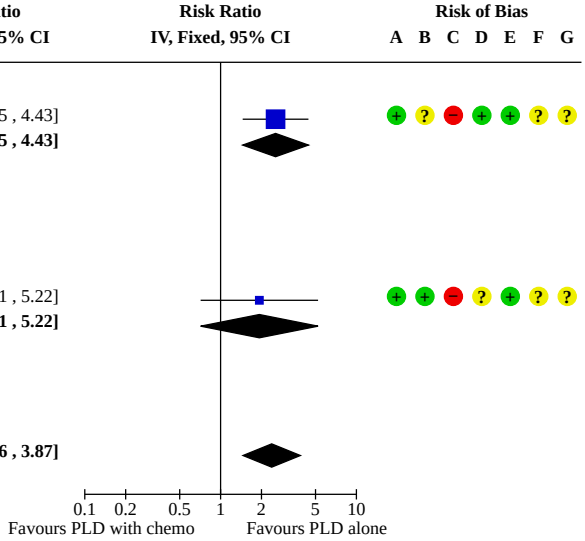


Footnotes
(1) participants regardless of platinum sensitivity status; treatment-emergent AEs

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.4. Comparison 4: Platinum-resistant recurrent EOC: PLD with chemotherapy versus PLD alone, Outcome 4: SevAE: Anaemia (grade ≥ 3)

Study or Subgroup	PLD with chemo Events	PLD with chemo Total	PLD alone Events	PLD alone Total	Weight	Risk Ratio IV, Fixed, 95% CI
4.4.1 PLD with trabectedin						
OVA-301 (1)	41	333	16	330	76.1%	2.54 [1.45 , 4.43]
Subtotal (95% CI)		**333**		**330**	**76.1%**	**2.54 [1.45 , 4.43]**
Total events:	41		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.28 (P = 0.001)						
4.4.2 PLD with canfosfamide						
ASSIST-5	11	65	5	57	23.9%	1.93 [0.71 , 5.22]
Subtotal (95% CI)		**65**		**57**	**23.9%**	**1.93 [0.71 , 5.22]**
Total events:	11		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.29 (P = 0.20)						
Total (95% CI)		**398**		**387**	**100.0%**	**2.38 [1.46 , 3.87]**
Total events:	52		21			
Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 3.49 (P = 0.0005)						
Test for subgroup differences: Chi² = 0.22, df = 1 (P = 0.64), I² = 0%						

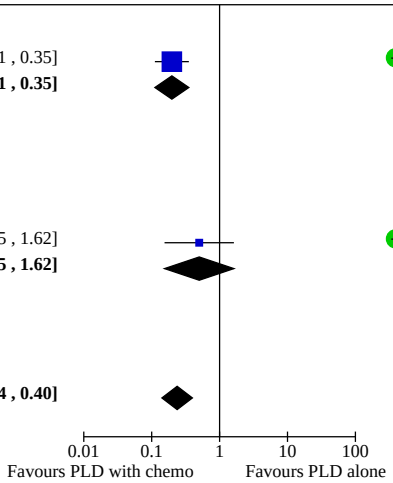


Footnotes
(1) participants regardless of platinum sensitivity status; treatment-emergent AEs

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.5. Comparison 4: Platinum-resistant recurrent EOC: PLD with chemotherapy versus PLD alone, Outcome 5: SevAE: Hand-foot syndrome (grade ≥ 3)

Study or Subgroup	PLD with chemo Events	PLD with chemo Total	PLD alone Events	PLD alone Total	Weight	Risk Ratio IV, Fixed, 95% CI
4.5.1 PLD with trabectedin						
OVA-301 (1)	13	333	65	330	80.7%	0.20 [0.11 , 0.35]
Subtotal (95% CI)		**333**		**330**	**80.7%**	**0.20 [0.11 , 0.35]**
Total events:	13		65			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.51 (P < 0.00001)						
4.5.2 PLD with canfosfamide						
ASSIST-5	4	65	7	57	19.3%	0.50 [0.15 , 1.62]
Subtotal (95% CI)		**65**		**57**	**19.3%**	**0.50 [0.15 , 1.62]**
Total events:	4		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.15 (P = 0.25)						
Total (95% CI)		**398**		**387**	**100.0%**	**0.24 [0.14 , 0.40]**
Total events:	17		72			
Heterogeneity: Chi² = 1.93, df = 1 (P = 0.16); I² = 48%						
Test for overall effect: Z = 5.46 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.93, df = 1 (P = 0.16), I² = 48.1%						



Footnotes

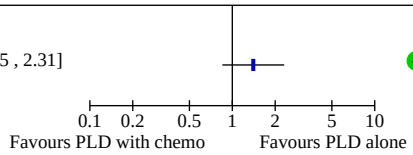
(1) participants regardless of platinum sensitivity status; treatment-emergent AEs

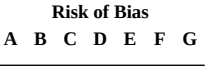
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.6. Comparison 4: Platinum-resistant recurrent EOC: PLD with chemotherapy versus PLD alone, Outcome 6: SevAE: Neurological (grade ≥ 3)

Study or Subgroup	PLD with chemo Events	PLD with chemo Total	PLD alone Events	PLD alone Total	Risk Ratio M-H, Fixed, 95% CI
4.6.1 PLD with trabectedin					
OVA-301 (1)	34	333	24	330	1.40 [0.85 , 2.31]





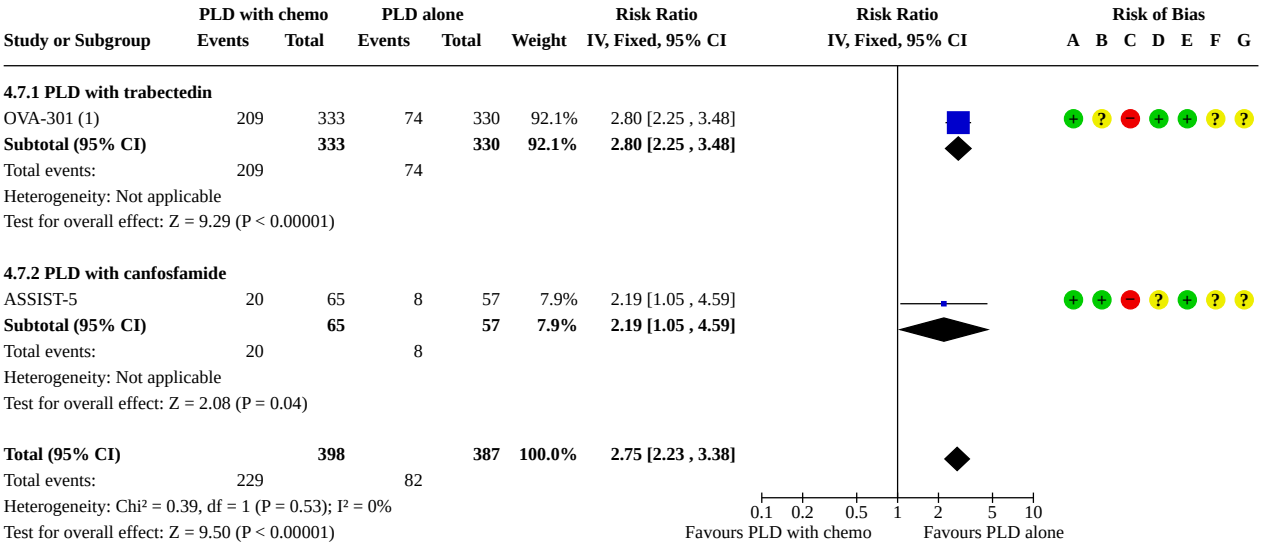
Footnotes

(1) participants regardless of platinum sensitivity status; neuropathy; treatment-emergent AEs

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.7. Comparison 4: Platinum-resistant recurrent EOC: PLD with chemotherapy versus PLD alone, Outcome 7: SevAE: Neutropenia (grade ≥ 3)



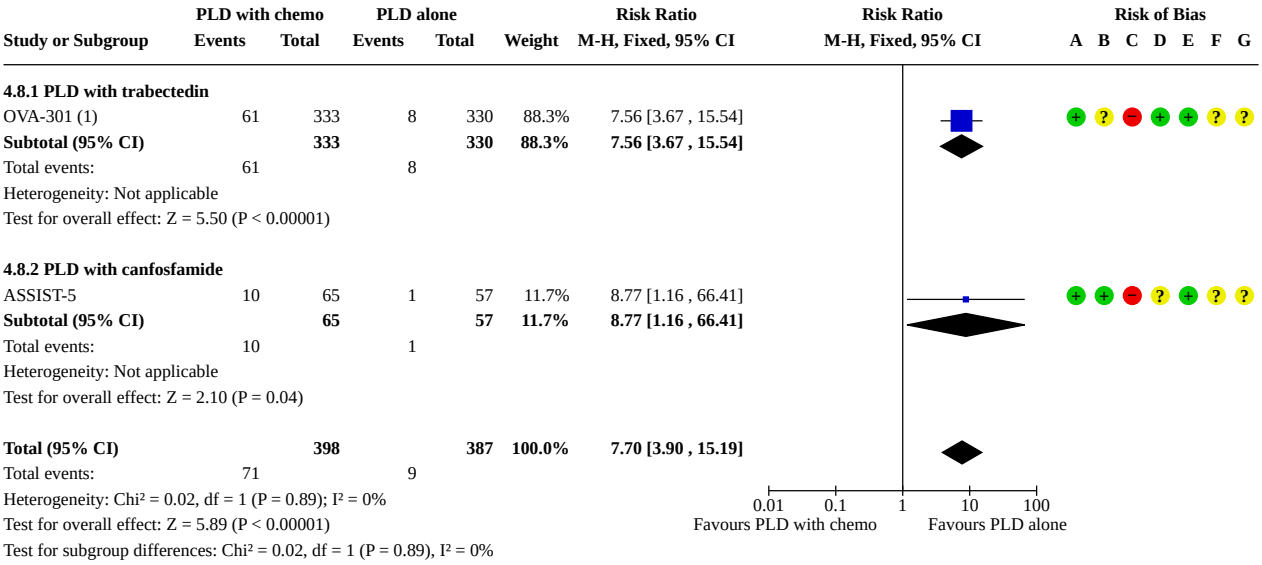
Footnotes

(1) participants regardless of platinum sensitivity status; treatment-emergent AEs

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.8. Comparison 4: Platinum-resistant recurrent EOC: PLD with chemotherapy versus PLD alone, Outcome 8: SevAE: Thrombocytopenia (grade ≥ 3)



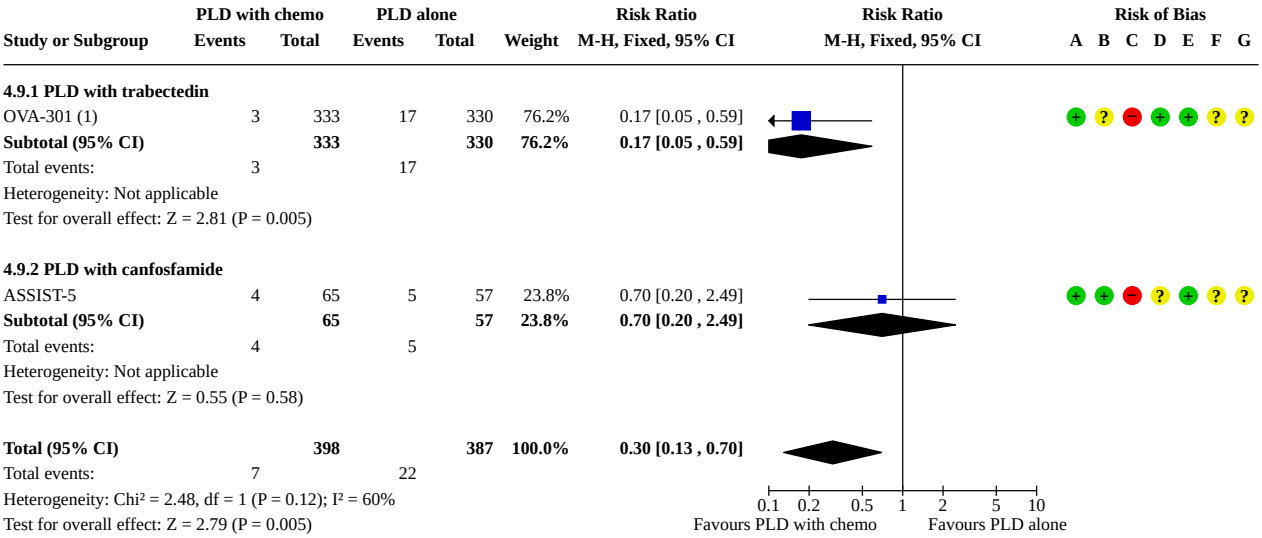
Footnotes

(1) participants regardless of platinum sensitivity status; treatment-emergent AEs

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.9. Comparison 4: Platinum-resistant recurrent EOC: PLD with chemotherapy versus PLD alone, Outcome 9: SevAE: Stomatitis (grade ≥ 3)



Footnotes

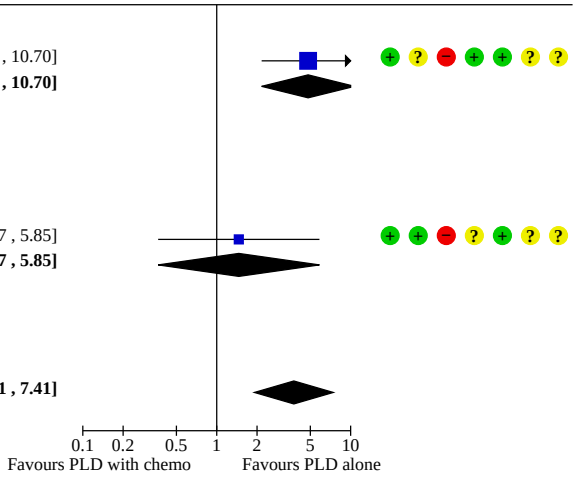
(1) participants regardless of platinum sensitivity status; treatment-emergent AEs

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.10. Comparison 4: Platinum-resistant recurrent EOC: PLD with chemotherapy versus PLD alone, Outcome 10: SevAE: Vomiting (grade ≥ 3)

Study or Subgroup	PLD with chemo Events	Total	PLD alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.10.1 PLD with trabectedin						
OVA-301 (1)	34	333	7	330	68.7%	4.81 [2.16 , 10.70]
Subtotal (95% CI)		**333**		**330**	**68.7%**	**4.81 [2.16 , 10.70]**
Total events:	34		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.85 (P = 0.0001)						
4.10.2 PLD with canfosfamide						
ASSIST-5	5	65	3	57	31.3%	1.46 [0.37 , 5.85]
Subtotal (95% CI)		**65**		**57**	**31.3%**	**1.46 [0.37 , 5.85]**
Total events:	5		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
Total (95% CI)		**398**		**387**	**100.0%**	**3.77 [1.91 , 7.41]**
Total events:	39		10			
Heterogeneity: Chi² = 2.15, df = 1 (P = 0.14); I² = 54%						
Test for overall effect: Z = 3.84 (P = 0.0001)						
Test for subgroup differences: Chi² = 2.13, df = 1 (P = 0.14), I² = 53.1%						

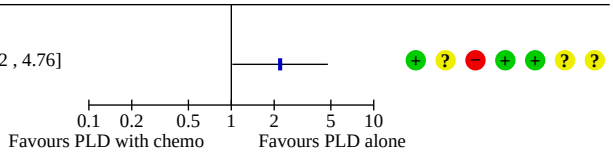


Footnotes
(1) participants regardless of platinum sensitivity status; treatment-emergent AEs

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.11. Comparison 4: Platinum-resistant recurrent EOC: PLD with chemotherapy versus PLD alone, Outcome 11: SevAE: Fatigue (grade ≥ 3)

Study or Subgroup	PLD with chemo Events	Total	PLD alone Events	Total	Risk Ratio M-H, Fixed, 95% CI
4.11.1 PLD with trabectedin					
OVA-301 (1)	20	333	9	330	2.20 [1.02 , 4.76]

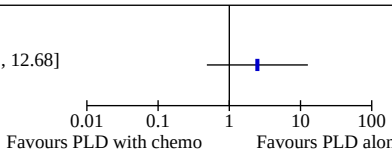


Footnotes
(1) participants regardless of platinum sensitivity status; treatment-emergent AEs

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.12. Comparison 4: Platinum-resistant recurrent EOC: PLD with chemotherapy versus PLD alone, Outcome 12: Serious AE: Treatment-related death

Study or Subgroup	PLD with chemo Events	Total	PLD alone Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
4.12.1 trabectedin with PLD vs PLD alone							
OVA-301 (1)	5	333	2	330	2.48 [0.48 , 12.68]		+ ? − + + ? ?

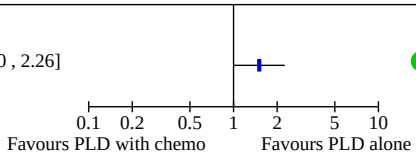


Footnotes
(1) participants regardless of platinum sensitivity status

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.13. Comparison 4: Platinum-resistant recurrent EOC: PLD with chemotherapy versus PLD alone, Outcome 13: Dose delays

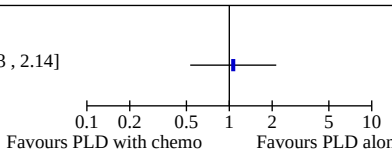
Study or Subgroup	PLD with chemo Events	Total	PLD alone Events	Total	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G
4.13.1 canfosfamide with PLD vs PLD alone							
ASSIST-5	48	259	34	276	1.50 [1.00 , 2.26]		+ + − ? + ? ?



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.14. Comparison 4: Platinum-resistant recurrent EOC: PLD with chemotherapy versus PLD alone, Outcome 14: Dose reductions

Study or Subgroup	PLD with chemo Events	Total	PLD alone Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
4.14.1 canfosfamide with PLD vs PLD alone							
ASSIST-5	15	259	15	276	1.07 [0.53 , 2.14]		+ + − ? + ? ?



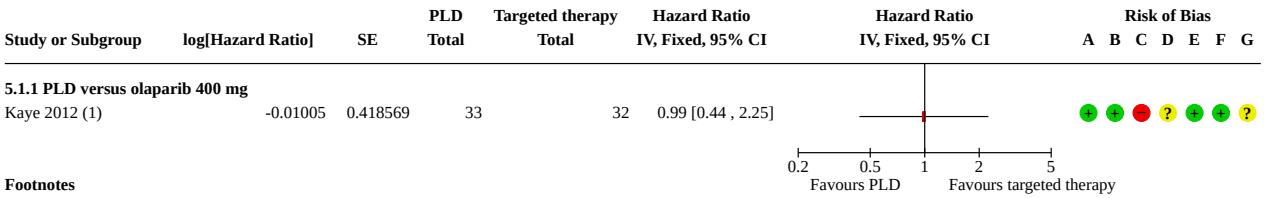
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 5. Platinum-resistant recurrent EOC: PLD versus targeted therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Overall survival	1		Hazard Ratio (IV, Fixed, 95% CI)	Totals not selected
5.1.1 PLD versus olaparib 400 mg	1		Hazard Ratio (IV, Fixed, 95% CI)	Totals not selected
5.2 Progression-free survival	2	160	Hazard Ratio (IV, Random, 95% CI)	1.23 [0.82, 1.84]
5.2.1 PLD versus lifastuzumab	1	95	Hazard Ratio (IV, Random, 95% CI)	1.28 [0.76, 2.16]
5.2.2 PLD versus olaparib 400mg	1	65	Hazard Ratio (IV, Random, 95% CI)	1.16 [0.62, 2.17]
5.3 Overall Severe Adverse Events (grade ≥ 3)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
5.3.1 PLD versus lifastuzumab	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
5.4 SevAE: Anaemia (grade ≥ 3)	2	157	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.02, 0.97]
5.4.1 PLD versus lifastuzumab	1	93	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.63]
5.4.2 PLD versus olaparib 400mg	1	64	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 1.98]
5.5 SevAE: Hand-foot syndrome (grade ≥ 3)	2	157	Risk Ratio (M-H, Random, 95% CI)	25.00 [1.54, 405.08]
5.5.1 PLD versus lifastuzumab	1	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
5.5.2 PLD versus olaparib 400mg	1	64	Risk Ratio (M-H, Random, 95% CI)	25.00 [1.54, 405.08]
5.6 SevAE: Neurological (grade ≥ 3)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
5.6.1 PLD versus lifastuzumab	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
5.7 SevAE: Neutropenia (grade ≥ 3)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
5.7.1 PLD versus lifastuzumab	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
5.8 SevAE: Stomatitis (grade ≥ 3)	2	157	Risk Ratio (M-H, Random, 95% CI)	5.87 [0.72, 47.84]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.8.1 PLD versus lifastuzumab	1	93	Risk Ratio (M-H, Random, 95% CI)	6.85 [0.36, 129.10]
5.8.2 PLD versus olaparib 400mg	1	64	Risk Ratio (M-H, Random, 95% CI)	5.00 [0.25, 100.20]
5.9 SevAE: Vomiting (grade ≥ 3)	2	157	Risk Ratio (IV, Random, 95% CI)	1.31 [0.30, 5.70]
5.9.1 PLD versus lifastuzumab	1	93	Risk Ratio (IV, Random, 95% CI)	1.47 [0.26, 8.38]
5.9.2 PLD versus olaparib 400mg	1	64	Risk Ratio (IV, Random, 95% CI)	1.00 [0.07, 15.30]
5.10 SevAE: Diarrhoea (grade ≥ 3)	2	157	Risk Ratio (M-H, Random, 95% CI)	2.06 [0.27, 15.56]
5.10.1 PLD versus lifastuzumab	1	93	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.06, 15.19]
5.10.2 PLD versus olaparib 400mg	1	64	Risk Ratio (M-H, Random, 95% CI)	5.00 [0.25, 100.20]
5.11 SevAE: Fatigue (grade ≥ 3)	2	157	Risk Ratio (IV, Random, 95% CI)	1.18 [0.38, 3.72]
5.11.1 PLD versus lifastuzumab	1	93	Risk Ratio (IV, Random, 95% CI)	1.47 [0.26, 8.38]
5.11.2 PLD versus olaparib 400mg	1	64	Risk Ratio (IV, Random, 95% CI)	1.00 [0.22, 4.59]
5.12 Dose reductions	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
5.12.1 PLD versus olaparib 400 mg	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5: Platinum-resistant recurrent EOC: PLD versus targeted therapy, Outcome 1: Overall survival



Footnotes

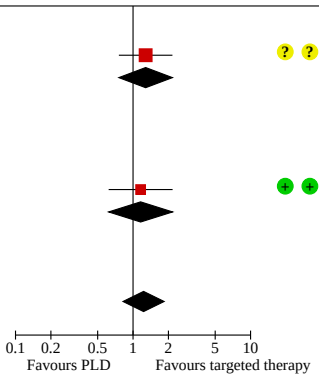
(1) participants regardless of platinum sensitivity status; recalculated HR for olaparib 400 arm as a comparator; no difference in effect between dosages HR 0.66 (95%CI 0.27, 1.55) for 200

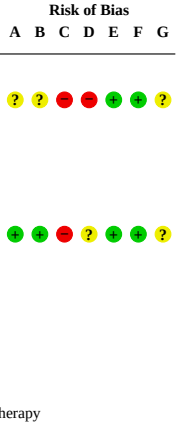
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.2. Comparison 5: Platinum-resistant recurrent EOC: PLD versus targeted therapy, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	PLD Total	Targeted therapy Total	Weight	Hazard Ratio IV, Random, 95% CI
5.2.1 PLD versus lifastuzumab						
Banerjee 2018 (1)	0.24686	0.267649	48	47	58.8%	1.28 [0.76 , 2.16]
Subtotal (95% CI)			**48**	**47**	**58.8%**	**1.28 [0.76 , 2.16]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.92 (P = 0.36)						
5.2.2 PLD versus olaparib 400mg						
Kaye 2012 (2)	0.14842	0.319588	33	32	41.2%	1.16 [0.62 , 2.17]
Subtotal (95% CI)			**33**	**32**	**41.2%**	**1.16 [0.62 , 2.17]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.64)						
Total (95% CI)			**81**	**79**	**100.0%**	**1.23 [0.82 , 1.84]**
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%						
Test for overall effect: Z = 1.01 (P = 0.31)						
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%						





Footnotes

(1) recalculated HR for lifastuzumab arm as a comparator

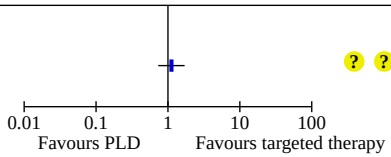
(2) participants regardless of platinum sensitivity status; recalculated HR for olaparib 400mg arm as a comparator; no difference in effect between dosages HR 1.10 (95%CI 0.58, 2.08) for 200mg dose

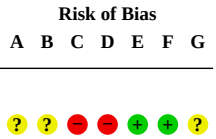
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.3. Comparison 5: Platinum-resistant recurrent EOC: PLD versus targeted therapy, Outcome 3: Overall Severe Adverse Events (grade ≥ 3)

Study or Subgroup	PLD Events	PLD Total	Targeted therapy Events	Targeted therapy Total	Risk Ratio IV, Fixed, 95% CI
5.3.1 PLD versus lifastuzumab					
Banerjee 2018	24	47	21	46	1.12 [0.73 , 1.71]

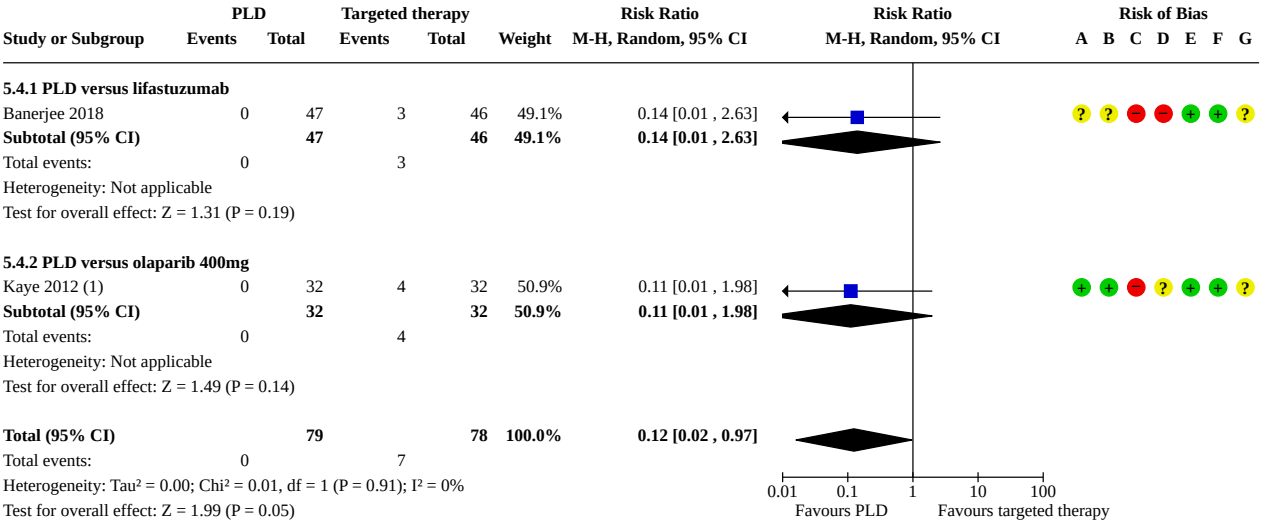




Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.4. Comparison 5: Platinum-resistant recurrent EOC: PLD versus targeted therapy, Outcome 4: SevAE: Anaemia (grade ≥ 3)



Footnotes

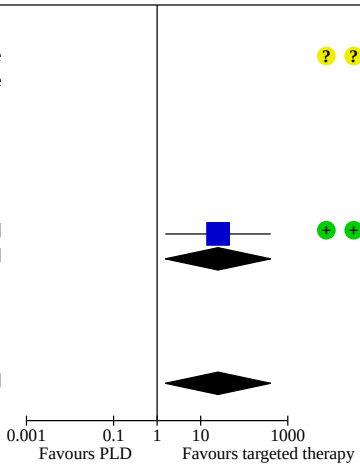
(1) participants regardless of platinum sensitivity status

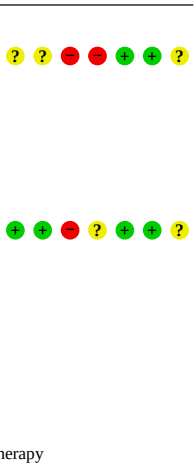
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.5. Comparison 5: Platinum-resistant recurrent EOC: PLD versus targeted therapy, Outcome 5: SevAE: Hand-foot syndrome (grade ≥ 3)

Study or Subgroup	PLD Events	PLD Total	targeted therapy Events	targeted therapy Total	Weight	Risk Ratio M-H, Random, 95% CI
5.5.1 PLD versus lifastuzumab						
Banerjee 2018	0	47	0	46		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
5.5.2 PLD versus olaparib 400mg						
Kaye 2012 (1)	12	32	0	32	100.0%	25.00 [1.54 , 405.08]
Subtotal (95% CI)		**32**		**32**	**100.0%**	**25.00 [1.54 , 405.08]**
Total events:	12		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.27 (P = 0.02)						
Total (95% CI)		**79**		**78**	**100.0%**	**25.00 [1.54 , 405.08]**
Total events:	12		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.27 (P = 0.02)						
Test for subgroup differences: Not applicable						





Footnotes

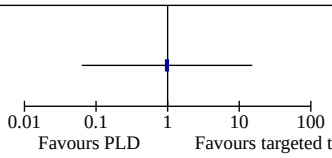
(1) participants regardless of platinum sensitivity status

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.6. Comparison 5: Platinum-resistant recurrent EOC: PLD versus targeted therapy, Outcome 6: SevAE: Neurological (grade ≥ 3)

Study or Subgroup	PLD Events	PLD Total	Targeted therapy Events	Targeted therapy Total	Risk Ratio IV, Fixed, 95% CI
5.6.1 PLD versus lifastuzumab					
Banerjee 2018	1	47	1	46	0.98 [0.06 , 15.19]

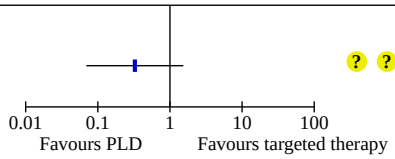


Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.7. Comparison 5: Platinum-resistant recurrent EOC: PLD versus targeted therapy, Outcome 7: SevAE: Neutropenia (grade ≥ 3)

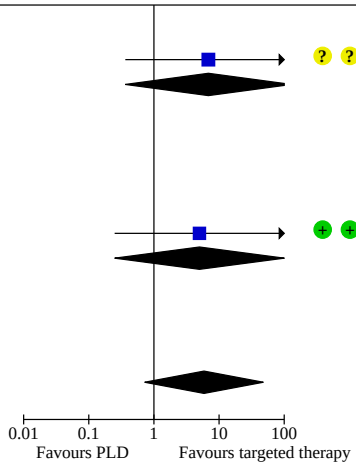
Study or Subgroup	PLD Events	PLD Total	targeted therapy Events	targeted therapy Total	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G
5.7.1 PLD versus lifastuzumab							
Banerjee 2018	2	47	6	46	0.33 [0.07 , 1.53]		? ? − − + + ?



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.8. Comparison 5: Platinum-resistant recurrent EOC: PLD versus targeted therapy, Outcome 8: SevAE: Stomatitis (grade ≥ 3)

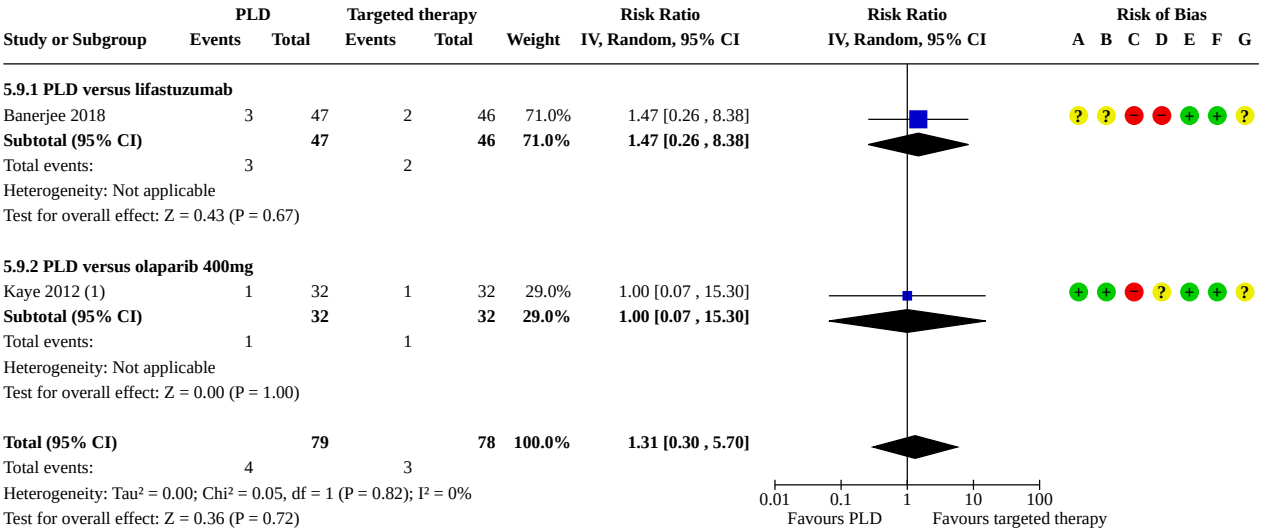
Study or Subgroup	PLD Events	PLD Total	Targeted therapy Events	Targeted therapy Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
5.8.1 PLD versus lifastuzumab								
Banerjee 2018	3	47	0	46	51.0%	6.85 [0.36 , 129.10]		? ? − − + + ?
Subtotal (95% CI)		**47**		**46**	**51.0%**	**6.85 [0.36 , 129.10]**		
Total events:	3		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.29 (P = 0.20)								
5.8.2 PLD versus olaparib 400mg								
Kaye 2012 (1)	2	32	0	32	49.0%	5.00 [0.25 , 100.20]		+ + − ? + + ?
Subtotal (95% CI)		**32**		**32**	**49.0%**	**5.00 [0.25 , 100.20]**		
Total events:	2		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.05 (P = 0.29)								
Total (95% CI)		**79**		**78**	**100.0%**	**5.87 [0.72 , 47.84]**		
Total events:	5		0					
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%								
Test for overall effect: Z = 1.65 (P = 0.10)								
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%								



Footnotes
(1) participants regardless of platinum sensitivity status

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.9. Comparison 5: Platinum-resistant recurrent EOC: PLD versus targeted therapy, Outcome 9: SevAE: Vomiting (grade ≥ 3)



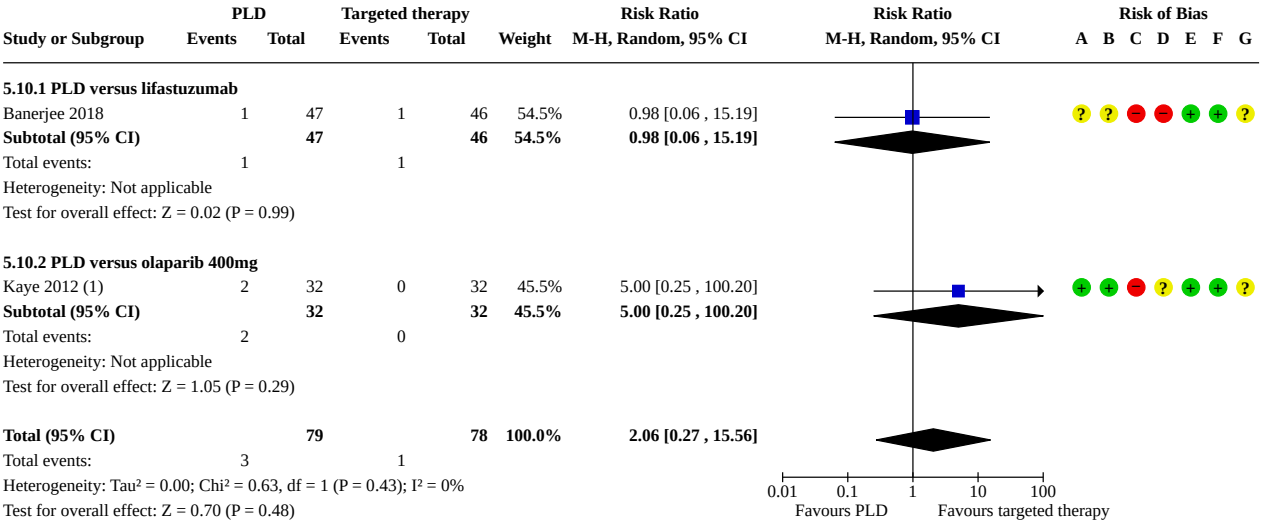
Footnotes

(1) participants regardless of platinum sensitivity status

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.10. Comparison 5: Platinum-resistant recurrent EOC: PLD versus targeted therapy, Outcome 10: SevAE: Diarrhoea (grade ≥ 3)



Footnotes

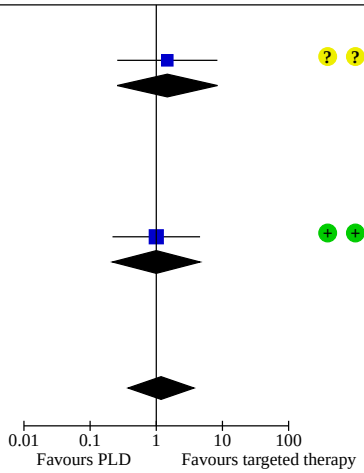
(1) participants regardless of platinum sensitivity status

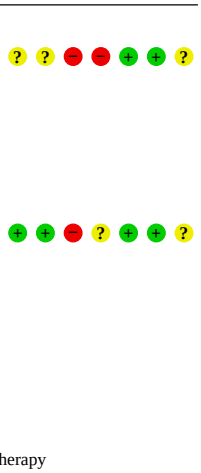
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.11. Comparison 5: Platinum-resistant recurrent EOC: PLD versus targeted therapy, Outcome 11: SevAE: Fatigue (grade ≥ 3)

Study or Subgroup	PLD Events	PLD Total	Targeted therapy Events	Targeted therapy Total	Weight	Risk Ratio IV, Random, 95% CI
5.11.1 PLD versus lifastuzumab						
Banerjee 2018	3	47	2	46	43.3%	1.47 [0.26 , 8.38]
Subtotal (95% CI)		**47**		**46**	**43.3%**	**1.47 [0.26 , 8.38]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.43 (P = 0.67)						
5.11.2 PLD versus olaparib 400mg						
Kaye 2012 (1)	3	32	3	32	56.7%	1.00 [0.22 , 4.59]
Subtotal (95% CI)		**32**		**32**	**56.7%**	**1.00 [0.22 , 4.59]**
Total events:	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**79**		**78**	**100.0%**	**1.18 [0.38 , 3.72]**
Total events:	6		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.28 (P = 0.78)						
Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.75), I² = 0%						



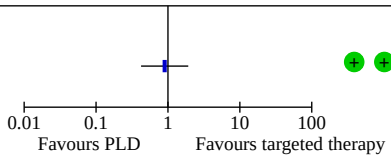


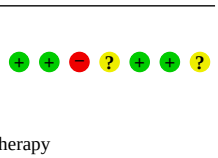
Footnotes
(1) participants regardless of platinum sensitivity status

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 5.12. Comparison 5: Platinum-resistant recurrent EOC: PLD versus targeted therapy, Outcome 12: Dose reductions

Study or Subgroup	PLD Events	PLD Total	Targeted therapy Events	Targeted therapy Total	Risk Ratio IV, Fixed, 95% CI
5.12.1 PLD versus olaparib 400 mg					
Kaye 2012 (1)	9	32	10	32	0.90 [0.42 , 1.92]





Footnotes
(1) participants regardless of platinum sensitivity status

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

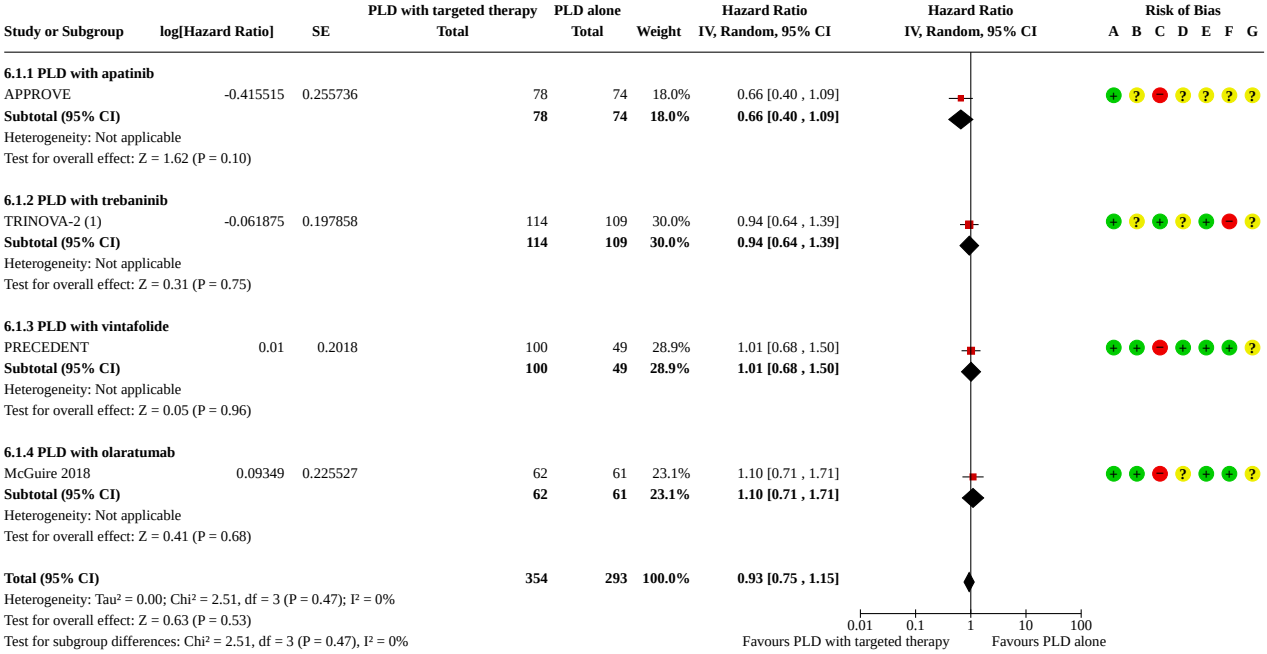
Comparison 6. Platinum-resistant recurrent EOC: PLD with targeted therapy versus PLD alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Overall survival	4	647	Hazard Ratio (IV, Random, 95% CI)	0.93 [0.75, 1.15]
6.1.1 PLD with apatinib	1	152	Hazard Ratio (IV, Random, 95% CI)	0.66 [0.40, 1.09]
6.1.2 PLD with trebaninib	1	223	Hazard Ratio (IV, Random, 95% CI)	0.94 [0.64, 1.39]
6.1.3 PLD with vintafolide	1	149	Hazard Ratio (IV, Random, 95% CI)	1.01 [0.68, 1.50]
6.1.4 PLD with olaratumab	1	123	Hazard Ratio (IV, Random, 95% CI)	1.10 [0.71, 1.71]
6.2 Progression-free survival	5	877	Hazard Ratio (IV, Random, 95% CI)	0.78 [0.58, 1.04]
6.2.1 PLD with apatinib	1	152	Hazard Ratio (IV, Random, 95% CI)	0.44 [0.28, 0.70]
6.2.2 PLD with trebaninib	1	223	Hazard Ratio (IV, Random, 95% CI)	0.92 [0.68, 1.24]
6.2.3 PLD with vintafolide	2	379	Hazard Ratio (IV, Random, 95% CI)	0.78 [0.52, 1.16]
6.2.4 PLD with olaratumab	1	123	Hazard Ratio (IV, Random, 95% CI)	1.04 [0.70, 1.56]
6.3 Overall Severe Adverse Events (grade ≥3)	4	794	Risk Ratio (IV, Random, 95% CI)	1.15 [0.90, 1.48]
6.3.1 PLD with apatinib	1	146	Risk Ratio (IV, Random, 95% CI)	2.22 [1.30, 3.81]
6.3.2 PLD with trebaninib	1	216	Risk Ratio (IV, Random, 95% CI)	1.02 [0.88, 1.18]
6.3.3 PLD with vintafolide	1	309	Risk Ratio (IV, Random, 95% CI)	1.22 [0.91, 1.65]
6.3.4 PLD with Olaratumab	1	123	Risk Ratio (IV, Random, 95% CI)	0.91 [0.69, 1.20]
6.4 SevAE: Anaemia (grade ≥ 3)	4	647	Risk Ratio (IV, Random, 95% CI)	0.63 [0.32, 1.26]
6.4.1 PLD with apatinib	1	146	Risk Ratio (IV, Random, 95% CI)	0.32 [0.03, 3.05]
6.4.2 PLD with trebananib	1	221	Risk Ratio (IV, Random, 95% CI)	0.72 [0.16, 3.13]
6.4.3 PLD with vintafolide	1	157	Risk Ratio (IV, Random, 95% CI)	0.53 [0.22, 1.28]
6.4.4 PLD with Olaratumab	1	123	Risk Ratio (IV, Random, 95% CI)	2.95 [0.32, 27.60]
6.5 SevAE: Hand-foot syndrome (grade ≥ 3)	4	647	Risk Ratio (IV, Random, 95% CI)	1.75 [1.07, 2.88]
6.5.1 PLD with apatinib	1	146	Risk Ratio (IV, Random, 95% CI)	1.95 [0.37, 10.30]
6.5.2 PLD with trebaninib	1	221	Risk Ratio (IV, Random, 95% CI)	1.62 [0.86, 3.05]
6.5.3 PLD with vintafolide	1	157	Risk Ratio (IV, Random, 95% CI)	2.57 [0.59, 11.16]
6.5.4 PLD with Olaratumab	1	123	Risk Ratio (IV, Random, 95% CI)	1.72 [0.53, 5.58]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.6 SevAE: Neurological (grade ≥ 3)	2	378	Risk Ratio (M-H, Random, 95% CI)	4.25 [0.23, 77.45]
6.6.1 PLD with trebaninib	1	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.6.2 PLD with vintafolide	1	157	Risk Ratio (M-H, Random, 95% CI)	4.25 [0.23, 77.45]
6.7 SevAE: Neutropenia (grade ≥ 3)	4	647	Risk Ratio (IV, Random, 95% CI)	1.09 [0.69, 1.74]
6.7.1 PLD with apatinib	1	146	Risk Ratio (IV, Random, 95% CI)	1.78 [0.70, 4.57]
6.7.2 PLD with trebaninib	1	221	Risk Ratio (IV, Random, 95% CI)	0.59 [0.25, 1.36]
6.7.3 PLD with vintafolide	1	157	Risk Ratio (IV, Random, 95% CI)	1.07 [0.55, 2.08]
6.7.4 PLD with olaratumab	1	123	Risk Ratio (IV, Random, 95% CI)	1.57 [0.55, 4.54]
6.8 SevAE: Thrombocytopenia (grade ≥ 3)	2	303	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.11, 9.49]
6.8.1 PLD with apatinib	1	146	Risk Ratio (M-H, Random, 95% CI)	4.87 [0.24, 99.65]
6.8.2 PLD with vintafolide	1	157	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.12, 1.79]
6.9 SevAE: Stomatitis (grade ≥ 3)	4	647	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.43, 2.19]
6.9.1 PLD with apatinib	1	146	Risk Ratio (M-H, Random, 95% CI)	4.87 [0.24, 99.65]
6.9.2 PLD with trebaninib	1	221	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.39, 3.21]
6.9.3 PLD with vintafolide	1	157	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.30, 2.96]
6.9.4 PLD with Olaratumab	1	123	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 1.99]
6.10 SevAE: Vomiting (grade ≥ 3)	3	490	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.35, 1.87]
6.10.1 PLD with apatinib	1	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.10.2 PLD with trebaninib	1	221	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.39, 3.21]
6.10.3 PLD with Olaratumab	1	123	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.13, 1.88]
6.11 SevAE: Diarrhoea (grade ≥ 3)	2	344	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.18, 2.24]
6.11.1 PLD with trebaninib	1	221	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.14, 2.34]
6.11.2 PLD with olaratumab	1	123	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.06, 15.38]
6.12 SevAE: Fatigue (grade ≥ 3)	3	490	Risk Ratio (M-H, Random, 95% CI)	2.08 [0.30, 14.52]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.12.1 PLD with apatinib	1	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.12.2 PLD with trebaninib	1	221	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.37, 2.46]
6.12.3 PLD with Olaratumab	1	123	Risk Ratio (M-H, Random, 95% CI)	6.89 [0.87, 54.32]
6.13 Serious AE: Treatment-related death	5	956	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.33, 3.20]
6.13.1 PLD with apatinib	1	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.13.2 PLD with trebaninib	1	221	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.14, 6.67]
6.13.3 PLD with vintafolide	2	466	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.26, 4.35]
6.13.4 PLD with olaratumab	1	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.14 Dose reductions	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.14.1 PLD with apatinib	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 6.1. Comparison 6: Platinum-resistant recurrent EOC: PLD with targeted therapy versus PLD alone, Outcome 1: Overall survival



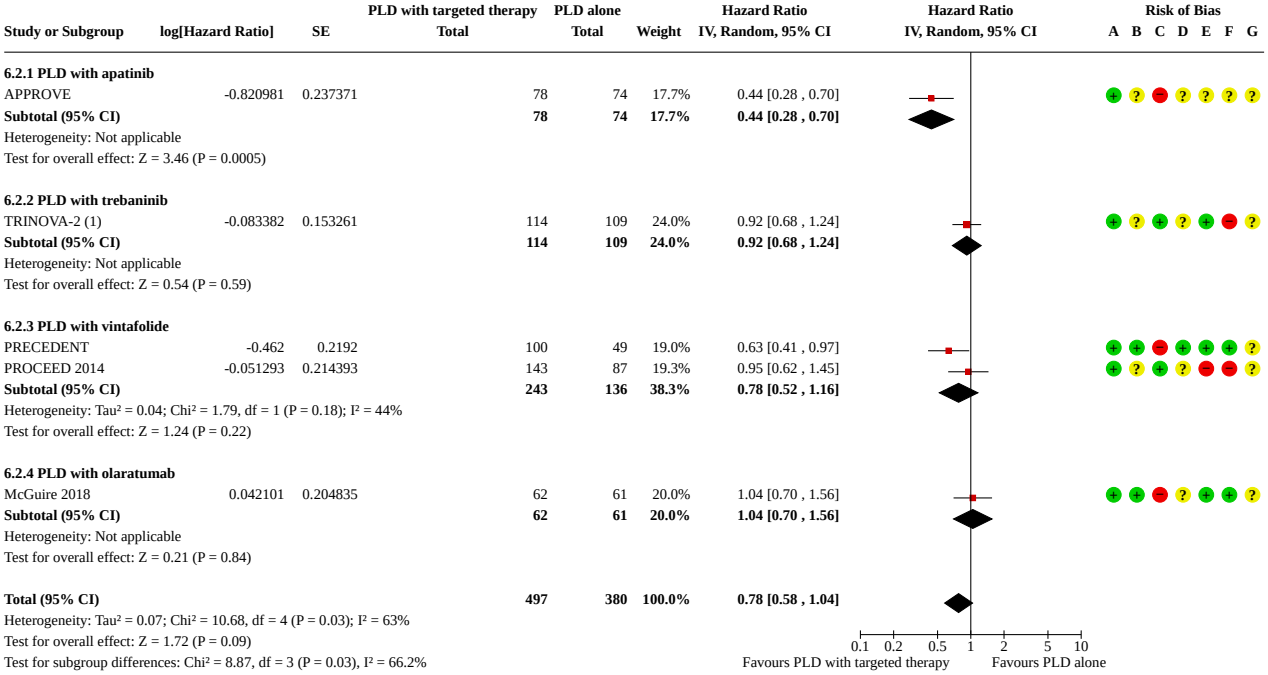
Footnotes

(1) participants regardless of platinum sensitivity status

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.2. Comparison 6: Platinum-resistant recurrent EOC: PLD with targeted therapy versus PLD alone, Outcome 2: Progression-free survival



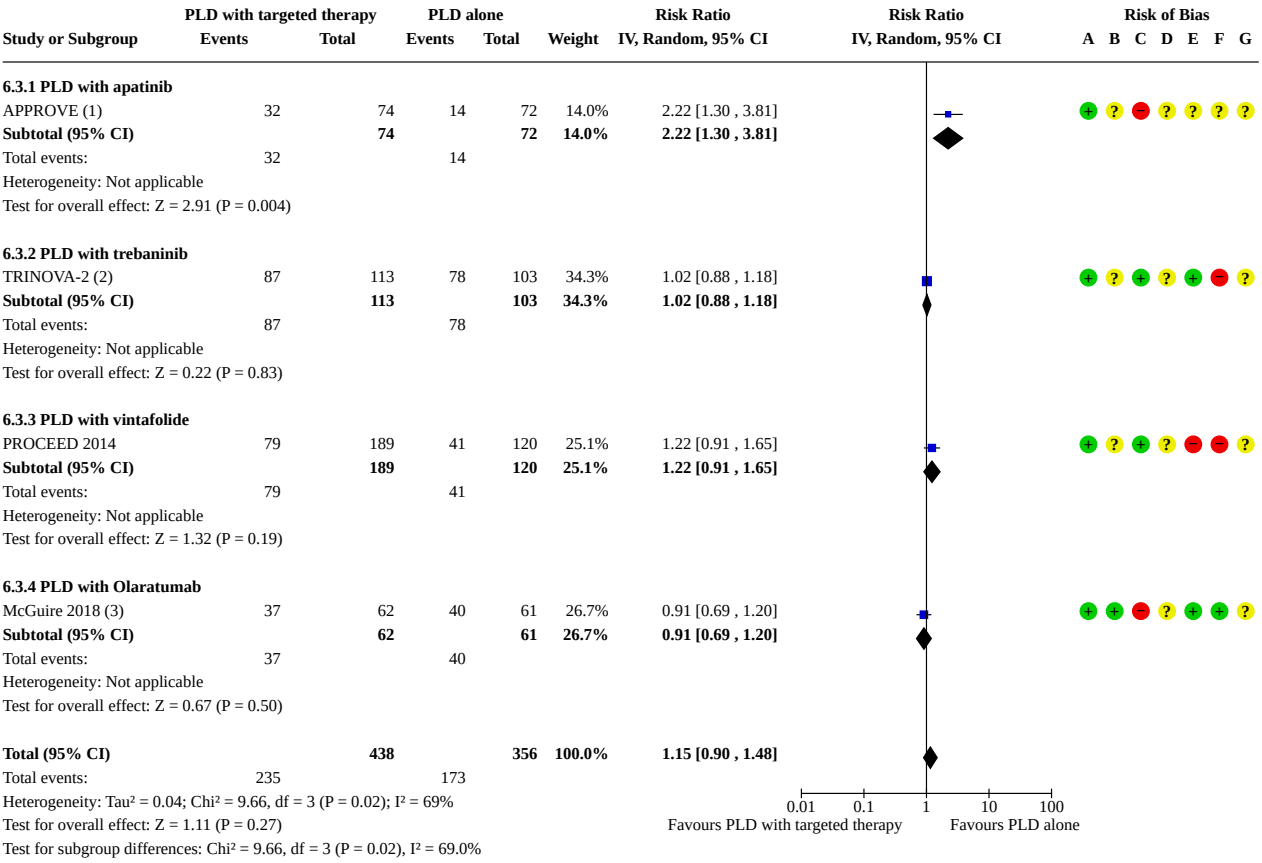
Footnotes

(1) participants regardless of platinum sensitivity status; evidence of the non-proportionality of hazards

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.3. Comparison 6: Platinum-resistant recurrent EOC: PLD with targeted therapy versus PLD alone, Outcome 3: Overall Severe Adverse Events (grade ≥3)



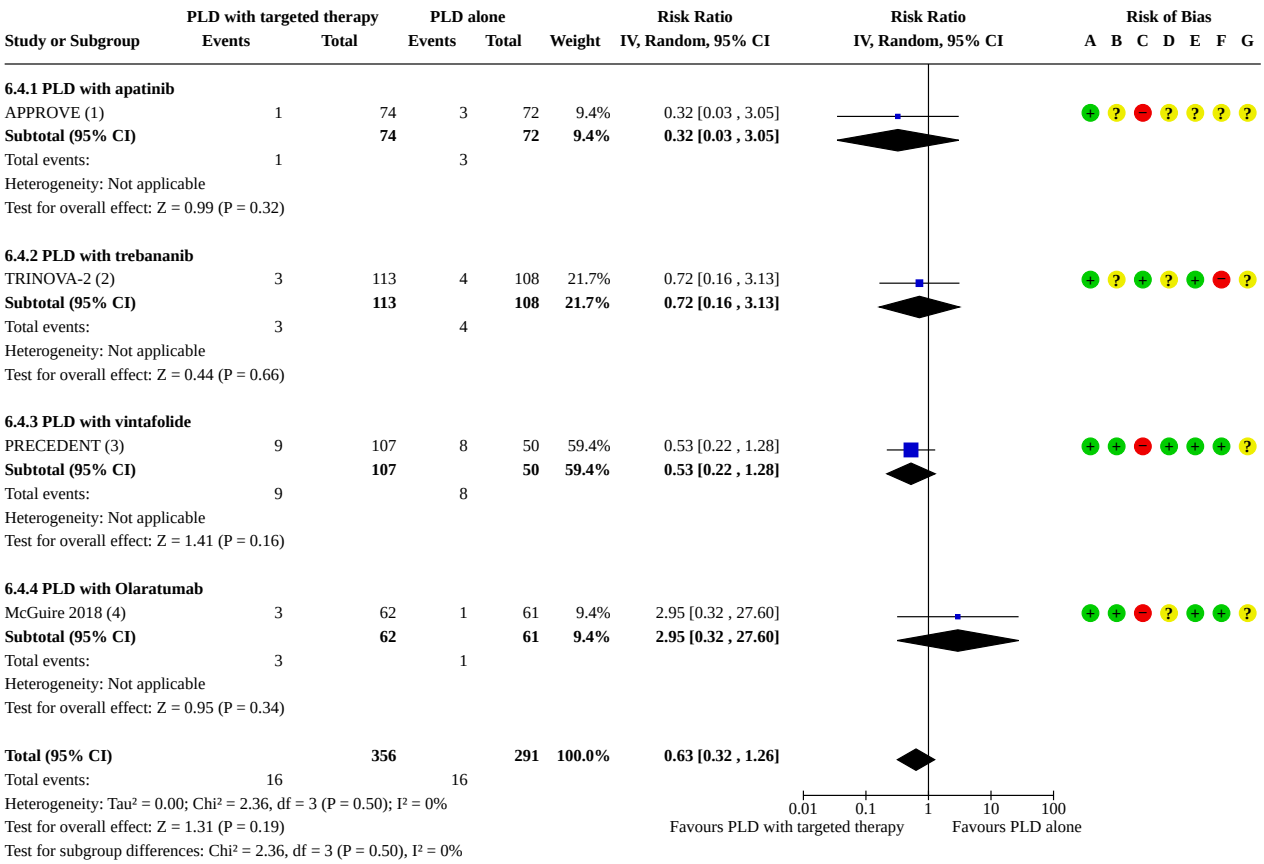
Footnotes

(1) treatment-emergent AEs
(2) treatment-emergent AEs; participants regardless of platinum sensitivity status
(3) Patients with an treatment emergent adverse event Grade ≥3 rather than any Grade ≥3 AE

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.4. Comparison 6: Platinum-resistant recurrent EOC: PLD with targeted therapy versus PLD alone, Outcome 4: SevAE: Anaemia (grade ≥ 3)



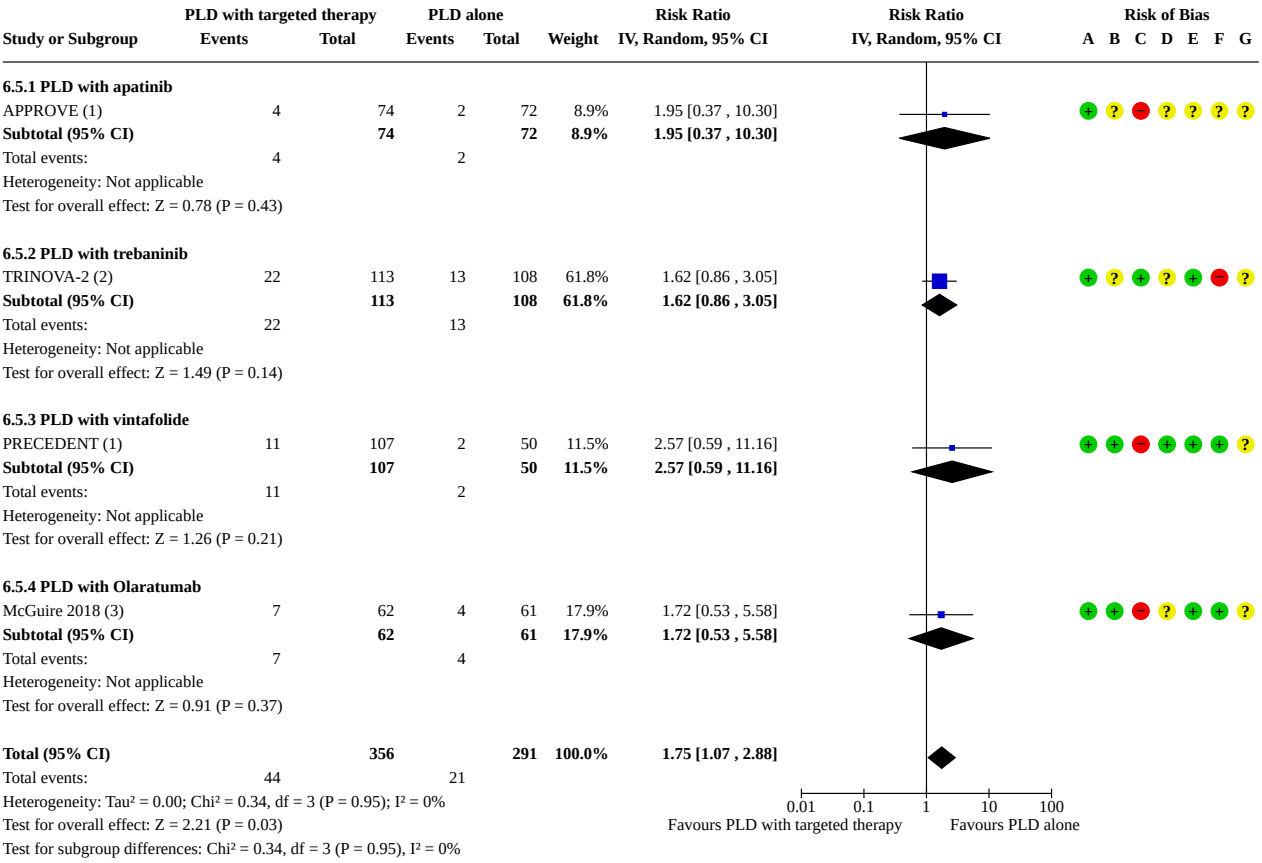
Footnotes

(1) treatment-emergent AE
(2) treatment-emergent AEs; participants regardless of platinum sensitivity status
(3) treatment-emergent AEs
(4) Treatment-emergent adverse events

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.5. Comparison 6: Platinum-resistant recurrent EOC: PLD with targeted therapy versus PLD alone, Outcome 5: SevAE: Hand-foot syndrome (grade ≥ 3)



Footnotes

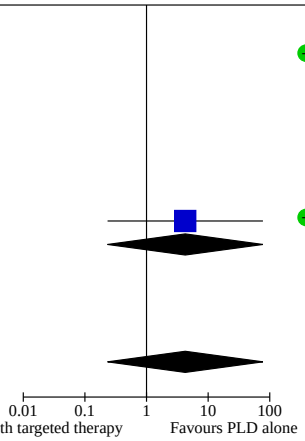
(1) treatment-emergent AEs
(2) treatment-emergent AEs; participants regardless of platinum sensitivity status
(3) Treatment-emergent adverse events

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.6. Comparison 6: Platinum-resistant recurrent EOC: PLD with targeted therapy versus PLD alone, Outcome 6: SevAE: Neurological (grade ≥ 3)

Study or Subgroup	PLD with targeted therapy Events	Total	PLD alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
6.6.1 PLD with trebaninib							
TRINOVA-2 (1)	0	113	0	108		Not estimable	+ ? + ? + − ?
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
6.6.2 PLD with vintafolide							
PRECEDENT (2)	4	107	0	50	100.0%	4.25 [0.23 , 77.45]	+ + − + + + ?
Subtotal (95% CI)		**107**		**50**	**100.0%**	**4.25 [0.23 , 77.45]**	
Total events:	4		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.98 (P = 0.33)							
Total (95% CI)		**220**		**158**	**100.0%**	**4.25 [0.23 , 77.45]**	
Total events:	4		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.98 (P = 0.33)							
Test for subgroup differences: Not applicable							



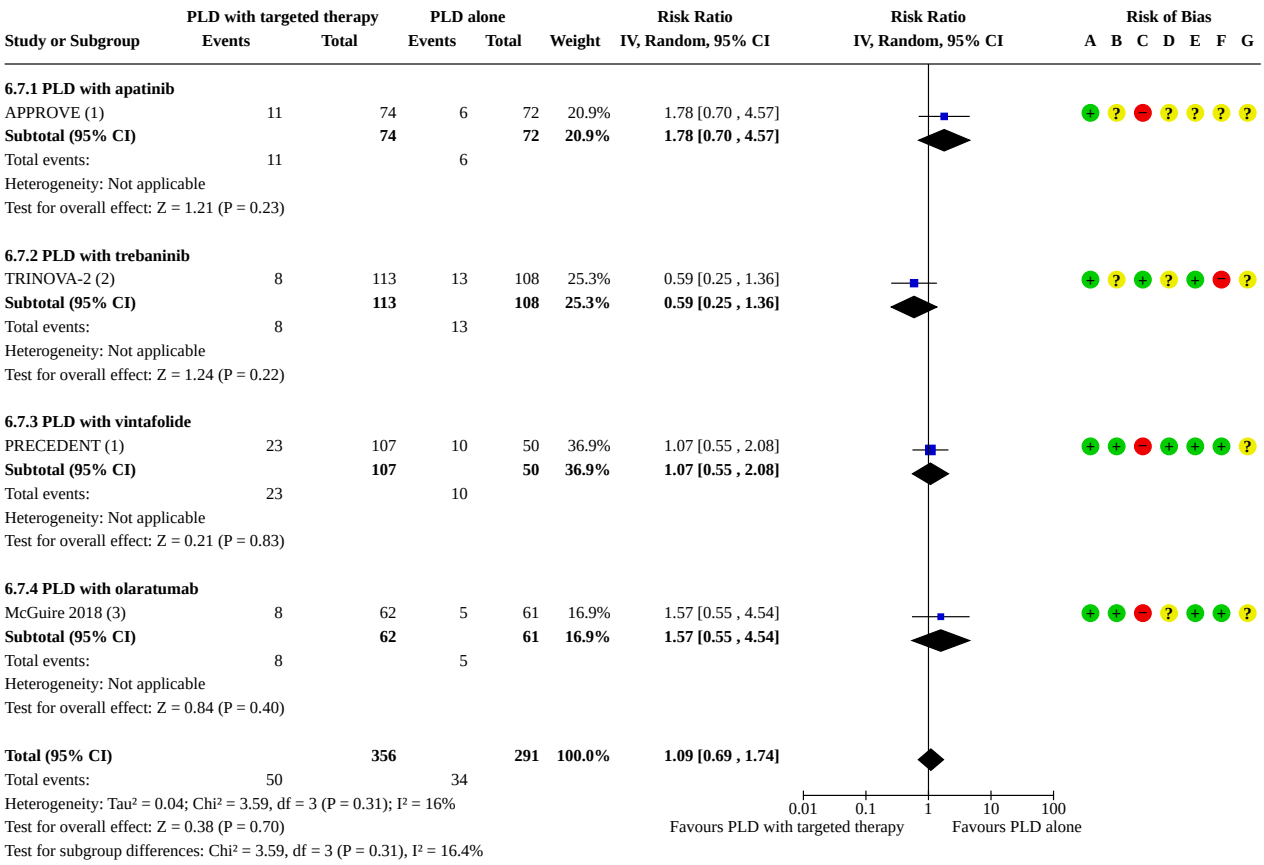
Footnotes

(1) treatment-emergent AEs; participants regardless of platinum sensitivity status
(2) treatment-emergent AEs

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.7. Comparison 6: Platinum-resistant recurrent EOC: PLD with targeted therapy versus PLD alone, Outcome 7: SevAE: Neutropenia (grade ≥ 3)



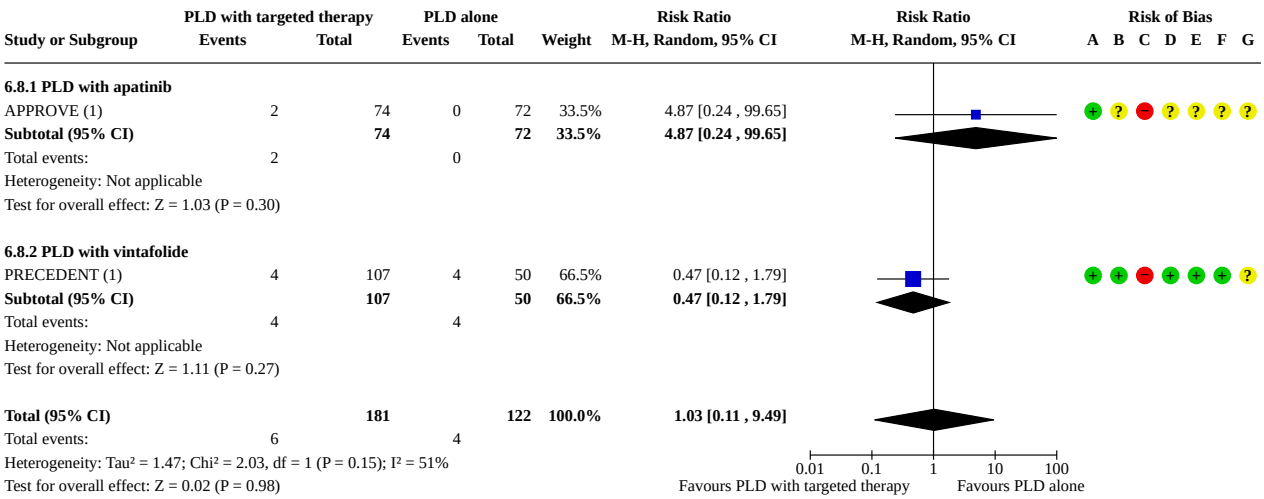
Footnotes

(1) treatment-emergent AEs
(2) treatment-emergent AEs; participants regardless of platinum sensitivity status
(3) Treatment-emeergent adverse events

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.8. Comparison 6: Platinum-resistant recurrent EOC: PLD with targeted therapy versus PLD alone, Outcome 8: SevAE: Thrombocytopenia (grade ≥ 3)



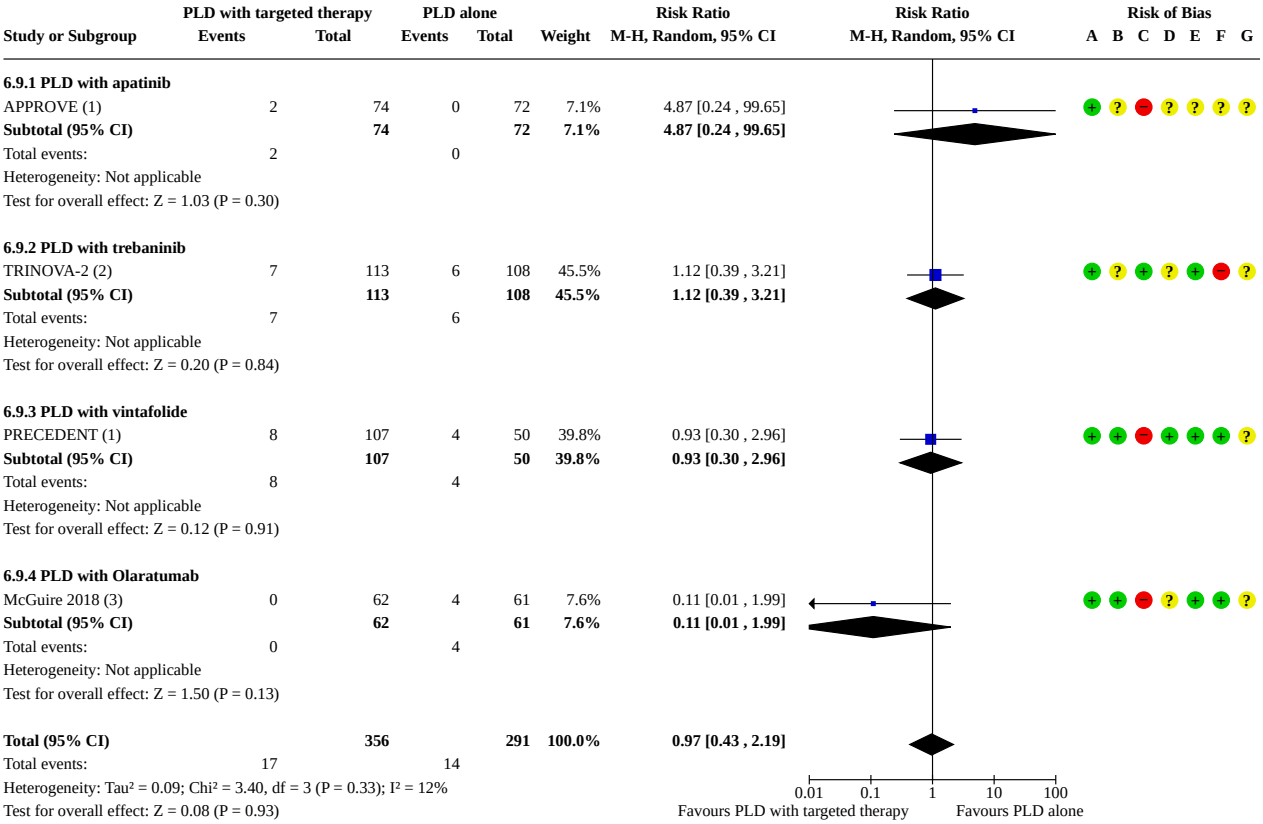
Footnotes

(1) treatment-emergent AEs

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.9. Comparison 6: Platinum-resistant recurrent EOC: PLD with targeted therapy versus PLD alone, Outcome 9: SevAE: Stomatitis (grade ≥ 3)



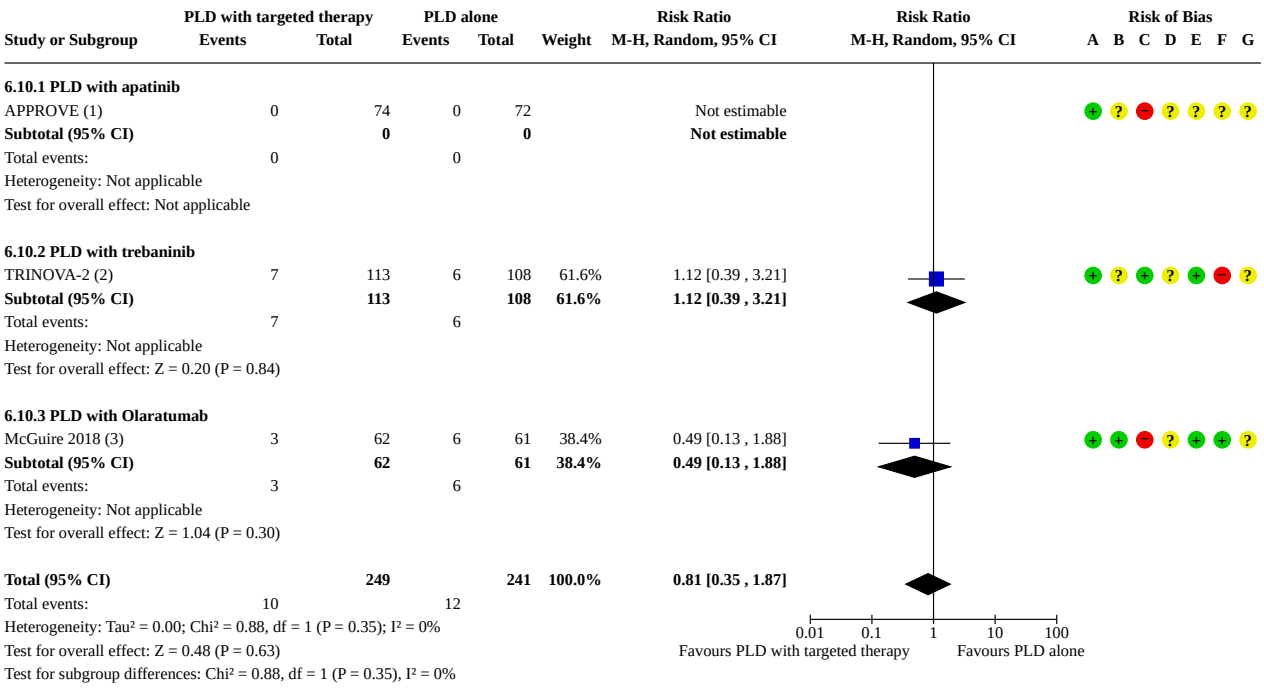
Footnotes

(1) treatment-emergent AEs
(2) treatment-emergent AEs; participants regardless of platinum sensitivity status
(3) Treatment-emergent adverse events; described as mucositis in paper

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.10. Comparison 6: Platinum-resistant recurrent EOC: PLD with targeted therapy versus PLD alone, Outcome 10: SevAE: Vomiting (grade ≥ 3)



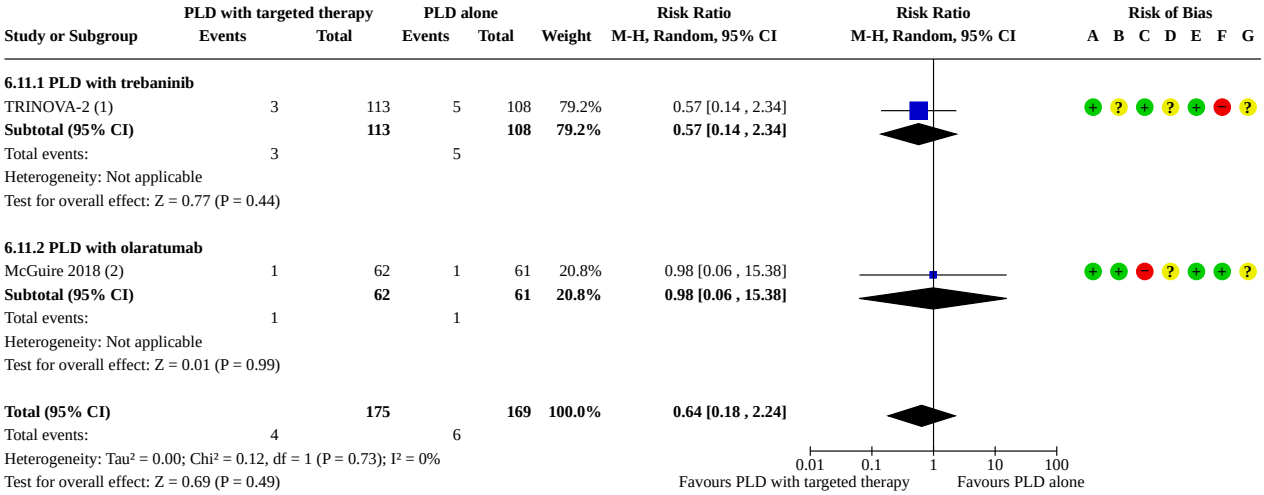
Footnotes

(1) treatment-emergent AEs
(2) treatment-emergent AEs; participants regardless of platinum sensitivity status
(3) Treatment-emergent adverse events

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.11. Comparison 6: Platinum-resistant recurrent EOC: PLD with targeted therapy versus PLD alone, Outcome 11: SevAE: Diarrhoea (grade ≥ 3)



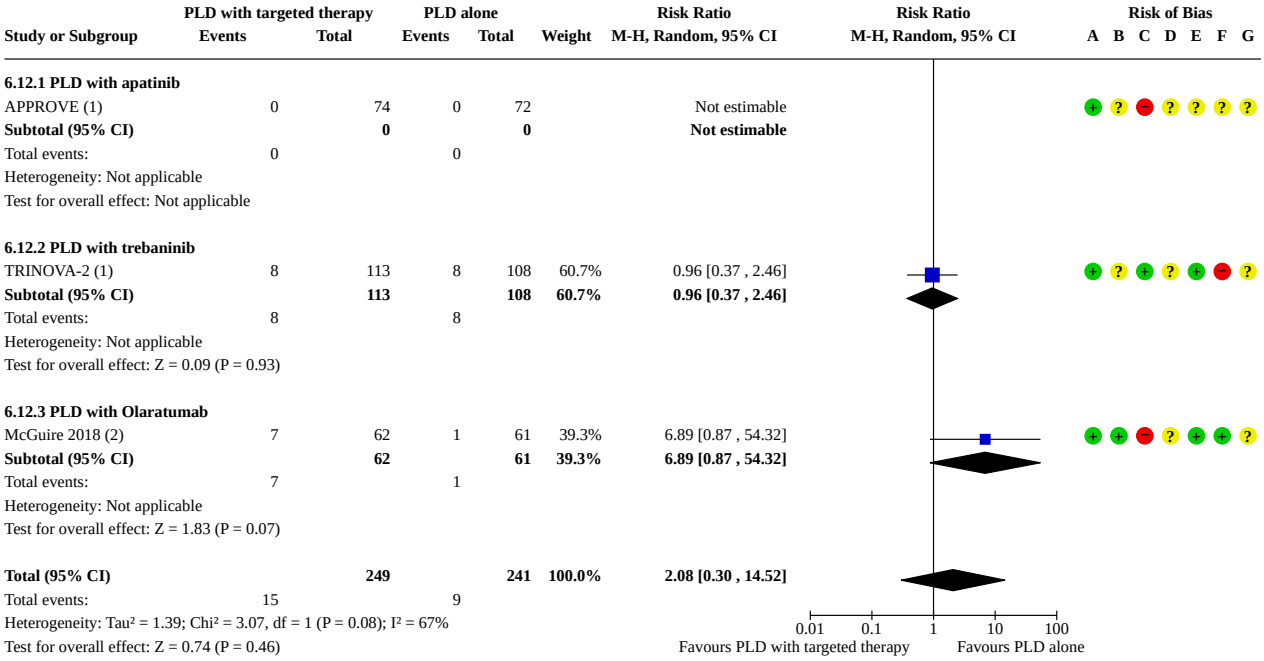
Footnotes

(1) treatment-emergent AEs
(2) Treatment-emergent adverse events

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.12. Comparison 6: Platinum-resistant recurrent EOC: PLD with targeted therapy versus PLD alone, Outcome 12: SevAE: Fatigue (grade ≥ 3)



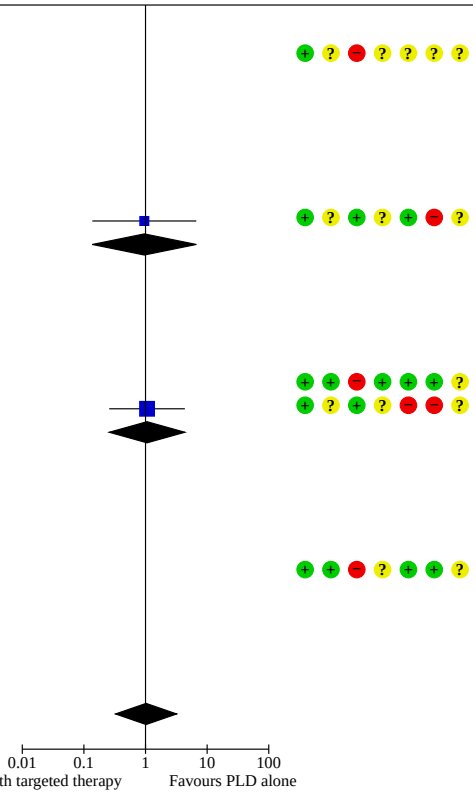
Footnotes

(1) treatment-emergent AEs
(2) Treatment-emergent adverse events

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.13. Comparison 6: Platinum-resistant recurrent EOC: PLD with targeted therapy versus PLD alone, Outcome 13: Serious AE: Treatment-related death



Study or Subgroup	PLD with targeted therapy Events	Total	PLD alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
6.13.1 PLD with apatinib							
APPROVE (1)	0	74	0	72		Not estimable	+ ? − ? ? ? ?
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
6.13.2 PLD with trebaninib							
TRINOVA-2 (1)	2	113	2	108	34.6%	0.96 [0.14 , 6.67]	+ ? + ? + − ?
Subtotal (95% CI)		**113**		**108**	**34.6%**	**0.96 [0.14 , 6.67]**	
Total events:	2		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.05 (P = 0.96)							
6.13.3 PLD with vintafolide							
PRECEDENT	0	107	0	50		Not estimable	+ + − + + + ?
PROCEED 2014	5	189	3	120	65.4%	1.06 [0.26 , 4.35]	+ ? + ? − − ?
Subtotal (95% CI)		**296**		**170**	**65.4%**	**1.06 [0.26 , 4.35]**	
Total events:	5		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.08 (P = 0.94)							
6.13.4 PLD with olaratumab							
McGuire 2018 (2)	0	62	0	61		Not estimable	+ + − ? + + ?
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total (95% CI)		**545**		**411**	**100.0%**	**1.02 [0.33 , 3.20]**	
Total events:	7		5				
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%							
Test for overall effect: Z = 0.04 (P = 0.97)							
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%							

Footnotes

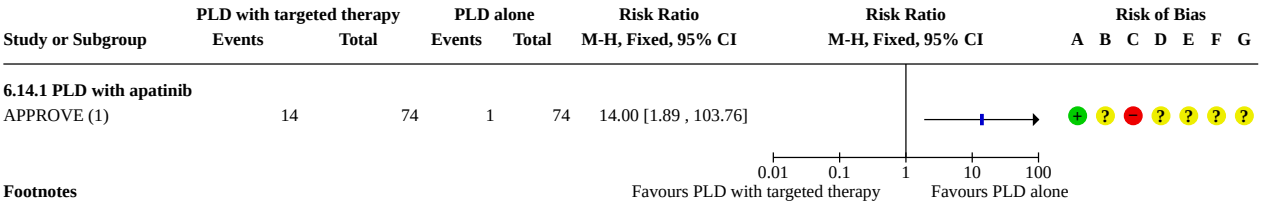
(1) treatment-emergent AEs

(2) No deaths within 21 days of last study treatment. Two patietns died during treatment: one from disease progression; and one from pulmonary embolism, neither thought to be attributable to s

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 6.14. Comparison 6: Platinum-resistant recurrent EOC: PLD with targeted therapy versus PLD alone, Outcome 14: Dose reductions



Footnotes

(1) Data available for 74 pts in apatinib with PLD arm; of 14 pts in this arm in 9 pts dose of apatinib was reduced and in 5pts of PLD

Risk of bias legend

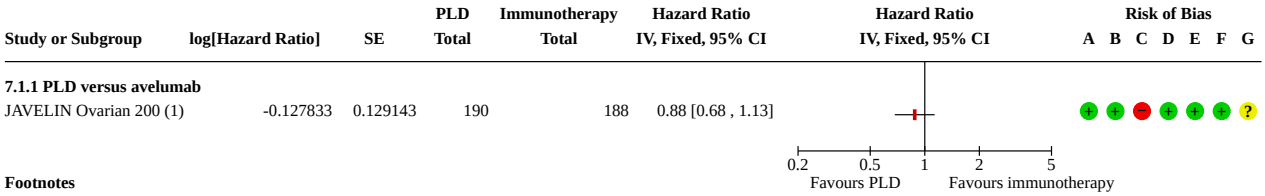
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 7. Platinum-resistant recurrent EOC: PLD versus immunotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Overall survival	1		Hazard Ratio (IV, Fixed, 95% CI)	Totals not selected
7.1.1 PLD versus avelumab	1		Hazard Ratio (IV, Fixed, 95% CI)	Totals not selected
7.2 Progression-free survival	1		Hazard Ratio (IV, Fixed, 95% CI)	Totals not selected
7.2.1 PLD versus avelumab	1		Hazard Ratio (IV, Fixed, 95% CI)	Totals not selected
7.3 Overall Severe Adverse Events (grade ≥ 3)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
7.3.1 PLD versus avelumab	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
7.4 SevAE: Anaemia (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.4.1 PLD versus avelumab	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.5 SevAE: Hand-foot syndrome (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.5.1 PLD versus avelumab	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.6 SevAE: Neutropenia (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.6.1 PLD versus avelumab	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.7 SevAE: Thrombocytopenia (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.7.1 PLD versus avelumab	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.8 SevAE: Stomatitis (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.8.1 PLD versus avelumab	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.9 SevAE: Vomiting (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.9.1 PLD versus avelumab	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.10 SevAE: Diarrhoea (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.10.1 PLD versus avelumab	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.11 SevAE: Fatigue (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.11.1 PLD versus avelumab	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.12 Dose reductions	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.12.1 PLD versus avelumab	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 7.1. Comparison 7: Platinum-resistant recurrent EOC: PLD versus immunotherapy, Outcome 1: Overall survival

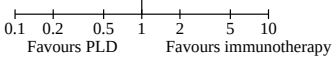


Footnotes
(1) recalculated stratified HR for avelumab arm as a comparator

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 7.2. Comparison 7: Platinum-resistant recurrent EOC: PLD versus immunotherapy, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	PLD Total	Immunotherapy Total	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G
7.2.1 PLD versus avelumab							
JAVELIN Ovarian 200 (1)	-0.518858	0.173083	190	188	0.60 [0.42 , 0.84]		+ + − + + + ?

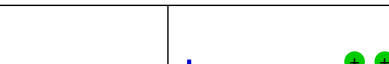


Footnotes
(1) recalculated stratified HR for avelumab arm as a comparator

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 7.3. Comparison 7: Platinum-resistant recurrent EOC: PLD versus immunotherapy, Outcome 3: Overall Severe Adverse Events (grade ≥ 3)

Study or Subgroup	PLD Events	PLD Total	Immunotherapy Events	Immunotherapy Total	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G
7.3.1 PLD versus avelumab							
JAVELIN Ovarian 200 (1)	56	177	30	187	1.97 [1.33 , 2.92]		+ + − + + + ?

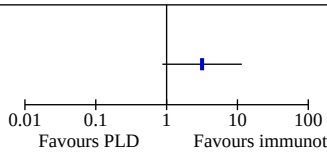


Footnotes
(1) treatment-emergent AEs

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 7.4. Comparison 7: Platinum-resistant recurrent EOC: PLD versus immunotherapy, Outcome 4: SevAE: Anaemia (grade ≥ 3)

Study or Subgroup	PLD Events	PLD Total	Immunotherapy Events	Immunotherapy Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
7.4.1 PLD versus avelumab							
JAVELIN Ovarian 200 (1)	9	177	3	187	3.17 [0.87 , 11.52]		+ + − + + + ?

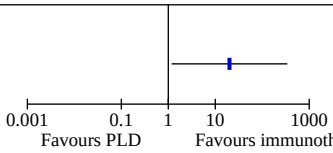


Footnotes
(1) treatment-emergent AEs

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 7.5. Comparison 7: Platinum-resistant recurrent EOC: PLD versus immunotherapy, Outcome 5: SevAE: Hand-foot syndrome (grade ≥ 3)

Study or Subgroup	PLD Events	PLD Total	Immunotherapy Events	Immunotherapy Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
7.5.1 PLD versus avelumab							
JAVELIN Ovarian 200 (1)	9	177	0	187	20.07 [1.18 , 342.24]		+ + − + + + ?

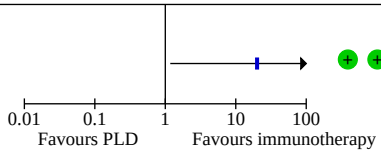


Footnotes
(1) treatment-emergent AEs

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 7.6. Comparison 7: Platinum-resistant recurrent EOC: PLD versus immunotherapy, Outcome 6: SevAE: Neutropenia (grade ≥ 3)

Study or Subgroup	PLD Events	PLD Total	Immunotherapy Events	Immunotherapy Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
7.6.1 PLD versus avelumab							
JAVELIN Ovarian 200 (1)	9	177	0	187	20.07 [1.18 , 342.24]		+ + − + + + ?

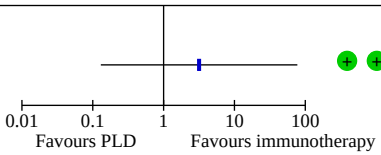


Footnotes
(1) treatment-emergent AEs

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 7.7. Comparison 7: Platinum-resistant recurrent EOC: PLD versus immunotherapy, Outcome 7: SevAE: Thrombocytopenia (grade ≥ 3)

Study or Subgroup	PLD Events	PLD Total	Immunotherapy Events	Immunotherapy Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
7.7.1 PLD versus avelumab							
JAVELIN Ovarian 200 (1)	1	177	0	187	3.17 [0.13 , 77.27]		+ + − + + + ?

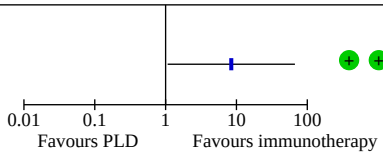


Footnotes
(1) treatment-emergent AEs

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 7.8. Comparison 7: Platinum-resistant recurrent EOC: PLD versus immunotherapy, Outcome 8: SevAE: Stomatitis (grade ≥ 3)

Study or Subgroup	PLD Events	PLD Total	Immunotherapy Events	Immunotherapy Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
7.8.1 PLD versus avelumab							
JAVELIN Ovarian 200 (1)	8	177	1	187	8.45 [1.07 , 66.89]		+ + − + + + ?

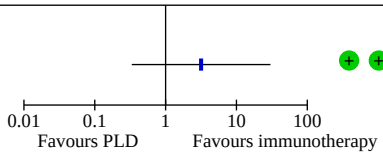


Footnotes
(1) treatment-emergent AEs

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 7.9. Comparison 7: Platinum-resistant recurrent EOC: PLD versus immunotherapy, Outcome 9: SevAE: Vomiting (grade ≥ 3)

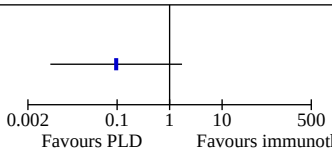
Study or Subgroup	PLD Events	PLD Total	Immunotherapy Events	Immunotherapy Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
7.9.1 PLD versus avelumab							
JAVELIN Ovarian 200	3	177	1	187	3.17 [0.33 , 30.19]		+ + − + + + ?



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 7.10. Comparison 7: Platinum-resistant recurrent EOC: PLD versus immunotherapy, Outcome 10: SevAE: Diarrhoea (grade ≥ 3)

Study or Subgroup	PLD Events	PLD Total	Immunotherapy Events	Immunotherapy Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
7.10.1 PLD versus avelumab							
JAVELIN Ovarian 200 (1)	0	177	5	187	0.10 [0.01 , 1.72]		+ + − + + + ?

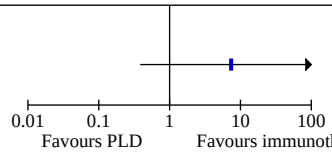


Footnotes
(1) treatment-emergent AEs

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 7.11. Comparison 7: Platinum-resistant recurrent EOC: PLD versus immunotherapy, Outcome 11: SevAE: Fatigue (grade ≥ 3)

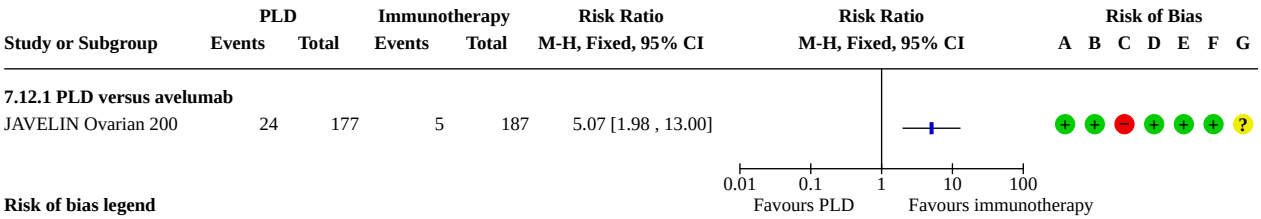
Study or Subgroup	PLD Events	PLD Total	Immunotherapy Events	Immunotherapy Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
7.11.1 PLD versus avelumab							
JAVELIN Ovarian 200 (1)	3	177	0	187	7.39 [0.38 , 142.12]		+ + − + + + ?



Footnotes
(1) treatment-emergent AEs

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 7.12. Comparison 7: Platinum-resistant recurrent EOC: PLD versus immunotherapy, Outcome 12: Dose reductions



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

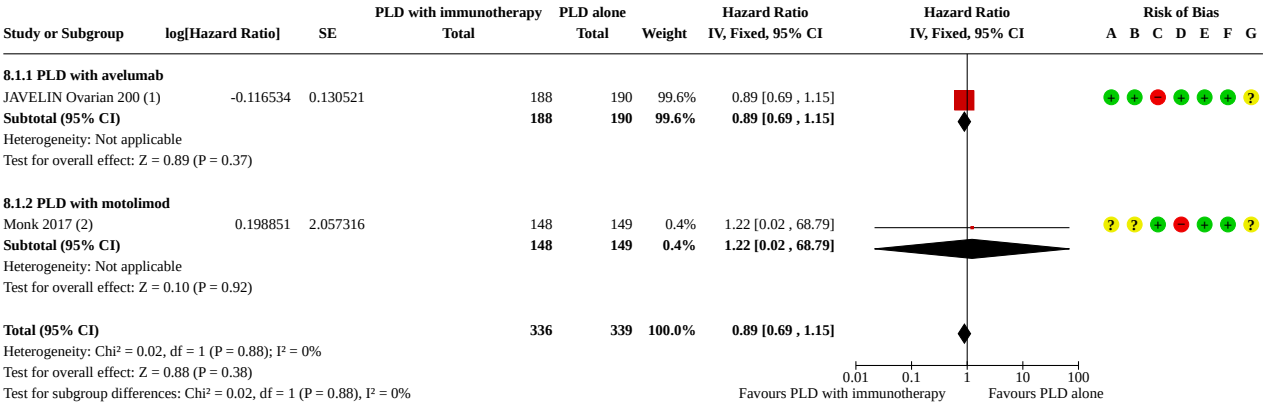
Comparison 8. Platinum-resistant recurrent EOC: PLD with immunotherapy versus PLD alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Overall survival	2	675	Hazard Ratio (IV, Fixed, 95% CI)	0.89 [0.69, 1.15]
8.1.1 PLD with avelumab	1	378	Hazard Ratio (IV, Fixed, 95% CI)	0.89 [0.69, 1.15]
8.1.2 PLD with motolimod	1	297	Hazard Ratio (IV, Fixed, 95% CI)	1.22 [0.02, 68.79]
8.2 Progression-free survival	2	675	Hazard Ratio (IV, Fixed, 95% CI)	0.78 [0.54, 1.14]
8.2.1 PLD vs avelumab	1	378	Hazard Ratio (IV, Fixed, 95% CI)	0.78 [0.54, 1.14]
8.2.2 PLD with motolimod	1	297	Hazard Ratio (IV, Fixed, 95% CI)	1.21 [0.01, 224.96]
8.3 Overall Severe Adverse Events (grade ≥ 3)	2	653	Risk Ratio (IV, Fixed, 95% CI)	1.12 [0.96, 1.30]
8.3.1 PLD with avelumab	1	359	Risk Ratio (IV, Fixed, 95% CI)	1.35 [1.03, 1.78]
8.3.2 PLD with motolimod	1	294	Risk Ratio (IV, Fixed, 95% CI)	1.03 [0.87, 1.23]
8.4 SevAE: Anaemia (grade ≥ 3)	2	653	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.27, 1.57]
8.4.1 PLD with avelumab	1	359	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.24, 1.78]
8.4.2 PLD with motolimod	1	294	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.11, 3.93]
8.5 SevAE: Hand-foot syndrome (grade ≥ 3)	2	653	Risk Ratio (IV, Fixed, 95% CI)	1.07 [0.81, 1.42]
8.5.1 PLD with avelumab	1	359	Risk Ratio (IV, Fixed, 95% CI)	1.95 [0.90, 4.21]
8.5.2 PLD with motolimod	1	294	Risk Ratio (IV, Fixed, 95% CI)	0.98 [0.73, 1.32]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.6 SevAE: Neurological (grade ≥ 3)	2	653	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.70, 1.37]
8.6.1 PLD with avelumab	1	359	Risk Ratio (M-H, Fixed, 95% CI)	2.92 [0.12, 71.15]
8.6.2 PLD with motolimod	1	294	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.68, 1.34]
8.7 SevAE: Neutropenia (grade ≥ 3)	2	653	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.47, 2.48]
8.7.1 PLD with avelumab	1	359	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.40, 2.39]
8.7.2 PLD with motolimod	1	294	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [0.18, 21.82]
8.8 SevAE: Thrombocytopenia (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.8.1 PLD with avelumab	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.9 SevAE: Stomatitis (grade ≥ 3)	2	653	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.62, 3.11]
8.9.1 PLD with avelumab	1	359	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.67, 3.72]
8.9.2 PLD with motolimod	1	294	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.12]
8.10 SevAE: Vomiting (grade ≥ 3)	2	653	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.38, 2.60]
8.10.1 PLD with avelumab	1	359	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.03, 3.09]
8.10.2 PLD with motolimod	1	294	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.45, 4.31]
8.11 SevAE: Diarrhoea (grade ≥ 3)	2	653	Risk Ratio (M-H, Fixed, 95% CI)	3.64 [0.60, 21.92]
8.11.1 PLD with avelumab	1	359	Risk Ratio (M-H, Fixed, 95% CI)	2.92 [0.12, 71.15]
8.11.2 PLD with motolimod	1	294	Risk Ratio (M-H, Fixed, 95% CI)	4.00 [0.45, 35.36]
8.12 SevAE: Fatigue (grade ≥ 3)	2	653	Risk Ratio (M-H, Fixed, 95% CI)	2.75 [1.00, 7.55]
8.12.1 PLD versus avelumab	1	359	Risk Ratio (M-H, Fixed, 95% CI)	3.24 [0.91, 11.58]
8.12.2 PLD with motolimod	1	294	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [0.37, 10.75]
8.13 Serious AE: Treatment-related death	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.13.1 PLD with motolimod	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.14 Dose reductions	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.14.1 PLD with avelumab	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

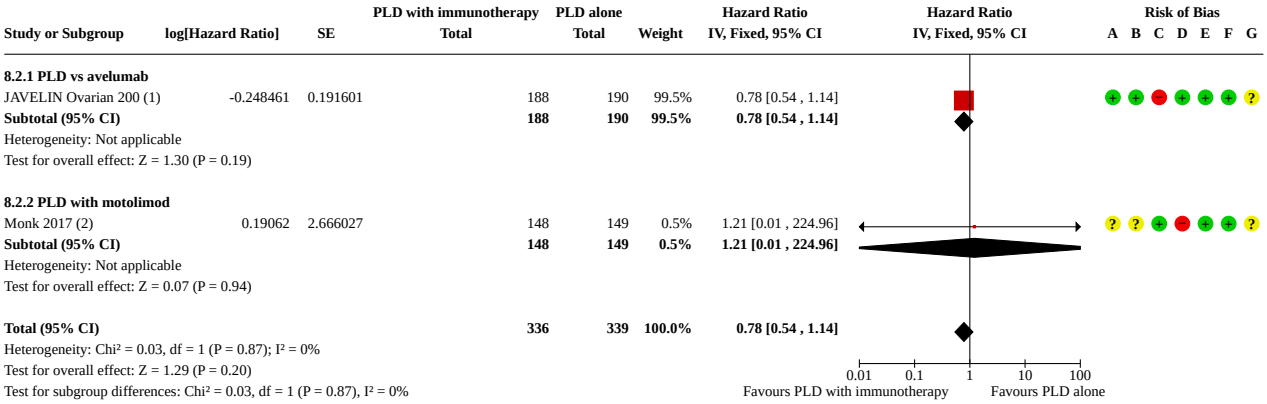
Analysis 8.1. Comparison 8: Platinum-resistant recurrent EOC: PLD with immunotherapy versus PLD alone, Outcome 1: Overall survival



Footnotes
(1) stratified HR
(2) participants regardless of platinum sensitivity status

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 8.2. Comparison 8: Platinum-resistant recurrent EOC: PLD with immunotherapy versus PLD alone, Outcome 2: Progression-free survival



Footnotes

(1) stratified HR

(2) participants regardless of platinum sensitivity status

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

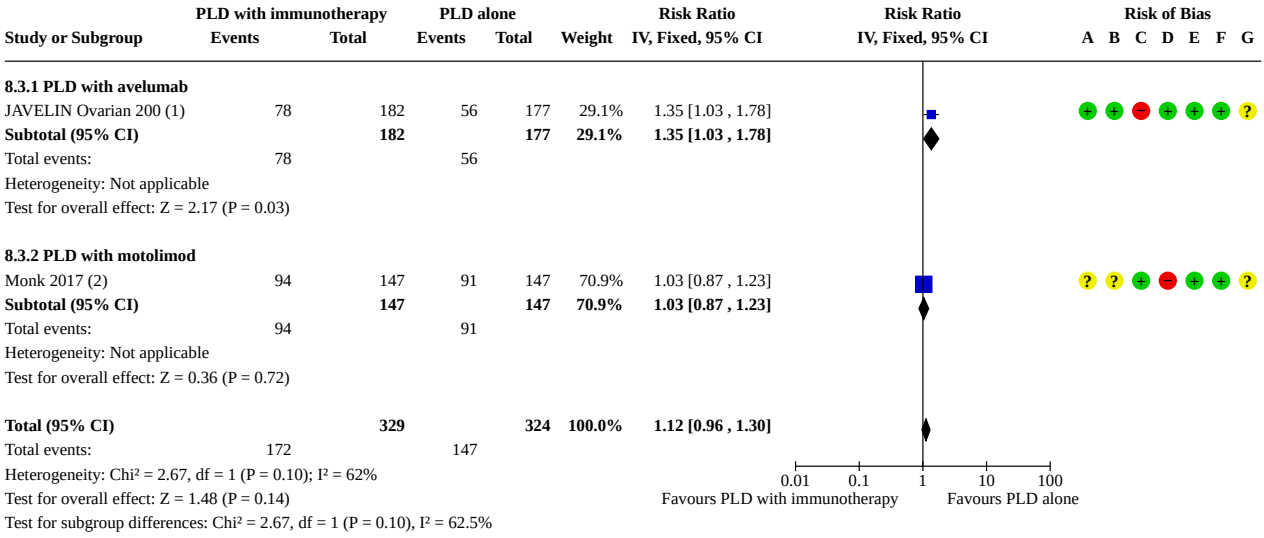
(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Analysis 8.3. Comparison 8: Platinum-resistant recurrent EOC: PLD with immunotherapy versus PLD alone, Outcome 3: Overall Severe Adverse Events (grade ≥ 3)



Footnotes

(1) Awaiting seperate numbers

(2) treatment-emergent AEs; participants regardless of platinum sensitivity status

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

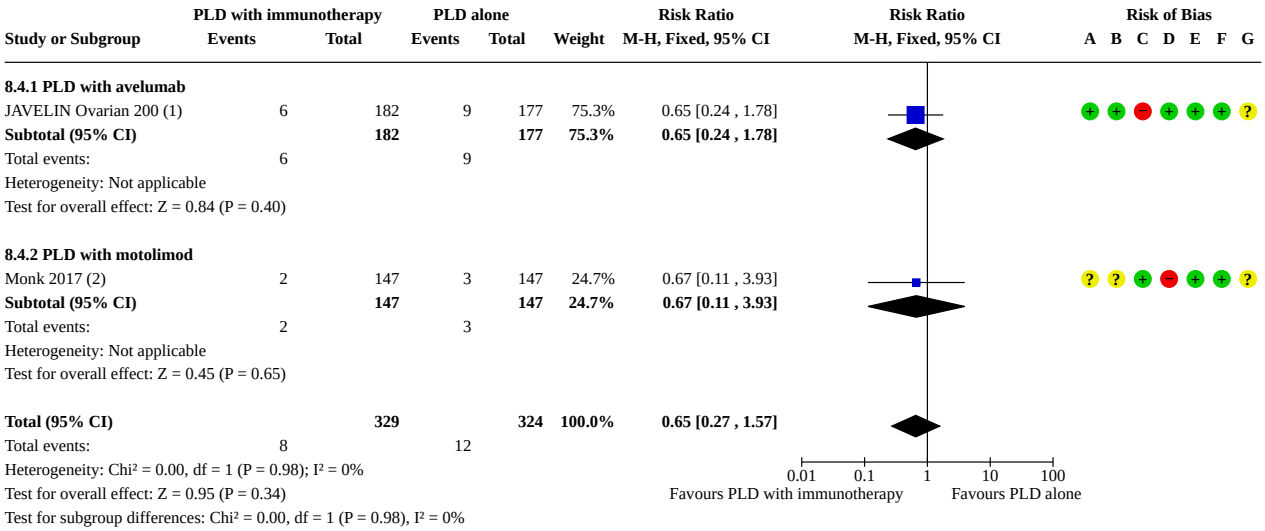
(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Analysis 8.4. Comparison 8: Platinum-resistant recurrent EOC: PLD with immunotherapy versus PLD alone, Outcome 4: SevAE: Anaemia (grade ≥ 3)



Footnotes

(1) treatment-emergent AEs

(2) treatment-emergent AEs; participants regardless of platinum sensitivity status

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

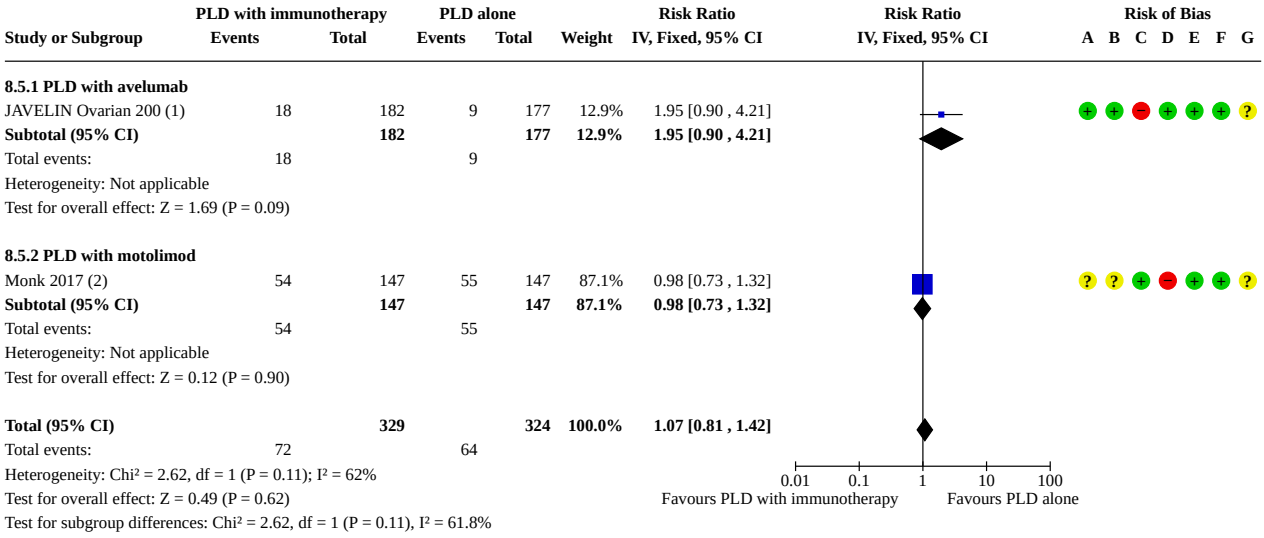
(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Analysis 8.5. Comparison 8: Platinum-resistant recurrent EOC: PLD with immunotherapy versus PLD alone, Outcome 5: SevAE: Hand-foot syndrome (grade ≥ 3)



Footnotes

(1) treatment-emergent AEs

(2) treatment-emergent AEs; participants regardless of platinum sensitivity status

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

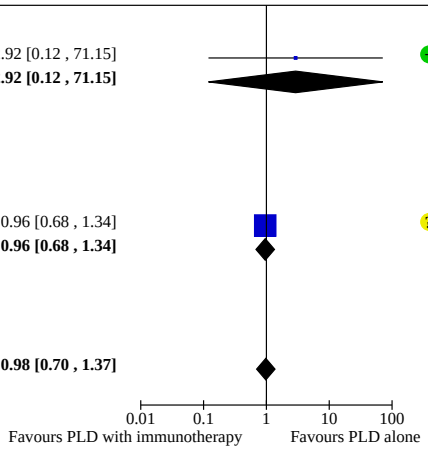
(E) Incomplete outcome data (attrition bias)

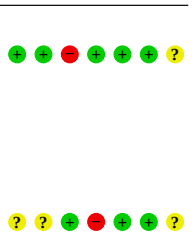
(F) Selective reporting (reporting bias)

(G) Other bias

Analysis 8.6. Comparison 8: Platinum-resistant recurrent EOC: PLD with immunotherapy versus PLD alone, Outcome 6: SevAE: Neurological (grade ≥ 3)

Study or Subgroup	PLD with immunotherapy Events	Total	PLD alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.6.1 PLD with avelumab						
JAVELIN Ovarian 200 (1)	1	182	0	177	1.1%	2.92 [0.12 , 71.15]
Subtotal (95% CI)		**182**		**177**	**1.1%**	**2.92 [0.12 , 71.15]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
8.6.2 PLD with motolimod						
Monk 2017 (2)	45	147	47	147	98.9%	0.96 [0.68 , 1.34]
Subtotal (95% CI)		**147**		**147**	**98.9%**	**0.96 [0.68 , 1.34]**
Total events:	45		47			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.80)						
Total (95% CI)		**329**		**324**	**100.0%**	**0.98 [0.70 , 1.37]**
Total events:	46		47			
Heterogeneity: Chi² = 0.47, df = 1 (P = 0.50); I² = 0%						
Test for overall effect: Z = 0.13 (P = 0.90)						
Test for subgroup differences: Chi² = 0.46, df = 1 (P = 0.50), I² = 0%						





Footnotes

(1) treatment-emergent AEs

(2) treatment-emergent AEs; participants regardless of platinum sensitivity status

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

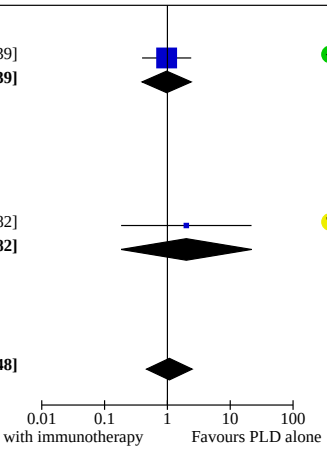
(E) Incomplete outcome data (attrition bias)

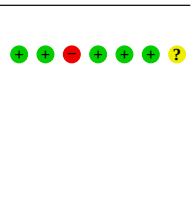
(F) Selective reporting (reporting bias)

(G) Other bias

Analysis 8.7. Comparison 8: Platinum-resistant recurrent EOC: PLD with immunotherapy versus PLD alone, Outcome 7: SevAE: Neutropenia (grade ≥ 3)

Study or Subgroup	PLD with immunotherapy Events	Total	PLD alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.7.1 PLD with avelumab						
JAVELIN Ovarian 200 (1)	9	182	9	177	90.1%	0.97 [0.40 , 2.39]
Subtotal (95% CI)		**182**		**177**	**90.1%**	**0.97 [0.40 , 2.39]**
Total events:	9		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.06 (P = 0.95)						
8.7.2 PLD with motolimod						
Monk 2017 (2)	2	147	1	147	9.9%	2.00 [0.18 , 21.82]
Subtotal (95% CI)		**147**		**147**	**9.9%**	**2.00 [0.18 , 21.82]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
Total (95% CI)		**329**		**324**	**100.0%**	**1.07 [0.47 , 2.48]**
Total events:	11		10			
Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² = 0%						
Test for overall effect: Z = 0.17 (P = 0.87)						
Test for subgroup differences: Chi² = 0.31, df = 1 (P = 0.58), I² = 0%						



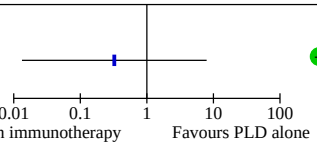


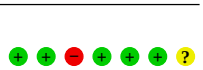
Footnotes
(1) treatment-emergent AEs
(2) treatment-emergent AEs; participants regardless of platinum sensitivity status

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 8.8. Comparison 8: Platinum-resistant recurrent EOC: PLD with immunotherapy versus PLD alone, Outcome 8: SevAE: Thrombocytopenia (grade ≥ 3)

Study or Subgroup	PLD with immunotherapy Events	Total	PLD alone Events	Total	Risk Ratio M-H, Fixed, 95% CI
8.8.1 PLD with avelumab					
JAVELIN Ovarian 200 (1)	0	182	1	177	0.32 [0.01 , 7.91]

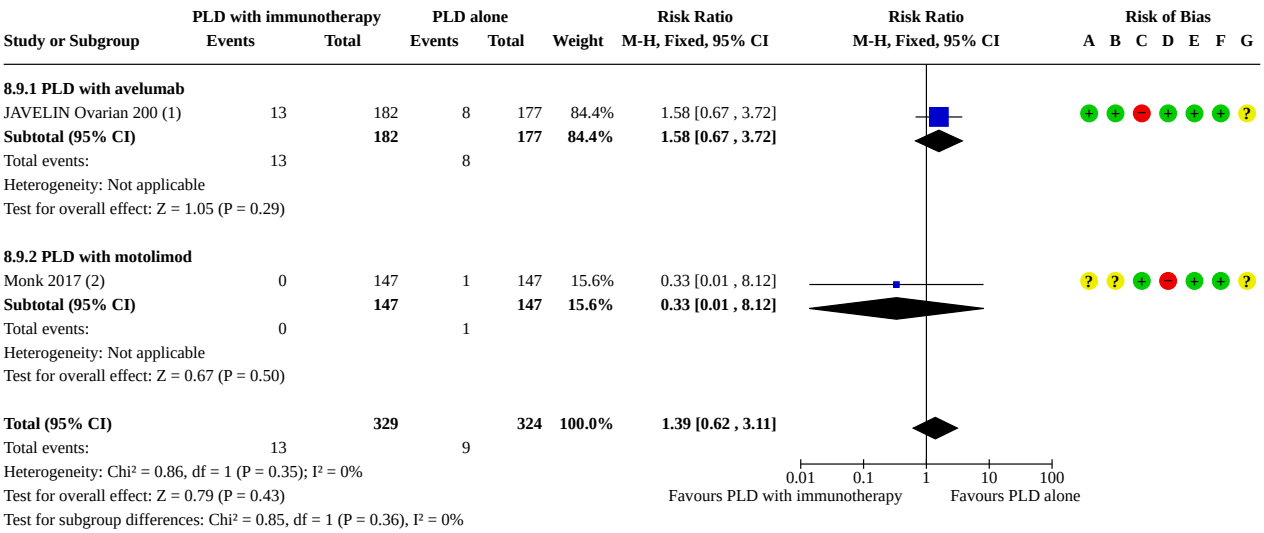




Footnotes
(1) treatment-emergent AEs

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 8.9. Comparison 8: Platinum-resistant recurrent EOC: PLD with immunotherapy versus PLD alone, Outcome 9: SevAE: Stomatitis (grade ≥ 3)



Footnotes

(1) treatment-emergent AEs

(2) treatment-emergent AEs; participants regardless of platinum sensitivity status

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

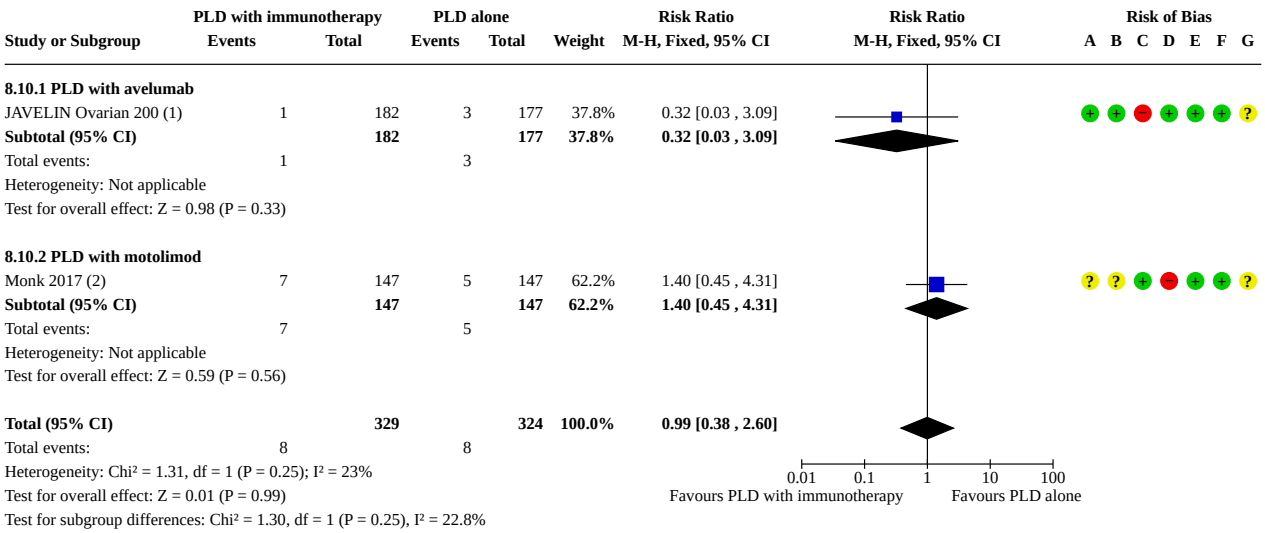
(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Analysis 8.10. Comparison 8: Platinum-resistant recurrent EOC: PLD with immunotherapy versus PLD alone, Outcome 10: SevAE: Vomiting (grade ≥ 3)



Footnotes

(1) treatment-emergent AEs

(2) treatment-emergent AEs; participants regardless of platinum sensitivity status

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

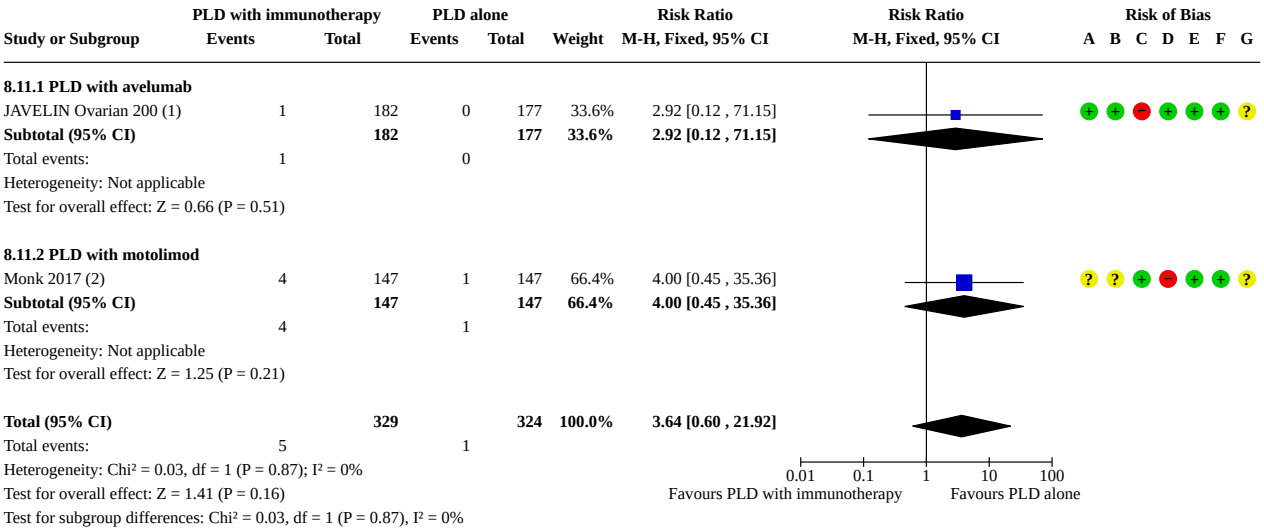
(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Analysis 8.11. Comparison 8: Platinum-resistant recurrent EOC: PLD with immunotherapy versus PLD alone, Outcome 11: SevAE: Diarrhoea (grade ≥ 3)



Footnotes

(1) treatment-emergent AEs

(2) treatment-emergent AEs; participants regardless of platinum sensitivity status

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

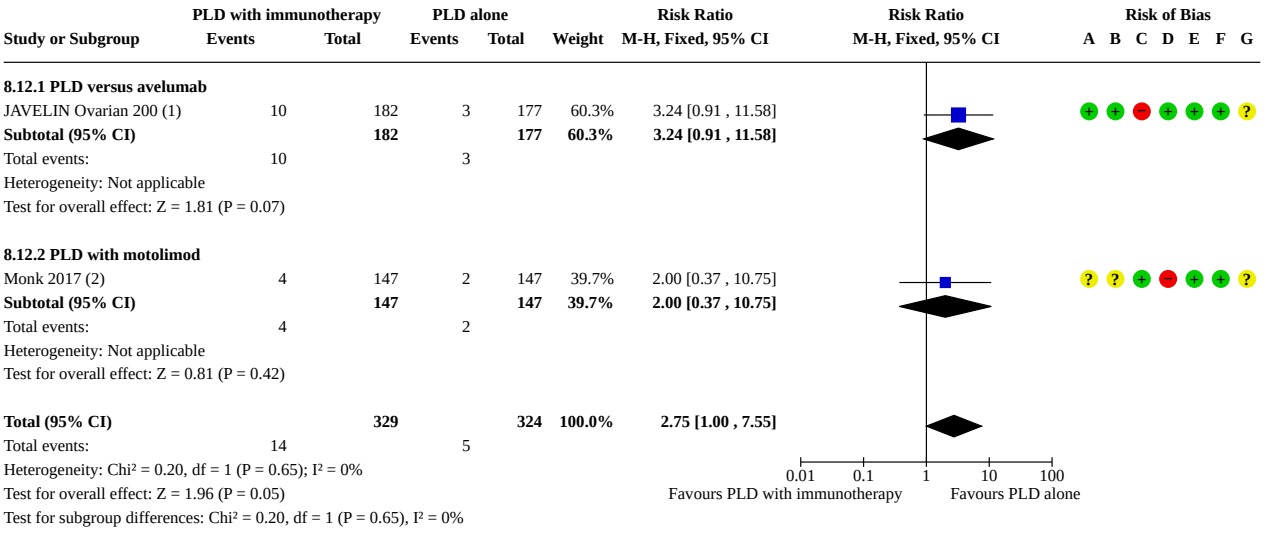
(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

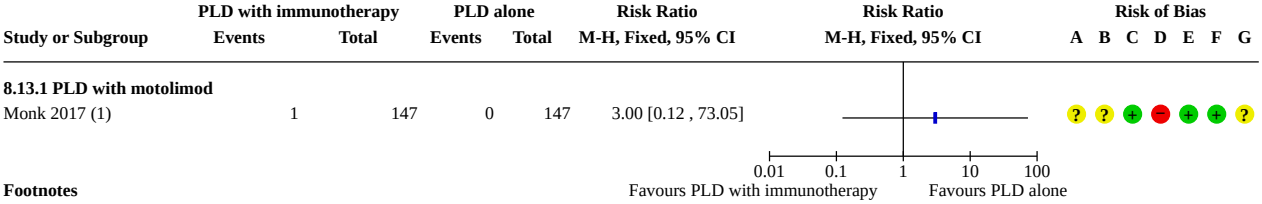
Analysis 8.12. Comparison 8: Platinum-resistant recurrent EOC: PLD with immunotherapy versus PLD alone, Outcome 12: SevAE: Fatigue (grade ≥ 3)



Footnotes
(1) treatment-emergent AEs
(2) treatment-emergent AEs; participants regardless of platinum sensitivity status

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

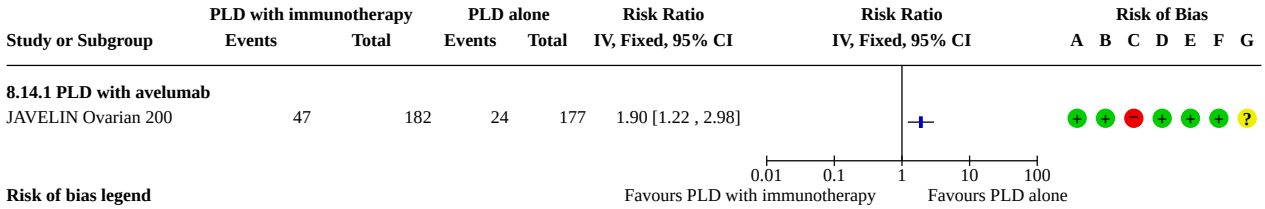
Analysis 8.13. Comparison 8: Platinum-resistant recurrent EOC: PLD with immunotherapy versus PLD alone, Outcome 13: Serious AE: Treatment-related death



Footnotes
(1) treatment-emergent AEs; participants regardless of platinum sensitivity status

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 8.14. Comparison 8: Platinum-resistant recurrent EOC: PLD with immunotherapy versus PLD alone, Outcome 14: Dose reductions



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

ADDITIONAL TABLES

Table 1. FIGO staging of ovarian cancer*

Stage	Extent of tumour	Substage	Details
I	Tumour confined to ovaries or fallopian tube(s)	Ia	Tumour limited to one ovary (capsule intact) or fallopian tube; no tumour on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings.
		Ib	Tumour limited to both ovaries (capsules intact) or fallopian tubes; no tumour on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings.
		Ic	IC: tumour limited to one or both ovaries or fallopian tubes, with any of the following: IC1: surgical spill; IC2: capsule ruptured before surgery or tumour on ovarian or fallopian tube surface; IC3: malignant cells in the ascites or peritoneal washings.
II	Tumour involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer	IIa	Extension and/or implants on uterus and/or fallopian tubes and/or ovaries
		IIb	Extension to other pelvic intraperitoneal tissues
III	Tumour involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the	IIIa	IIIA1: positive retroperitoneal lymph nodes only (cytologically or histologically proven): IIIA1(i) Metastasis up to 10 mm in greatest dimension; IIIA1(ii) Metastasis more than 10 mm in greatest dimension; IIIA2: microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes.

Table 1. FIGO staging of ovarian cancer* *(Continued)*

	retroperitoneal lymph nodes	IIIb	Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes.
		IIIc	IIIC: macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumour to capsule of liver and spleen without parenchymal involvement of either organ)
IV	Distant metastasis excluding peritoneal metastases	IVa	Pleural effusion with positive cytology
		IVb	Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity)

FIGO: International Federation of Gynaecology and Obstetrics. * From FIGO 2014.

Table 2. Included studies by comparison group

Study Name	Alternative name/ trial registry number	2016 Review	Number of participants	Study design	Experimental treatment	Control treatment	Mechanism of action	Platinum sensitivity	Dose of PLD	Duration of FU	6-month PFS rate	2-year OS rate	Notes
Platinum sensitive													
Other conventional chemotherapy													
SWOG S0200	NCT00043082		61	Phase III multicentre RCT; open-label	Carboplatin (AUC 5) AND PLD every 4 weeks	Carboplatin (AUC 5) every 4 weeks	C: alkylating agent. Forms platinum complexes, causing inter- and intra-strand DNA cross-linkage. Resultant alteration to DNA structure, inhibiting synthesis.	PS	30 mg/m^2	Median 22.4 months	Not known	Not known	
CALYPSO	NCT00538603		976	Phase III multicentre non-inferiority RCT; open-label	Carboplatin (AUC 5) AND PLD every 4 weeks	Carboplatin (AUC 5) AND Paclitaxel (175mg/m^2) every 3 weeks	C: as above P: impairs cellular division and causes cytotoxicity by inhibiting microtubule formation.	PS	30 mg/m^2	Median 49 months (0 to 68 months)	85.2% PLD+C 79.9% C+T	61.2% PLD+C 64.2% C+T	
HeCOG 2010	ACTRN12609000436279	Yes	204 (189 eligible)	Phase II RCT; open-label	Carboplatin (AUC 5) AND PLD every 4 weeks	Carboplatin (AUC 5) AND Paclitaxel (175mg/	As above	PS	45 mg/m^2	Median 43.6 months (95% CI 0.1 to 74.8)	NR	NR	

Table 2. Included studies by comparison group *(Continued)*

						m^2) every 3 weeks						
Fujiwara 2019	UMIN 000,005,487	No	100	Phase II RCT; open-label	Carboplatin (AUC 5) AND PLD every 4 weeks	Carboplatin (AUC 4) AND Gemcitabine (1000 mg/m^2) on days 1 and 8, every 3 weeks	C: as above G: a nucleoside analogue that interferes with DNA synthesis. S-phase specific.	PS	30 mg/m^2	24 months	77.6% PLD+C 80% G +C	63.3%PLD +C 66% G +C
Pfisterer 2020	NCT01837251	No	682	Phase III multicentre RCT; open-label	Bevacizumab (10 mg/kg) AND Carboplatin (AUC 4) AND PLD every 4 weeks Followed by maintenance bevacizumab (15 mg/kg) every 3 weeks	Bevacizumab (15 mg/kg) AND Carboplatin (AUC 4) AND Gemcitabine 1000 mg/m^2 every 3 weeks Followed by maintenance bevacizumab (15 mg/	B: angiogenesis inhibitor; selectively targets VEGF	PS	30 mg/m^2	30 months	84.9% C+PLD +Bev 84.3% C+G +Bev	53.7% C+PLD +Bev vs 56.5% C+PLD +Bev

Table 2. Included studies by comparison group *(Continued)*

					kg) every 3 weeks							
Monk 2020	NCT01846611	581 (576 assigned to treatment)	Phase III multi-centre RCT; open-label	Trabectedin (1.1 mg/m^2) AND PLD every 3 weeks	PLD every 4 weeks	Complex and not fully understood. Blocks DNA binding and reverses transcription.	PS	30 mg/m^2 in combined arm. 50 mg/m^2 in alone arm.	Median 23.8 months	40.1% TBD/PLD vs 41.1% PLD	28.9% TBD/PLD vs 19.9% PLD	
Targeted therapy												
TRINOVA-2	NCT01281254	223	Phase III multi-centre RCT; double-blind	Trebananib AMG386 (15 mg/kg) every week AND PLD every 4 weeks	PLD every 4 weeks AND Placebo every week	Angiogenesis inhibitor; selectively targets angiopoietin-1/-2	PS	50 mg/m^2	Median 12.4 months	59.6% PLD/TREB vs 48.6% PLD/Placebo	10.5% PLD/TREB vs 8.3% PLD/Placebo	
Platinum resistant												
Other conventional chemotherapy												
Mutch 2007	NCT00191607	195	Phase III open-label multicentre RCT	Gemcitabine (1000 mg/m^2) day 1 and 8, every 3 weeks	PLD every 4 weeks	As above	PR	50 mg/m^2	29.2 months	Data not available	Data not available	Kaplan-Meier curves shown in paper but without numbers at each time point. Authors

Table 2. Included studies by comparison group *(Continued)*

											contacted for further details.
ASSIST-5	NCT00350948	125	Phase III, multicentre RCT, open-label	Canfosfamide 1000 mg/m^2 AND PLD every 4 weeks	PLD every 4 weeks	As above	PR	50 mg/m^2	The median PFS was 5.6 months for canfosfamide + PLD (n = 65) versus 3.7 months for PLD (n = 60) (hazards ratio, 0.92; P = 0.7243)	Study terminated	Study terminated	
ASSIST-3	NCT00102973	247	Phase III multicentre RCT	Canfosfamide (750 mg/m^2) AND Carboplatin (AUC 5) every 4 weeks	PLD every 4 weeks	Glutathione analogue. Activated by glutathione S-transferase P1-1, inhibiting cancer cell proliferation and driving apoptosis.	PR	50 mg/m^2	NR	NR	NR	
Colombo 2012	NCT00262926	829	Phase III open-label RCT	Patupilone (10 mg/m^2) every 3 weeks	PLD every 4 weeks	Impairs cellular division and causes cytotoxicity by inhibiting microtubule formation.	PR	50 mg/m^2	27 months	21.1% PAT vs 18% PLD	13.8% PAT vs 12.3% PLD	
CORAIL	NCT02421588	442	Phase III multicen-	Lurbinectedin (3.2 mg/m^2) every 3 weeks	PLD every 4 weeks	Prevents DNA transcription and also influences the tumour	PR	40mg/m^2	30 months	Not available	Not available	

Table 2. Included studies by comparison group *(Continued)*

		(10 did not receive study treatment)	tre, open-label RCT		OR Topotecan 1.50 mg/m^2 days 1 to 5, every 3 weeks	microenvironment to prevent cancer growth.				for PLD alone (18.6% LUR vs 17.2% PLD/ TOP)	for PLD alone (18.6% LUR vs 17.6% PLD/ TOP)
Targeted therapy											
AP-PROVE	NCT04348032	152	Phase II, multicentre RCT; open-label	Apatinib 250 mg orally once daily AND PLD every 4 weeks	PLD every 4 weeks	Selectively inhibits VEGFR-2	PR	40 mg/ m^2	Median 8.1 months	NR	NR
Banerjee 2018	NCT01991210	95	Phase II multi-centre RCT; open-label	Lifastuzumab vedotin (2.4 mg/kg) every 3 weeks. Dose modification if BMI ≥ 35 kg/m^2	PLD every 4 weeks	Targeted chemotherapy (monomethyl auristatin E); antibody drug conjugate. Inhibits cellular division through prevention of tubulin polymerisation.	PR	40 mg/ m^2	Median 6.6 months	19.6% PLD vs 14.9% LIFA	NR
McGuire 2018	NCT00913835	125 randomised (123 treated)	Phase II multi-centre RCT	Olaratumab (20 mg/kg) every 2 weeks AND PLD every 4 weeks	PLD every 4 weeks	Monoclonal antibody PDGFRα inhibitor, inhibiting cell growth	PR	40 mg/ m^2	NR	35.5% OLA/ PLD vs 34.4% PLD	31.5% OLA/ PLD vs 42.9% PLD
PRECEDENT	NCT00722592	149	Phase II multi-centre RCT	Vintafolide (2.5 mg IV three times per week during weeks 1 and 3) AND	PLD every 4 weeks	Small molecule drug conjugate. Folic acid-desacetylvinblastine conjugate, binding to the folate receptor. Subsequently, microtubule dys-	PR	50 mg/ m^2	18 months	44% Vintafolide + PLD v 32.7% PLD alone	NR

Table 2. Included studies by comparison group *(Continued)*

				PLD every 4 weeks		function and cellular death occurs.					
PRO-CEED 2014	NCT01170650	150 (A.C.)	321	Phase III multi-centre RCT	Vintafolide (2.5 mg IV three times per week during weeks 1 and 3) AND PLD every 4 weeks	PLD every 4 weeks	Small molecule drug conjugate. Folic acid-desacetylvinblastine conjugate, binding to the folate receptor. Subsequently, microtubule dysfunction and cellular death occurs.	PR	50 mg/m^2	2.8 months	NR	NR
Immunotherapy											
JAVELIN Ovarian 200	NCT02580058		566	Phase III, multicentre RCT; open-label	Arm 1 (188): Avelumab (10 mg/kg) every 2 weeks	Arm 3 (190): PLD every 4 weeks.	PD-L1 inhibitor, reversing immune-evasion and inducing T-cell-induced cancer cell death.	PR	40 mg/m^2	30 months	NR	NR
JAVELIN Ovarian 200	NCT02580058		566	Phase III, multicentre RCT; open-label	Arm 2 (188): Avelumab 10 mg/kg every 2 weeks AND PLD every 4 weeks	Arm 3 (190): PLD every 4 weeks.	As above	PR	40 mg/m^2	30 months	NR	NR
Platinum resistant and sensitive											
Other conventional chemotherapy											
MITO-3		Yes	153	Phase III multicentre RCT	Gemcitabine (1000 mg/m^2) days 1, 5, 8, and 15, every 4 weeks	PLD every 4 weeks	As above	PR and PPS	40 mg/m^2	39 weeks	NR (reported TTP)	At 24 weeks GEM 81.0% vs PLD 71.4%

Table 2. Included studies by comparison group *(Continued)*

Gordon 2001	Yes	481	Phase III multicentre open-label RCT	Topotecan (1.5 mg/m^2) every 3 weeks	PLD every 4 weeks	Topoisomerase I inhibitor, required for transcription, replication, mitosis. Resultant impaired cell division.	PR and PS	50 mg/m^2	Requested from authors	Requested from authors	Requested from authors	
NCT00653952	NCT00653952	216 (220 recruited according to 2002 abstract)	Phase III open-label RCT	Paclitaxel 175 mg/m^2 every 3 weeks	PLD 50 mg/m^2 every 4 weeks	As above	PS and PR	50 mg/m^2	Minimum of 12 months	NR	NR	"The study was closed to new subjects in 1999, because of poor accrual after paclitaxel was approved for use in combination with platinum-based therapy for the first-line treatment of ovarian cancer by the European

Table 2. Included studies by comparison group *(Continued)*

													Agency for the Evaluation of Medicinal Products."
NCT01840943	NCT01840943	No	32 (planned recruitment 120)	Phase III multicentre RCT (methodology unclear)	Topotecan (1.25 mg/m^2) days 1 and 5, every 4 weeks	PLD every 4 weeks	As above	PR and PS	50 mg/m^2	NR	PLD 42.9% vs topotecan 16.7%	Data not available	8/32 lost to follow up; 11/32 withdrew consent. Data not included in meta-analysis due to high RoB.
OVA-301		Yes	672	Phase III multi-centre RCT; open-label	Trabectedin 1.1 mg/m^2 every 3 weeks AND PLD	PLD every 4 weeks	As above	PR and PS	30 mg/m^2 in combined arm. 50 mg/m^2 in alone arm	Median 17 months	36.9% TBD/PLD vs 29.3% PLD	NR	
Targeted therapy													
Kaye 2012	NCT00628251	Yes	97	Phase II open-label	Olaparib 200 mg twice daily	PLD every 4 weeks	Polyadenosine diphosphate–ribose polymerase (PARP)	PR and PPS	50 mg/m^2	NR	46.9% olaparib	NR	

Table 2. Included studies by comparison group *(Continued)*

			multicentre RCT	continuously (32 women) OR Olaparib 400 mg twice daily continuously (32 women)		inhibitor, resulting in impaired DNA damage repair.				vs 45.5% PLD	
M200	NCT00635193	127	Multicentre open-label RCT	Volociximab M200 (15 mg/kg) every week OR M200 (15 mg/kg) every 2 weeks AND PLD every 4 weeks	PLD every 4 weeks	Angiogenesis inhibitor; anti-integrin antibody targeting α5β1. Resultantly induces endothelial cell apoptosis	PR and PS	40 mg/m²	NR	NR	NR
Immunotherapy											
Monk 2017	NCT01666444	297	Phase II multi-centre RCT; double-blind	Motolimod (VTX-2337) AND PLD	PLD AND placebo	Motolimod, a TLR 8 inhibitor, reversing immune-evasion and inducing T-cell-induced cancer cell death.	PR and PS	40 mg/m²	NR	NR	NR

Abbreviations: AUC = area under the curve; BEV = bevacizumab; CAN = canfosfamide; carbo = carboplatin; GEM = gemcitabine; HR = hazard ratio; LIFA = lifastuzumab vedotin; LUR = lurbinectedin; MOT = motolimod (VTX-2337); NA = not available; NR = not recorded; OLA = olaparib; OMab = olaratumab; OS = overall survival; PAC = paclitaxel; PARP = poly adenosine diphosphate–ribose polymerase; PAT = patupilone; PD-L1 = programmed cell death ligand 1; PFI = platinum-free interval; PFS= progression-free survival; PLD = pegylated liposomal doxorubicin; PPS = partially platinum-sensitive (recurrence of 7 to 12 months of platinum-based therapy); PR = platinum-resistant (recurrence within 6 months of platinum-based therapy); PRef = platinum-refractory (recurrence within 1 month of, or during, platinum-based therapy); PS = platinum-sensitive (recurrence > 12 months after platinum-based therapy); RCT = randomised control trial; RR = relative risk; TBD = trabectedin; TLR = toll-like receptor; TOP = topotecan; TTD = time to death; TTP = time to progression; VEGF = vascular endothelial growth factor; VEGFR-2 = vascular endothelial growth factor receptor-2

Table 3. Platinum sensitivity status and median survival times in participants of included studies

STUDY NAME	Other drug arm	PLD arm	N (other drug)	N (PLD)	Median PFS for other arm in weeks	Median PFS for PLD arm in weeks	Median OS for other arm in weeks	Median OS for PLD arm in weeks	Comment
Platinum-resistant data (PFI ≤6 months)									
Colombo 2012	PAT	PLD	412	416	16	16	57	54	17% of these women had non-measurable disease.
Mutch 2007	GEM	PLD	99	96	15	13	54	58	36% of these women had non-measurable disease.
Gordon 2001	TOP	PLD	125	130	14	9	41	36	It is unclear why survival in the PLD arm of this PR subgroup is so much shorter than that of the other trials.
ASSIST-3	CAN/carbo	PLD	NA	NA	15	15	NA	NA	Limited available data. Additional data were requested from Telik but not obtained.
Kaye 2012	OLA	PLD	16	14	NA	NA	NA	NA	Small study, subgroup data not available.
McGuire 2018	PLD/OMab	PLD	62	61	17	16	66	65	PFS data also provided by PR and platinum-refractory, but small numbers
MITO-3	GEM	PLD	43	43	NA	NA	NA	NA	Subgroup data not available.
PRECEDENT	EC145/ PLD	PLD	100	49	21	12	60	72	Unpublished OS data. Study was not adequately powered to assess OS.
OVA-301	TBD/PLD	PLD	118	124	17	16	61	53	Subgroup analysis was pre-planned for PFS but was exploratory for OS.
ASSIST-5	CAN/PLD	PLD	65	60	24	16	NA	NA	Pre-planned subgroup analysis favoured the CAN/PLD group for PFS. Final OS results were not published. Additional data were requested from Telik but not obtained.
Partially platinum-sensitive data (PFI 6 to 12 months)									
CALYPSO	PAC/carbo	PLD/carbo	183	161	38	40	NA	NA	PFS HR = 0.73 (95% CI 0.58 to 0.90, P = 0.004) from Gladieff 2012;

Table 3. Platinum sensitivity status and median survival times in participants of included studies *(Continued)*

									OS HR = 1.01 (0.80 to 1.28) from Wagner 2012.
OVA-301	TBD/PLD	PLD	123	90	32	24	96	71	TTP data from Poveda 2011 and exploratory TTD data from Monk 2012. PFS HR = 0.65 (95% CI 0.45 to 0.92; P = 0.015); OS HR = 0.64 (95% CI 0.47 to 0.86; P = 0.0027).
Platinum-sensitive data (PFI > 6months)									
Gordon 2001	TOP	PLD	111	109	23	29	70	108	Exploratory analysis. The greatest effect was seen in the PPS subgroup (N = 112; HR = 1.58, 95% CI 1.07 to 2.34; P = 0.021).
OVA-301	TBD/PLD	PLD	215	202	39	32	116	103	Subgroup analysis was pre-planned for PFS but was exploratory for OS.
SWOG S0200	Carbo	PLD/carbo	30	31	34	51	77	133	Small study which closed early.
HeCOG 2010	PAC/carbo	PLD/carbo	96	93	46	51	126	106	-
CALYPSO	PAC/carbo	PLD/carbo	509	466	40	48	141	132	-
Platinum-resistant and platinum-sensitive data combined									
MITO-3	GEM	PLD	76	77	20	16	51	56	PR + PPS
Kaye 2012	OLA	PLD	32	33	38	30	NA	76	PR + PPS. Unpublished TTD data obtained from investigators. Phase II study not powered to assess survival.
Monk 2017	MOT/PLD	PLD	148	149	20.6	22.3	77.6	81	PR + PPS
NCT00653952	PAC	PLD	108	108	NA	NA	56.3	46.4	PR + PS
Gordon 2001	TOP	PLD	235	239	17	16.1	60	63	PR + PS
OVA-301	TBD/PLD	PLD	337	335	31	25	95	81	PR + PS

Conversions from published data (months to weeks) were performed assuming one month to be 4.3 weeks, and then rounding the answer to the nearest week.

*This is from the comparison CAN versus active control (PLD and TOP data combined). The PLD group had an improved PFS compared with the TOP group, but we were unable to obtain separate data.

Abbreviations: CAN = canfosfamide; carbo = carboplatin; GEM = gemcitabine; HR = hazard ratio; MOT = motolimod (VTX-2337); NA = not available; OLA = olaparib; OMab = olaratumab; OS = overall survival; PAC = paclitaxel; PAT = patupilone; PFI = platinum-free interval; PFS= progression-free survival; PLD = pegylated liposomal doxorubicin; PPS = partially platinum-sensitive (recurrence of 7 to 12 months of platinum-based therapy); PR = platinum-resistant (recurrence within 6 months of platinum-based therapy); PRef = platinum-refractory (recurrence within 1 month of, or during, platinum-based therapy); PS = platinum-sensitive (recurrence >12 months after platinum-based therapy); TBD = trabectedin; TOP = topotecan; TTD = time to death; TTP = time to progression

Table 4. Studies awaiting classification by comparison group

Study Name	Alternative name/ trial registry number	2016 Review	Number of participants	Study design	Experimental treatment	Control treatment	Mechanism of action	Platinum sensitivity	Dose of PLD	Duration of FU	6-month PFS rate	2-year OS rate	Notes
Platinum sensitive													
Other conventional chemotherapy													
MITO-16 MANGO OV2b	NCT01802749	N9	406	Phase III open-label multicentre RCT	Carboplatin AND Paclitaxel OR Gemcitabine OR PLD	Bevacizumab AND Carboplatin AND Paclitaxel OR Gemcitabine OR PLD	B: angiogenesis inhibitor; selectively targets VEGF C: alkylating agent. Forms platinum complexes, causing inter- and intra-strand DNA cross-linkage. Resultant alteration to DNA structure, inhibiting synthesis. P: impairs cellular division and causes cytotoxicity by inhibiting microtubule formation. G: a nucleoside analogue that interferes with DNA synthesis. S-phase specific.	PS	30 mg/ m^2	NR (abstract only accessible)	NR (abstract only accessible)	NR (abstract only accessible)	

Table 4. Studies awaiting classification by comparison group *(Continued)*

MITO-8 2017	NCT65787878	Yes	215	Phase III multicentre RCT; open-label	Carboplatin AND Paclitaxel THEN PLD	PLD THEN Carboplatin AND Paclitaxel	As above	PPS	40 mg/m^2	NR	NR at 6 months	41.7% PBC then NPBC versus 31.8% NPBC versus PBC	Amendment made during study to include topotecan, gemcitabine, carboplatin/gemcitabine or any other drug approved in this setting as NPBC.
MITO-23	NCT02903004		242	Phase III multicentre RCT; open-label	Trabectedin (1.3 mg/m^2)	Chemotherapy of physician's choice (PLD or topotecan or gemcitabine or weekly paclitaxel or carboplatin)	T: inhibition of transcription factor-DNA binding. Also binds and alkylates DNA.	PS	40 mg/m^2	NR (time frame for study: 4 years)	NR (abstract only reported)	NR (abstract only reported)	National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4.0
HECTOR	NCT00170677		550	Phase III multicentre RCT	Topotecan (0.75 mg/m^2)	Carboplatin AND Paclitaxel	T: topoisomerase I inhibitor, required for transcription, replication, mitosis. Resultant impaired cell division.	PS	30 mg/m^2	Median 20 months	NR	NR	

Table 4. Studies awaiting classification by comparison group *(Continued)*

				AND carboplatin every 3 weeks	OR Gemcitabine OR PLD						
Targeted therapy											
MORAb-003	NCT02289950	211	Randomised phase II placebo control trial	Farletuzumab (weekly 10 mg/kg first 2 weeks followed by 5 mg/kg) OR placebo	Carboplatin AND Paclitaxel OR Carboplatin OR PLD	Humanised monoclonal antibody that minds to the human folate receptor alpha	PS	30 mg/m^2	NR	NR	NR
PROVE 2011	NCT01388621	96	Open-label randomised phase II trial	Panitumumab 6 mg/kg day 1 and day 15, every 3 or 4 weeks	Investigators Choice of Carboplatin AND gemcitabine, 3 weekly OR carboplatin (AUC5) AND PLD (40 mg/m^2) 4 weekly	Human monoclonal antibody targeting the epidermal growth factor receptor	PS	40 mg/m^2	NR	NR	NR
Platinum resistant											
Other conventional chemotherapy											
Oza 2019	NCT01696032	103	Multicentre, randomised, open-	Guadicitabine (30mg/m2)	Topotecan OR PLD	Decitabine prodrug, inducing non-specific genome-wide hypomethylation, inducing cell cycle S-phase arrest	PR	40 to 50 mg/m^2	NR	NR	NR

Table 4. Studies awaiting classification by comparison group *(Continued)*

				label phase II trial	AND Carboplatin AUC 4	OR Paclitaxel OR Gemcitabine							
AURELIA 2012	NCT00976911	No	361	Phase II, mutlicentre, open-label, RCT	Bevacizumab (10mg/kg)	Paclitaxel OR PLD OR Topotecan	As above	PR	40 mg/m^2	13.9 months chemo arm/13.0 months in bevacizumab arm	20.3% in chemo arm versus 49.2% bevacizumab arm	15.9% in chemo arm versus 41.9% in bevacizumab arm	2.2% gastrointestinal perforation rate in bevacizumab arm
ASSIST-1 2009	PMID 19515553	No	461	Phase III active control trial	Canfosfamide (1000mg/m^2) 3 weekly	PLD OR Topotecan	Glutathione analog phosphorodiamidate prodrug, activated by GST P1-1 in cancer cells	PR	50 mg/m^2	NR	NR	NR	Allocation to PLD or topotecan dependent on previous therapy received
Targeted therapy													
FORWARD I	NCT02631876	No	366	Multicentre, randomised phase III trial	Mirvetuximab soravtansine (6mg/kg)	Paclitaxel OR PLD OR Topotecan	Folate receptor alpha specific antibody-drug conjugate (maytansinoid payload DM4), an anti-tubulin agent	PR	40 mg/m^2	Median 12.5 months	21.8% in mirvetuximab arm versus 22.9% in physi-	11.7% in mirvetuximab arm versus 9.3% in physician's	

Table 4. Studies awaiting classification by comparison group *(Continued)*

											cian's chemotherapy arm	chemotherapy arm	
Volasertib Trial	NCT01121406	110	Phase II open-label multicentre RCT	Volastertib	Paclitaxel OR Gemcitabine OR Topotecan OR PLD	PLK1 (polo-like kinase 1) inhibitor, inducing mitotcycle arrest and apoptosis, notably in rapidly dividing cancer cells	PR	40 mg/m^2	NR	27.8% volasertib versus 38.2% chemotherapy	NR	PFS reported at 24 weeks rather than 6 months
Platinum resistant and sensitive													
Targeted therapy													
SOLO3	NCT00628251	266	Phase II open-label multicentre RCT	Olaparib 300 mg twice a day	PLD OR Paclitaxel OR Gemcitabine OR Topotecan	Poly adenosine diphosphate–ribose polymerase (PARP) inhibitor, resulting in impaired DNA damage repair.	PR or PPS	50 mg/m^2	Median 13.8 months olaparib and 3.9 months chemotherapy	70.8% olaparib versus 53.4% chemotherapy	NR	

Abbreviations: AUC = area under the curve; BEV = bevacizumab; CAN = canfosfamide; carbo = carboplatin; CTC = common toxicity criteria; DNA = deoxyribonucleic acid; GEM = gemcitabine; GST P1-1 = glutathione S-transferase P1-1; HR = hazard ratio; LIFA = Lifastuzumab vedotin; LUR = Lurbinectedin; MOT = motolimod (VTX-2337); NA = not available; NCI = National Cancer Institute; NPBC = non-platinum-based chemotherapy: NR = not recorded; OLA = olaparib; OMab = olaratumab; OS = overall survival; PAC = paclitaxel; PARP = poly adenosine diphosphate–ribose polymerase; PBC =platinum-based chemotherapy; PAT = patupilone; PD-L1 = programmed cell death ligand 1; PLK1 = polo-like kinase 1; PFI = platinum-free interval; PFS= progression-free survival; PLD = pegylated liposomal doxorubicin; PPS = partially platinum-sensitive (recurrence of 7 to 12 months of platinum-based therapy); PR = platinum-resistant (recurrence within 6 months of platinum-based therapy); PRef = platinum-refractory (recurrence within 1 month of, or during, platinum-based therapy); PS = platinum-sensitive (recurrence >12 months after platinum-based therapy); RCT = randomised control trial; RR = relative risk; TBD = trabectedin; TLR = toll-like receptor; TOP = topotecan; TTD = time to death; TTP = time to progression; VEGF = vascular endothelial growth factor; VEGFR-2 = vascular endothelial growth factor receptor-2

Table 5. Adverse events

Study Name	Alternative name/ trial registry number	AE code (CTCAE, MedDRA)	AEs listed or AE number only	Results listed as number of participants with at least one AE, or total number of AEs	Type of AE: are AEs in the TRAEs or all AEs/TEAEs?
Platinum sensitive					
Other conventional chemotherapy					
SWOG S0200	NCT00043082	CTCAE 2.0	G3 and G4 AEs are split in table	Number of participants experiencing any particular AE, listing the highest grade they experienced (may have had the same AE twice)	Not stated but looks like all AEs
CALYPSO	NCT00538603	CTCAE (version not stated)	G3 and G4 AEs are split in table	Number of participants experiencing any particular AE, listing the highest grade they experienced (may have had the same AE twice)	Not stated but looks like all AEs
HeCOG 2010	ACTRN12609000436279	Toxicity as per WHO classification	G3 and G4 AEs are split in table	Number of participants experiencing any particular AE - does not state if this is the highest grade they experienced, if they had the same AE > 1 time	Not stated but looks like all AEs
Fujiwara 2019	UMIN 000,005,487	Not stated	G3 and G4 AEs are split in table	Number of participants experiencing any particular AE - does not state if this is the highest grade they experienced, if they had the same AE > 1 time.	Not stated but looks like all AEs
Pfisterer 2020	NCT01837251	CTCAE 4.03	Table lists Grade 1 to 2 in > 10% of total participants, and any grade ≥ 3 G3 and G4 AEs split in table	Number of participants experiencing any particular AE - does not state if this is the highest grade they experienced, if they had the same AE > 1 time.	All AEs
Monk 2020	NCT01846611	CTCAE 4.0	G3 or G4 if occurring in ≥ 5% total participants G3 and G4 AEs split in table	Number of participants experiencing any particular AE - does not state if this is the highest grade they experienced, if they had the same AE > 1 time.	TEAEs
Targeted therapy					
TRINOVA-2	NCT01281254	CTCAE 3.0	Table lists treatment-AEs if occurring in 10% of total participants Table lists cumulative values (i.e. G3 or higher)	Number of participants experiencing any particular AE - does not state if this is the highest grade they experienced, if they had the same AE > 1 time.	TEAEs
Platinum resistant					

Table 5. Adverse events *(Continued)*

Other conventional chemotherapy					
Mutch 2007	Not listed	CTCAE 2.0	G3 and G4 AEs split in table	Number of participants experiencing any particular AE - does not state if this is the highest grade they experienced, if they had the same AE > 1 time.	All
ASSIST-5	NCT00350948	Not stated	Not reported	Not reported	Not reported
ASSIST-3	NCT00102973	Not stated	Only information on AE: "Dose reductions for HFS and stomatitis were 15% and 4% respectively, in the intervention arm compared with 42% and 25% respectively in the PLD arm"	Not reported	Not reported
Colombo 2012	NCT00262990	Not stated	Table shows AEs occurring in >10% participants, regardless of relationship to drug G3 and G4 combined in the table.	Number of participants experiencing any particular AE - does not state if this is the highest grade they experienced, if they had the same AE > 1 time.	TEAEs
CORAIL	NCT02421588	CTCAE 4.0	Table shows TRAEs occurring in ≥ 10% of participants in any of the treatment arms. G3 and G4 combined in the table.	Number of participants experiencing any particular AE - does not state if this is the highest grade they experienced, if they had the same AE > 1 time.	TRAEs
Targeted therapy					
APPROVE	NCT04348032	CTCAE 4.0	Table: TEAEs occurring in > 10% of participants in either group. G3 and G4 AEs split in table.	Number of participants experiencing any particular AE - does not state if this is the highest grade they experienced, if they had the same AE > 1 time.	Treatment-emergent
Banerjee 2018	NCT01991210	Not stated	All AEs listed if occurring in ≥ 20% of participants in either arm	Number of participants experiencing any particular AE - does not state if this is the highest grade they experienced, if they had the same AE > 1 time.	All AEs
McGuire 2018	NCT00913835	CTCAE 3.0	TEAEs occurring in ≥ 10% of participants and with a ≥ 5% between-arm difference	Number of participants experiencing any particular AE - does not state if this is the highest grade they experienced, if they had the same AE > 1 time.	TEAEs

Table 5. Adverse events *(Continued)*

PRECEDENT	NCT00722592	CTCAE 3.0	Grade 3/4 AEs listed together.	Not clear but looks like number of participants experiencing any particular AE	TEAEs
Immunotherapy					
JAVELIN Ovarian 200	NCT02580058	CTCAE 4.03	TRAEs of G1–2 occurring in ≥ 10% of participants and G3–5 occurring in ≥2% of participants are shown G3/G4/G5 are all shown separately on table.	Number of participants experiencing any particular AE - does not state if this is the highest grade they experienced, if they had the same AE > 1 time.	TRAEs
JAVELIN Ovarian 200	NCT02580058	CTCAE 4.03	TRAEs of G1 to 2 occurring in ≥ 10% of participants and G3 to 5 occurring in ≥2% of participants are shown G3/G4/G5 are all shown separately on table.	Number of participants experiencing any particular AE - does not state if this is the highest grade they experienced, if they had the same AE > 1 time.	TRAEs
Monk 2017	NCT01666444	CTCAE 4.0	TEAEs with ≥ 5% difference incidence between arms.	Number of participants experiencing any particular AE - does not state if this is the highest grade they experienced, if they had the same AE > 1 time.	TEAEs
Platinum resistant and sensitive					
Other conventional chemotherapy					
NCT00653952 (Formerly O'Byrne 2002 in the previous, 2013 review)	NCT00653952	Not stated	Only information on AE: "The overall number of adverse events was equivalent in either arm. Nausea and vomiting, stomatitis and plantar-palmar erythrodysesthesia were seen more frequently with PLD whereas alopecia, myalgia, arthralgia and paraesthesiae occurred more commonly with paclitaxel"	Not reported	Not reported
MITO-3	Not listed	Not stated	SAE and PPE numbers only	Not clear but looks like number of participants experiencing any particular AE	Not stated but looks like all AEs
Gordon 2001	Not listed	Not stated	Not reported	Not reported	Not reported
NCT01840943	NCT01840943	MedDRA 15.0	G3/4 AEs listed together	Not stated	Not stated

Table 5. Adverse events *(Continued)*

OVA-301	PMID 20516432	CTCAE 3.0	Table: TEAEs occurring in > 5% of participants in either group. G3 and G4 AEs split in table.	Number of participants experiencing any particular AE - does not state if this is the highest grade they experienced, if they had the same AE > 1 time.	TRAEs
Targeted therapy					
Kaye 2012	NCT00628251	CTCAE 3.0	Table: AEs (any grade) occurring in > 30% of participants in either group. Split into G1&2 or G3&4.	Number of participants experiencing any particular AE - does not state if this is the highest grade they experienced, if they had the same AE > 1 time.	All AEs
M200	NCT00635193	Not stated	Only information regarding AE: "The incidence of AEs was balanced across treatment groups. The most common Grade 3/4 AEs (≥ 5% in any group) were abdominal pain, intestinal obstruction, ascites, fatigue, hypoalbuminemia, and cytopenias"	Not reported	Not stated

Abbreviations: AE - Adverse Events; CTCAE - Common Terminology Criteria for Adverse Events; G1 - Grade 1; G2 - Grade 2; G3 - Grade 3; HFS - Hand-Foot Syndrome; NCT - National Clinical Trial; PLD - Pegylated Liposomal Doxorubicin; PPE - Palmar Plantar Erythrodysesthesia; SAE - Serious Adverse Event; TEAE - Treatment-Emergent Adverse Events; TRAE - Treatment-Related Adverse Events; WHO - World Health Organisation

APPENDICES

Appendix 1. CENTRAL search strategy

CENTRAL

1. MeSH descriptor Ovarian Neoplasms explode all trees
2. ovar* near/5 (cancer* or neoplas* or tumor* or tumour* or carcinoma* or malignan*)
3. (#1 OR #2)
4. MeSH descriptor Doxorubicin explode all trees
5. doxorubicin
6. caelyx
7. doxil
8. (#4 OR #5 OR #6 OR #7)
9. (#3 AND #8)

Appendix 2. MEDLINE search strategy

Medline Ovid

1. exp Ovarian Neoplasms/
2. (ovar* adj5 (cancer* or neoplas* or tumor* or tumour* or carcinoma* or malignan*)).mp.

3. 1 or 2
4. exp Doxorubicin/
5. doxorubicin.mp.
6. caelyx.mp.
7. doxil.mp.
8. 4 or 5 or 6 or 7
9. 3 and 8
10. randomized controlled trial.pt.
11. controlled clinical trial.pt.
12. randomized.ab.
13. placebo.ab.
14. clinical trials as topic.sh.
15. randomly.ab.
16. trial.ti.
17. 10 or 11 or 12 or 13 or 14 or 15 or 16
18. 9 and 17
19. exp animals/ not humans.sh.
20. 18 not 19

Key:

mp = protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier
pt = publication type
ab = abstract
ti = title
sh = subject heading

Appendix 3. EMBASE search strategy

EMBASE Ovid

1. exp ovary tumor/
2. (ovar* adj5 (cancer* or neoplas* or tumor* or tumour* or carcinoma* or malignan*)).mp.
3. 1 or 2
4. exp doxorubicin/
5. doxorubicin.mp.
6. caelyx.mp.
7. doxil.mp.
8. 4 or 5 or 6 or 7
9. 3 and 8
10. crossover procedure/
11. randomized controlled trial/
12. single blind procedure/
13. random*.mp.
14. factorial*.mp.
15. (crossover* or cross over* or cross-over).mp.
16. placebo*.mp.
17. (doubl* adj blind*).mp.
18. (singl* adj blind*).mp.
19. assign*.mp.
20. allocat*.mp.
21. volunteer*.mp.
22. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 9 and 22

Key:

mp = protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier
pt = publication type
ab = abstract
ti = title
sh = subject heading

WHAT'S NEW

Date	Event	Description
3 July 2023	New search has been performed	New search undertaken on 4 January 2022.
3 July 2023	New citation required but conclusions have not changed	Twelve new studies added.

HISTORY

Protocol first published: Issue 1, 2008
Review first published: Issue 7, 2013

Date	Event	Description
21 September 2016	Amended	Contact details updated.
1 April 2015	Amended	Contact details updated.
11 February 2015	Amended	Contact details updated.
27 March 2014	Amended	Contact details updated.
15 October 2012	Amended	New search performed.
24 June 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

- RN, EN and KE-S contributed equally to the review and are joint first authors.
- For this latest update EN, RN, EB, SV and JM sifted the results of the searches, with appeal to JM, where there were disagreements.
- RN, EN, KE-S, EB and SV performed full text screening. Disagreements were resolved by discussion with JM and referral to Dr Miller for expert advice, as required.
- RN, EN, KE-S, EB and SV contributed to data extraction and risk of bias assessment. Disagreements were resolved by discussion with JM.
- ER, RN and JM performed the data analysis, with the GRADE assessment performed by ER and JM.
- RN, EN, KE-S, EB and SV contacted authors and pharmaceutical companies for additional information.
- JM, RN, KE-S, EN, ER, and KE-S wrote the final review.
- All current authors approved the final version of the review.

DECLARATIONS OF INTEREST

RN - attended GSK-sponsored educational event but no direct funding received
EN - declares no conflict of interest

KE-S - attended industry-sponsored educational events but no direct funding received. Declares no other conflicts of interests and no funding received.
ER - declares no conflict of interest
EB - delares no conflict of interest
SV - declares no conflict of interest
JM - declares no conflict of interest

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  NHS Cochrane Collaboration Programme Grant Scheme CPG-10/4001/12 for original version of review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In Types of interventions we have included 'PLD in combination with other agent/s versus PLD alone or with placebo', whereas this comparison was not included in the original protocol. In addition, we have removed the comparison 'PLD versus best supportive care', which was included in the protocol. These changes were as per the previous version of the review and were therefore a priori decisions for this update.

An a priori decision was made to include only participants with high-grade EOC in this update, since low-grade serous ovarian cancer (LGSOC) is now considered to be a different disease with different aetiology, genetic mutations and biology.

As explained in the text, we changed the comparison groups in the review to align with clinical scenarios of platinum-sensitive or platinum-resistant/refractory relapse, in line with other reviews (Gaitskell 2023, Tattersall 2022). This was a decision for this update to be more in line with information required for clinical decision-making, rather than by intervention.

In comparison to the previous version of the review, our main approach to meta-analysis was by applying a fixed-effect model. Our decision was based on the assumption that the evaluated drugs within the individual comparisons are estimating a common treatment effect. The random-effects model was only applied in comparisons where we incorporated trials with individuals with recurrent EOC regardless of platinum-sensitivity status. In case of non-proportionality of hazards (reported or visible on Kaplan Meier curve) we decided to use a hazard ratio estimate as a measure of effect, if available, but acknowledge its limitations.

INDEX TERMS

Medical Subject Headings (MeSH)

*Antineoplastic Agents [adverse effects]; Carcinoma, Ovarian Epithelial [drug therapy]; *Ovarian Neoplasms [drug therapy]; Randomized Controlled Trials as Topic; Recurrence; Systematic Reviews as Topic

MeSH check words

Female; Humans