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Review Article

Combinational use of trabectedin and pegylated liposomal doxorubicin for recurrent ovarian cancer: a meta-analysis of phase III randomized controlled trials

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Abstract: Background: In recent years, pegylated liposomal doxorubicin (PLD) has been widely used to improve the survival of patients with ovarian cancer; however, it is unclear whether the combinational use of PLD with other drugs is more effective. Therefore, this meta-analysis aimed to confirm the efficacy and safety of trabectedin, combined with PLD, in the treatment of recurrent ovarian cancer. Methods: Data corresponding to all eligible clinical trials as of May 15, 2022, was retrieved using several electronic retrieval databases including PubMed, Medical Literature Analysis and Retrieval System Online (MEDLINE), ClinicalTrials.gov, Excerpta Medica Database (EMBASE) and Cochrane Library clinical controlled trials (CENTRAL). Comprehensive hazard ratios (HRs), risk ratios (RRs), and 95% confidence intervals (CIs) were calculated using the Review Manager software 5.4 (RevMan 5.4). Results: From two phase III randomized controlled trials, 1248 patients with recurrent ovarian cancer were included in this meta-analysis. Results of meta-analysis revealed that trabectedin, combined with PLD chemotherapy, significantly improved overall survival (OS) in patients with BReast CAncer gene (*BRCA*)-associated recurrence (HR, 0.49; 95% CI, [0.33-0.73]; $P = 0.0004$) and platinum-sensitive recurrence whose platinum-free interval (PFI) was 6-12 months (HR, 0.66; 95% CI, [0.52-0.84]; $P = 0.0005$). In addition, compared with PLD alone, combination therapy significantly improved the progression-free survival (PFS) in patients with recurrent ovarian cancer (HR, 0.86; 95% CI, [0.74-0.99]; $P = 0.03$). Combination therapy also significantly improved PFS in patients with *BRCA*-associated recurrence (HR, 0.58; 95% CI, [0.40-0.58]; $P = 0.004$), and platinum-sensitive recurrence (HR, 0.73; 95% CI, [0.56-0.95]; $P = 0.02$). Trabectedin combined with PLD was more prone to grade 3-4 toxic side effects than PLD alone ($P < 0.05$); however, fatal adverse events related to non-toxic side effects occurred. Conclusion: Trabectedin combined with PLD significantly improves OS and PFS in patients with *BRCA*-associated and platinum-sensitive recurrent ovarian cancers. The potential use of trabectedin combined with PLD should be selected according to the PFI and *BRCA* mutation status of patients.

Keywords: Trabectedin, pegylated liposomal doxorubicin, meta-analysis, chemotherapy, relapsed ovarian cancer

Introduction

Ovarian cancer is a gynecological malignancy known to have a very high mortality rate [1], and it is difficult to detect at an early stage and is often clinically diagnosed at later stages [2]. Despite ideal tumor cell reduction surgery and platinum-based chemotherapy, it recurs in over 70% of the patients, resulting in death within three years [3-6]. Therefore, after the first round of treatment with platinum chemotherapy, the patient's sensitivity to platinum drugs should be evaluated [5]. The key lies in the alternative use of drugs with different mechanisms of action, prolonging the platinum-free survival interval (PFI), delaying platinum resistance and improving the prognosis of recurrent ovarian cancer [5, 7, 8].

Pegylated liposomal doxorubicin (PLD) is a small molecular nanoparticle prepared by embedding doxorubicin in polyethylene glycol

liposomes using nanotechnology [9, 10]. Presently, it is widely used as a new doxorubicin nano-formulation because of its strong targeting ability, low toxicity to the bone marrow and heart, and high stability of the embedded drugs *in vivo* [10]. The national comprehensive cancer network (NCCN) recommended carboplatin combined with PLD and PLD combined with bevacizumab (Bev) as the initial chemotherapy regimen for patients with ovarian cancer and platinum-resistant recurrent ovarian cancer, respectively [11, 12]. The results of a phase III randomized controlled clinical trial conducted in 2001, showed that PLD and topotecan (TOP) had similar objective response rates (ORRs) (19.7% vs. 17.0%, $P = 0.390$), and the overall survival (OS) and progression-free survival (PFS) of patients treated with PLD were higher than those of patients treated with TOP [13]. Takei et al. showed that when the number of previous chemotherapy regimens in patients with recurrent ovarian cancer was < 3, the disease control rate (DCR) of PLD and gemcitabine was similar (53.8% [$P > 0.05$]); however, when it was ≥ 3, the treatment effect of PLD alone was significantly higher than that of gemcitabine group (64.7% vs. 30.8%, $P = 0.037$) [14]. The survival analysis conducted by Gordon et al. revealed that, compared with TOP alone, TOP combined with PLD could reduce the mortality rate in patients with recurrent ovarian cancer [15].

Trabectedin (a tetrahydroisoquinoline alkaloid) is a new alkylating agent-based antitumor drug composed of three subunits (A, B, and C) that bind to DNA and transcription factors, respectively. It has a special anti-cancer effect and has multiple mechanisms and is complementarity with platinum, which allows its insertion between platinum regimens in patients with relapsed platinum-responsive ovarian cancer [16-18]. The phase III randomized controlled clinical trial, OVA-301, compared the efficacy of trabectedin combined with PLD and PLD alone in patients with recurrent ovarian cancer [19-21]. It revealed that, compared with PLD alone, the combined drug delayed disease progression or death by 21%, prolonged the median PFS of platinum-sensitive (9.2 months vs. 7.5 months, $P = 0.017$) and OS of some platinum-sensitive recurrence patients (22.4 months vs. 16.4 months, $P = 0.0027$) [22]. These results suggest that the survival benefit of some patients with platinum-sensitive recurrent ovarian cancer may be due to PFI prolongation, which leads to OS prolongation after subsequent platinum chemotherapy. Mito-8 is a study that investigated whether non-platinum therapy prolonged PFI and improved the prognosis of some patients with platinum-sensitive recurrent ovarian cancer. The results showed that the median OS of the observation and the standard groups was similar (21.8 months vs. 24.5 months, $P = 0.06$), whereas the median PFS was not improved in the observation group (12.8 months vs. 16.4 months, $P = 0.0025$) [23].

Given the controversial treatment of recurrent ovarian cancer with trabectedin combined with PLD, we conducted a meta-analysis of published clinical trials, retrospective studies and paired analyses to evaluate the efficacy and safety of trabectedin combined with PLD in treating recurrent ovarian cancer.

Methods

Search strategy

This study strictly conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology. PubMed, Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (EMBASE), Cochrane Library clinical controlled trials (CENTRAL) and ClinicalTrials.gov databases were mined to retrieve potentially eligible clinical trials and conference proceedings as of May 15, 2022. “Trabectedin”, “Pegylated Liposomal Doxorubicin”, “Ovarian Cancer”, and “RCT or randomized controlled trial or Randomized or placebo” were used as keywords. The criteria for the study were limited to humans; languages were not limited.

Inclusion criteria

All the studies included in this meta-analysis followed the Participants, Intervention, Comparison and Outcomes, Study design (PICOS) principles. The following inclusion criteria were applied: (1) P: patients with recurrent ovarian cancer, primary peritoneal cancer, or fallopian tube cancer; (2) I: all patients had received platinum-based chemotherapy; (3) C: therapeutic

efficacy and toxicity analysis; (4) O: OS and PFS were classed as major while hematologic and non-hematologic toxicities were classed as negative outcomes; (5) S: randomized controlled trials (RCTs).

Exclusion criteria

Studies were excluded if: (1) unpublished; (2) non-controlled; (3) non-RCT; or (4) contained incomplete results. Article titles and abstracts were first screened according to the inclusion and exclusion criteria, followed by full-text screening, extraction of trial data, and tabulation. The follow-up time, interventions, PFS, OS, and adverse events were key information extracted through database mining.

Statistical analysis

Review Manager software 5.4 (RevMan, v.5.4; Cochrane Collaboration, Oxford, UK) was used to compile summary statistics. We assessed survival outcomes (OS, PFS) and chemotherapy severe toxicity profile (G3-G4 toxicity) of patients by hazard ratios (HR) and 95% confidence intervals (CIs). The X^2 and I^2 statistical and quantitative heterogeneity tests were used in each study, where $P < 0.10$ or $I^2 > 50\%$ indicated heterogeneity in each study and the random effect model was used for analysis. However, $P > 0.10$ or $I^2 < 50\%$ indicated no statistical heterogeneity and the fixed-effect model was used for analysis. A p-value > 0.05 was considered significant, and all p-values were 2-sided.

Results

Study selection

After the preliminary search, we retrieved 408 articles and ten clinical trials, including five RCTs and five observational trials (**Table 1**). Two of the five RCTs have been completed so far. The registration numbers of the two completed trials (phase III clinical trials) on the ClinicalTrials.gov website are NCT01846611 and NCT00113607. Through abstract and title screening, 387 articles were excluded. Through full-text screening, 17 articles were excluded because they were not RCTs, had no control, and were review articles. Three articles related to the NCT00113607 trial [19-21] and one related to NCT01846611 [24] were ultimately included in this meta-analysis. The literature screening flow chart is shown in **Figure 1**.

Eligible studies and characteristics

The Cochrane risk of bias tool analysis (ACROBAT) was used to analyze the data. The two open-label clinical trials included in this study did not indicate randomization methods. There were selective reports in the clinical trial NCT00113607. Clinical trial NCT01846611 was an open-label, randomized, multicenter, phase III trial conducted between 2013 and 2019 that included 572 patients with recurrent ovarian, peritoneal, and fallopian tube cancers.

Clinical trial NCT00113607 was an open-label, randomized, multicenter, Phase III clinical trial completed in 2007 and included 672 patients with recurrent ovarian, peritoneal, and tubal cancer. Both trials reported OS, PFS, and grade 3-4 toxicity with trabectedin combined with PLD and PLD alone. The detailed risk of bias information is shown in **Figure 2**. **Table 2** shows the essential characteristics of both trials.

Overall survival

OS data from the two trials contained 1231 patients, with 619 and 612 patients in the trabectedin + PLD and PLD groups, respectively. Forest plots showed no significant difference in the OS between the two groups (HR, 0.88; 95% CI, [0.77-1.02]; $P = 0.08$) (**Figure 3**). Subgroup analysis showed significant difference in OS comparisons among patients with *BRCA* mutations (HR, 0.49; 95% CI, [0.33-0.73]; $P = 0.0004$) (**Figure 4**). A significant difference in OS comparison was observed in platinum-based partially sensitive patients with a PFI of 6-12 months (HR, 0.66; 95% CI, [0.52-0.84]; $P = 0.0005$) (**Figure 5**). Among patients with *BRCA* mutations and/or PFI of 6-12 months, those administered trabectedin and PLD chemotherapy had significantly improved OS, compared with those administered PLD alone ($P < 0.05$) (**Figure 6**).

Progression-free survival

Forest plot results showed that compared with PLD alone, trabectedin combined with PLD che-

Table 1. Characteristics of clinical trials

Identifier	Status	Year	Study Type	Estimated Enrollment	Intervention	Study Groups/Cohorts	Conditions	Primary Outcome
NCT03446495	Unknown	2018	Observational	60	Trabectedin + PLD	Trabectedin + PLD	Recurrent Partial-platinum Sensitive Ovarian Cancer	PFS
NCT03690739	Recruiting	2018	Interventional (Clinical Trial) Randomized	330	Drug: Carboplatin Drug: Gemcitabine Drug: Bevacizumab Drug: PLD Drug: Paclitaxel Drug: Trabectedin Drug: Cisplatin	Arm A: Active Comparator: platinum-based chemo-therapy Arm B: PLD + Trabectedin	Recurrent Ovarian Carcinoma	Symptom Benefit Rate, PFS, OS
NCT02825420	Completed	2016	Observational	224	Trabectedin + PLD	Trabectedin + PLD	Relapsed Ovarian Cancer	PFS
NCT02394015	Completed	2015	Observational	90	Trabectedin + PLD	Trabectedin + PLD	Recurrent Partial-platinum Sensitive Ovarian Cancer	PFS+OS
NCT02163720	Completed	2014	Observational	101	Yondelis®-Caelyx®	Yondelis®-Caelyx®-relapse	Recurrent Partial-platinum Sensitive Ovarian Cancer	PFS+OS
NCT01846611 /ET743-OVC-3006	Completed	2013	Interventional (Clinical Trial) Randomized	576	Drug: Trabectedin Drug: DOXIL Drug: Dexamethasone	Arm A: Trabectedin + DOXIL Arm B: DOXIL	Ovarian Neoplasms Peritoneal Neoplasms Fallopian Tube Neoplasms	PFS+OS
NCT01869400	Completed	2013	Observational	83	Yondelis-Pegylated liposomal Doxorubicin	Yondelis-Pegylated liposomal Doxorubicin	Platinum-sensitive ovarian cancer relapse	Safety and tolerability
NCT01379989	Active, not recruiting	2011	Interventional (Clinical Trial) Randomized	588	Drug: Carboplatin Drug: PLD Drug: Trabectedin	Arm A: Carboplatin + PLD Arm B: Trabectedin + PLD	Recurrent Partial-platinum Sensitive Ovarian Cancer	PFS+OS
EUCTR2010-022949-17-AT	Unknown	2010	Interventional (Clinical Trial) Randomized	600	Trabectedin PLD Carboplatin	Arm A: Trabectedin + PLD Arm B: Carboplatin + PLD	Recurrent Partial-platinum Sensitive Ovarian Cancer	PFS+OS
NCT00113607/ OVA-301	Completed	2005	Interventional (Clinical Trial) Randomized	672	Drug: Trabectedin Drug: DOXIL Drug: Dexamethasone	Arm A: DOXIL + trabectedin Arm B: DOXIL	Advanced Relapsed Ovarian Cancer	PFS+OS

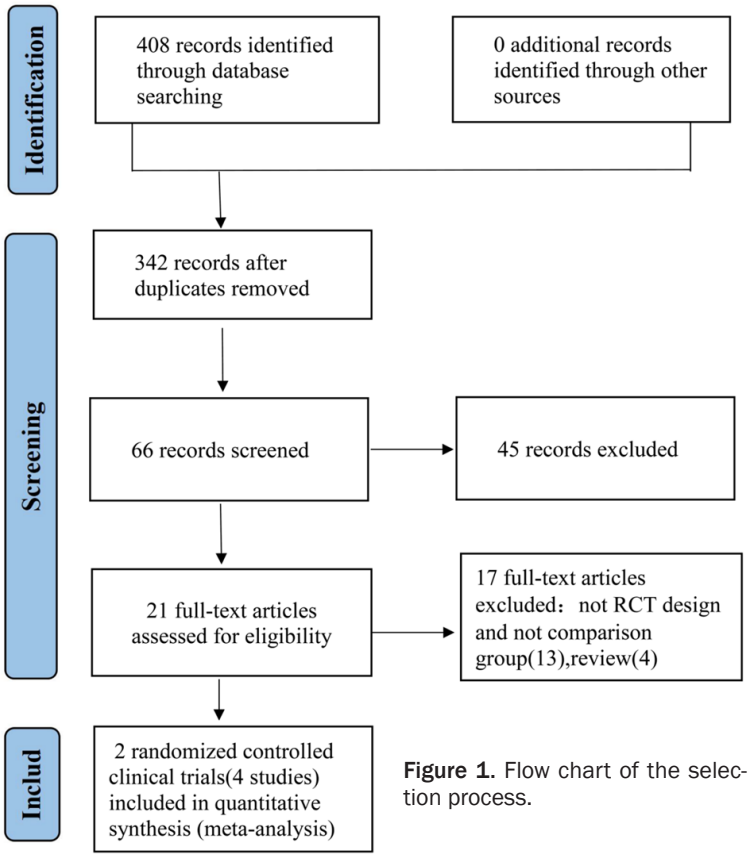


Figure 1. Flow chart of the selection process.

motherapy significantly improved PFS in patients with recurrent ovarian cancer (HR, 0.86; 95% CI, [0.74-0.99]; *P* = 0.03) (**Figure 7**). Subgroup analysis revealed that compared with PLD alone, trabectedin combined with PLD significantly improved PFS in patients with *BRCA* mutations (HR, 0.58; 95% CI, [0.40-0.58]; *P* = 0.004); PFS was not significantly improved in patients without *BRCA* mutations (HR, 0.94; 95% CI, [0.78-1.13]; *P* = 0.50) (**Figure 8**).

Grade 3-4 toxicities

According to the forest plot results, grade 3 toxicity showed that compared with PLD alone, trabectedin combined with PLD was more likely to lead to nausea (odd ratio [OR], 4.40; 95% CI, [2.32-8.36]; *P* < 0.0001), vomiting (OR, 3.50; 95% CI, [1.94-6.29]; *P* < 0.0001) (OR, 4.50; 95% CI, [2.37-8.52]; *P* < 0.00001), and the difference was statistically significant. However, stomatitis was more likely to occur with PLD chemotherapy than trabectedin plus PLD (OR, 0.20; 95% CI, [0.09-0.43]; *P* < 0.0001) (**Figure 9**). Grade 4 toxicity showed that compared with PLD alone, trabectedin combined with PLD was more likely to cause anemia (OR, 4.20; 95% CI, [106-16.67]; *P* = 0.04), neutropenia (OR, 5.77; 95% CI, [4.06-8.20]; *P* = 0.0001), leukopenia (OR, 2.94; 95% CI, [1.55.59]; *P* = 0.001), thrombocytopenia (OR, 20.77; 95% CI, [5.79-74.51]; *P* < 0.0001), febrile neutropenia (OR, 9.66; 95% CI, [2.24-41.64]; *P* = 0.002), and increased alanine aminotransferase (OR, 21.46; 95% CI, [2.88-159.95]; *P* = 0.003). However, there was no significant difference in vomiting (OR, 2.98; 95% CI, [0.12-73.46]; *P* = 0.5), stomatitis (OR, 0.33; 95% CI, [0.30-3.17]; *P* = 0.34), increased acid aminotransferase (OR, 3.99; 95% CI, [0.84-18.88]; *P* = 0.08), fatigue (OR, 0.99; 95% CI, [0.06-15.91]; *P* = 0.99), and increased aspartate aminotransferase (OR, 3.99; 95% CI, [0.84-18.88]; *P* = 0.08) (**Figure 10**).

Discussion

It is important to select the appropriate treatment plan after ovarian cancer recurrence to improve the survival of patients, and consider the impact of initial platinum therapy on disease recurrence [5]. The use of alternative treatment that delays platinum resistance and improves the prognosis of patients [4, 5, 25]. This treatment strategy is based on PFI, which refers to the progression time after platinum treatment and is divided into refractory (progression during treatment) drug resistance (< 6 months) and partial (6-12 months) or complete sensitivity (> 12 months) [5]. The European Society of Medical Oncology (ESMO)/European Society of Gynecological Oncology (ESGO) consensus guidelines for ovarian cancer recommends that patients with a platinum responsive recurrence should reselect platinum therapy; however, platinum therapy may not be the best choice for early symptom recur-

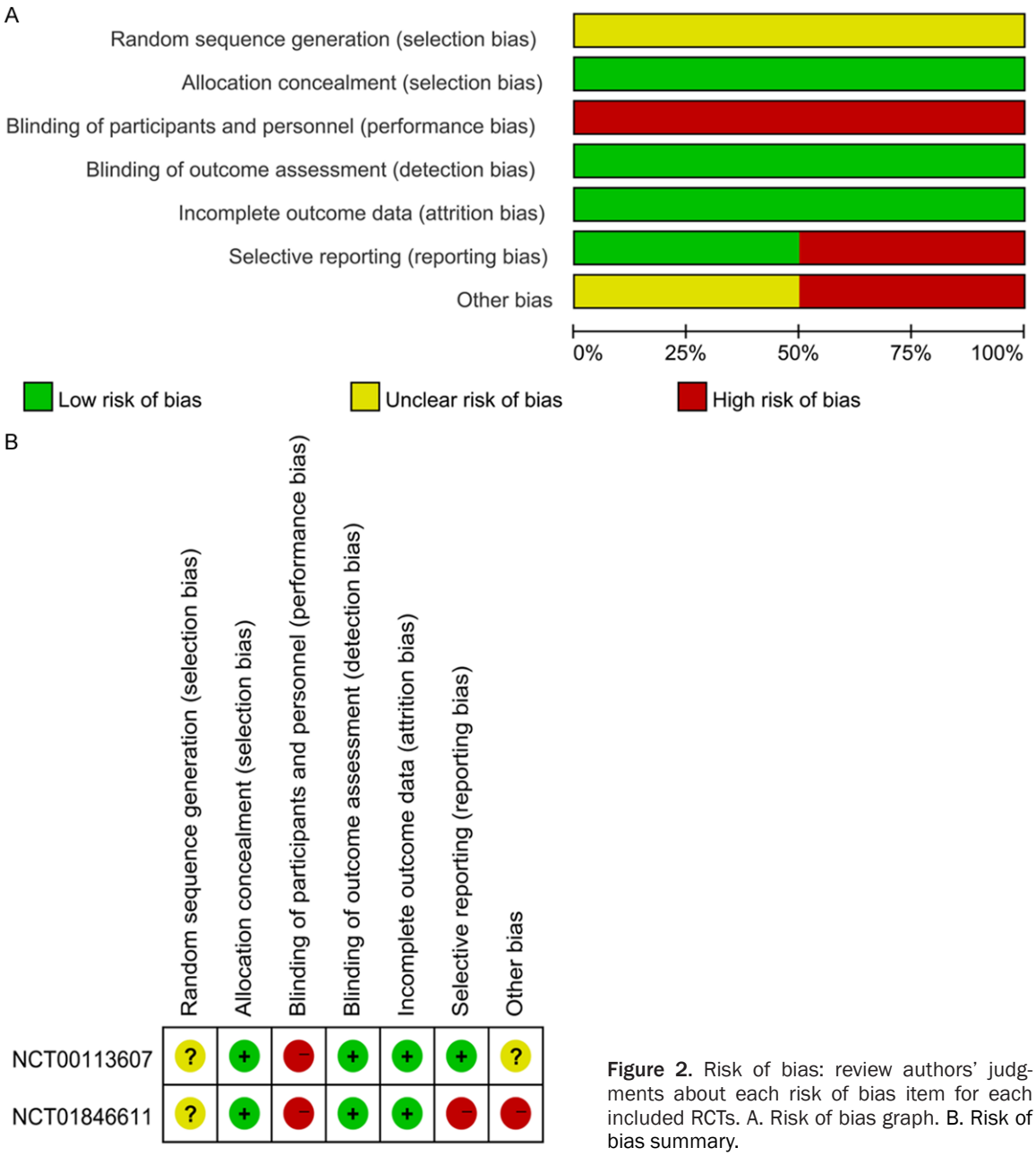


Figure 2. Risk of bias: review authors' judgments about each risk of bias item for each included RCTs. A. Risk of bias graph. B. Risk of bias summary.

rence, previous platinum therapy progress, or platinum intolerance recurrence [5, 16].

It has been proven that the biological characteristics of tumors must be considered when selecting the best treatment for recurrent ovarian cancer [5, 25]. Approximately 50% of patients with high-grade serous ovarian cancer have homologous recombination defects (HRD), such as germline or systemic *BRCA*1/2 mutations [26, 27]. These patients show special clinical behavior, respond to platinum chemotherapy, and are effective in the treatment of poly (ADP-ribose) polymerase inhibitor (PARPi). PARPi maintenance therapy effectively prolongs PFS in patients with *BRCA* mutations or recurrent HRD ovarian cancer [23, 25, 27].

The meta-analysis included two randomized controlled trials involving 1248 patients with recurrent ovarian, fallopian tube, and primary peritoneal cancers [20, 24]. Both studies reported OS, PFS, and subgroups on *BRCA* gene mutations and platinum-free interval

Table 2. Characteristics of eligible studies

ClincalTrials.gov identifier: NCT01846611/ET743-OVC-3006 Study: Bradley J 2019	
Methods	Phase 3 randomized, open-label, multicenter trial Study duration: May 2013 and April 2019
Participants	576 women with Histologically proven advanced-relapsed epithelial ovarian, primary peritoneal, or fallopian tube cancer Eastern Cooperative Oncology Group (ECOG) performance status grade of 0 or 1 Received first-line treatment with a platinum-based regimen and had no evidence of disease progression for ≥ 6 months after the last dose Received second-line treatment with a platinum-based regimen, with progression of disease after attaining a response Progression of disease based on imaging after the second-line platinum-based regimen (individuals treated with a pegylated liposomal doxorubicin-containing regimen as a second-line therapy are eligible if subsequent disease progression occurs ≥ 9 months from the first dose) Evidence of measurable disease at screening as evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) (Version 1.1) Participants no longer need to be able to receive intravenous (IV) dexamethasone or an equivalent IV corticosteroid Have a known BRCA 1/2 mutation status (for participants who do not have a known BRCA 1/2 status at screening, a blood sample will be collected to determine the status with the results available prior to randomization) Laboratory values within protocol - defined parameters Have left ventricular ejection fraction by multigated acquisition scan (MUGA) scan or 2D-ECHO within normal limits for the institution Have side effects (except alopecia) of prior treatment resolved to at least Grade 1 according to the National Cancer Institute - Common Terminology Criteria of Adverse Events (NCICTCAE) (Version 4.0) Have a negative urine or serum pregnancy test at screening Agrees to protocol-defined use of effective contraception
Interventions	Experimental: Arm A: trabectedin + DOXIL (pegylated liposomal doxorubicin) Participants will receive DOXIL 30 millgram per meter square (mg/m^2) administered as an intravenous (IV) infusion over approximately 90 minutes followed by trabectedin 1.1 mg/m^2 administered as an IV infusion over approximately 3 hours, every 3 weeks. Participants will be pretreated with 20 mg dexamethasone IV (or the IV equivalent) approximately 30 minutes before DOXIL study drug. As of Amendment 6, treatment with trabectedin will be discontinued for participants on treatment with trabectedin and no new participants will receive trabectedin. Participants who, in the opinion of the investigator, are deriving clinical benefit may continue treatment with single-agent DOXIL as per the local standard of care Active Comparator: Arm B: DOXIL (pegylated liposomal doxorubicin) Participants will receive DOXIL, 50 mg/m^2 administered as an IV infusion over approximately 90 minutes every 4 weeks
Outcomes	Primary Outcome Measures: Overall Survival (OS) Secondary Outcome Measures: Progression-Free Survival (PFS) and Objective Response Rate (ORR)

Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No statement regarding method of random sequence generation provided
Allocation concealment (selection bias)	Low risk	Individuals assigned to study treatment by chance

Blinding of participants and personnel (performance bias)	High risk	Open - label (identity of assigned study drug will be known)
Blinding of outcome assessment (detection bias)	Low risk	No statement regarding blinding of outcome assessment. However, the outcomes of interest were unlikely to be affected by lack of blinding of outcome assessor
Incomplete outcome data (attrition bias)	Low risk	Data analyses based on all participants
Selective reporting (reporting bias)	Low risk	Data analyses based on all participants
Other bias	High risk	Data analysed according to an intention-to-treat basis
ClincalTrials.gov identifier: NCT00113607/OVA-301 Study: Bradley J 2010, Bradley J 2012, B.J 2015		
Methods	Phase 3 randomized, open-label, multicenter trial Study duration: April 2005 to May 2007	
Participants	672 women with Histologically proven epithelial ovarian cancer, epithelial fallopian tube cancer, or primary peritoneal cancer Prior treatment with only 1 platinum based chemotherapy regimen Eastern Cooperative Oncology Group status of not more than 2 Progression more than 6 months after the start of initial chemotherapy treatment	
Interventions	Experimental: trabectedin + DOXIL (pegylated liposomal doxorubicin) Combination arm - Trabectedin + DOXIL: DOXIL 30 mg/m^2 intravenous (IV) infusion over 90 minutes + trabectedin 1.1 mg/m^2 IV infusion over 3 hours every 3 weeks. Patients will be premedicated with 20 mg dexamethasone or its equivalent IV infusion over 30 minutes prior to the DOXIL infusion Active Comparator: DOXIL (pegylated liposomal doxorubicin) Monotherapy arm - DOXIL: 50 mg/m^2 IV infusion over 90 minutes every 4 weeks	
Outcomes	Primary Outcome Measures: Progression-Free Survival (PFS) Secondary Outcome Measures: Overall Survival (OS), Duration of Response, Median Area Under Curve (AUC) of Trabectedin, Median Maximum Plasma Concentration (Cmax) of Trabectedin and Objective Response Rate (ORR)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No statement regarding method of random sequence generation provided
Allocation concealment (selection bias)	Low risk	Study medication is assigned by chance
Blinding of participants and personnel (performance bias)	High risk	Open - label (all people know the identity of the intervention)
Blinding of outcome assessment (detection bias)	Low risk	No statement regarding blinding of outcome assessment. However, the outcomes of interest were unlikely to be affected by lack of blinding of outcome assessor
Incomplete outcome data (attrition bias)	Low risk	Data analyses based on all participants
Selective reporting (reporting bias)	High risk	Data analyses based on all participants
Other bias	High risk	Data analysed according to an intention-to-treat basis

(PFI). Meta-analysis showed that trabectedin combined with PLD could not improve OS in recurrent ovarian cancer compared with PLD alone (HR, 0.88; 95% CI, [0.77-1.02]; P = 0.08);

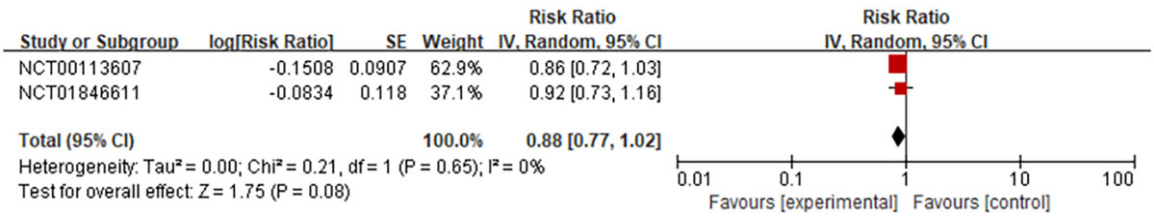


Figure 3. Forest plots of overall survival (OS).

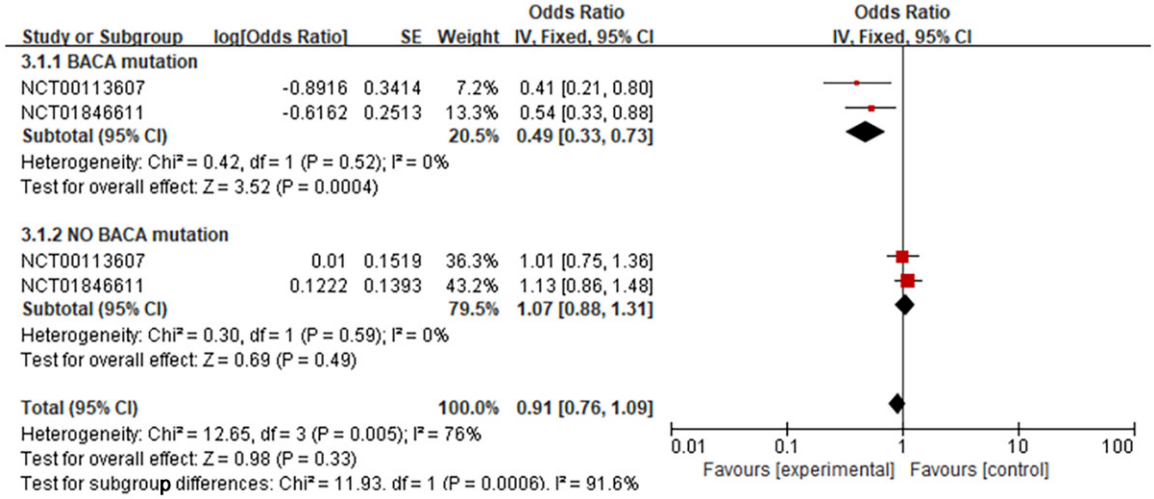


Figure 4. Forest plots of overall survival for patients with *BRCA* mutations.

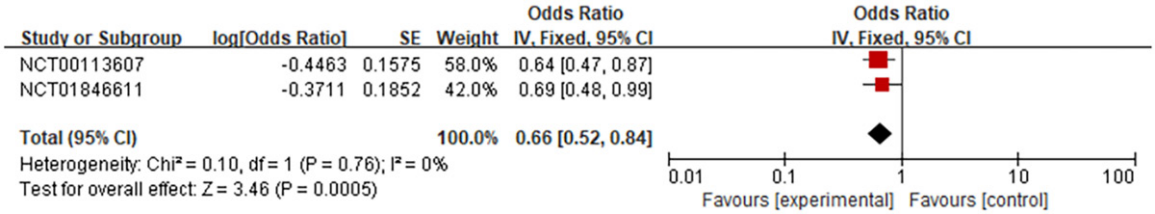


Figure 5. Forest plots of overall survival for patients with platinum-free interval (PFI) of 6-12 months.

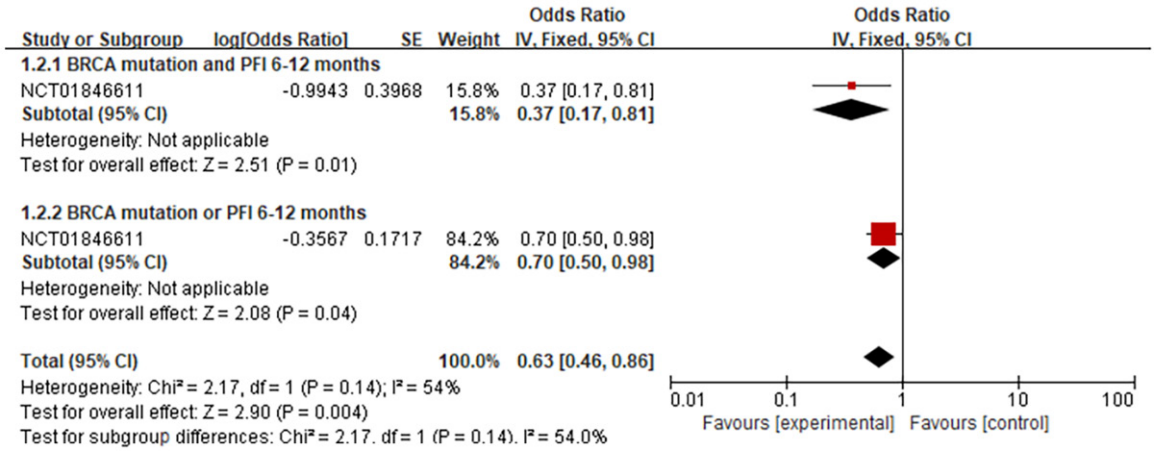


Figure 6. Forest plots of overall survival for patients with *BRCA* mutation and/or PFI of 6-12 months.

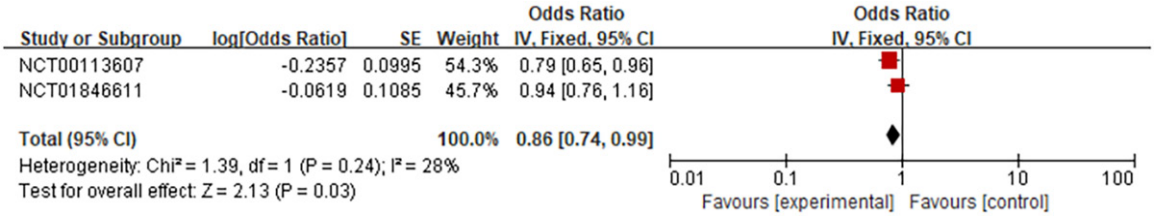


Figure 7. Forest plots of progression-free survival (PFS).

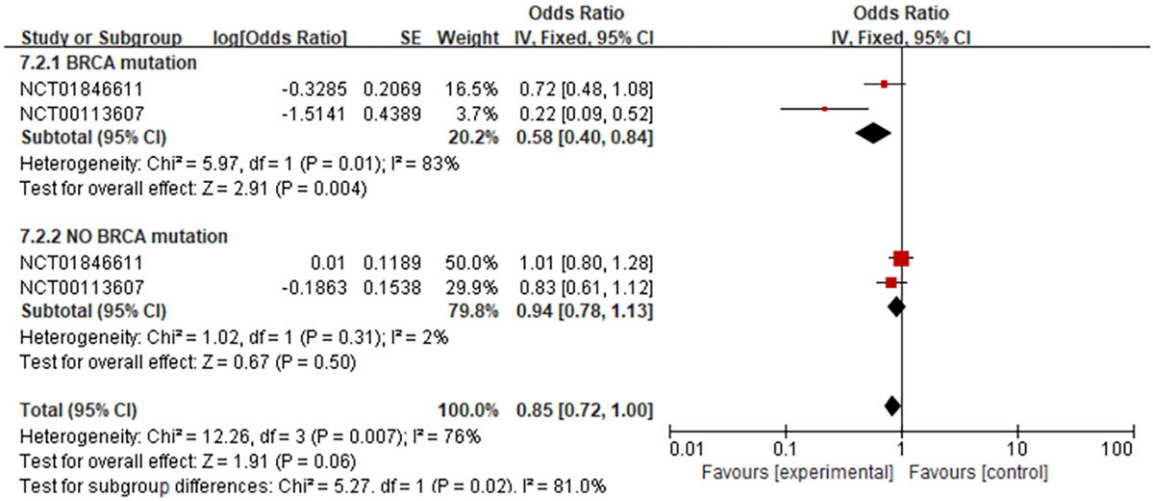
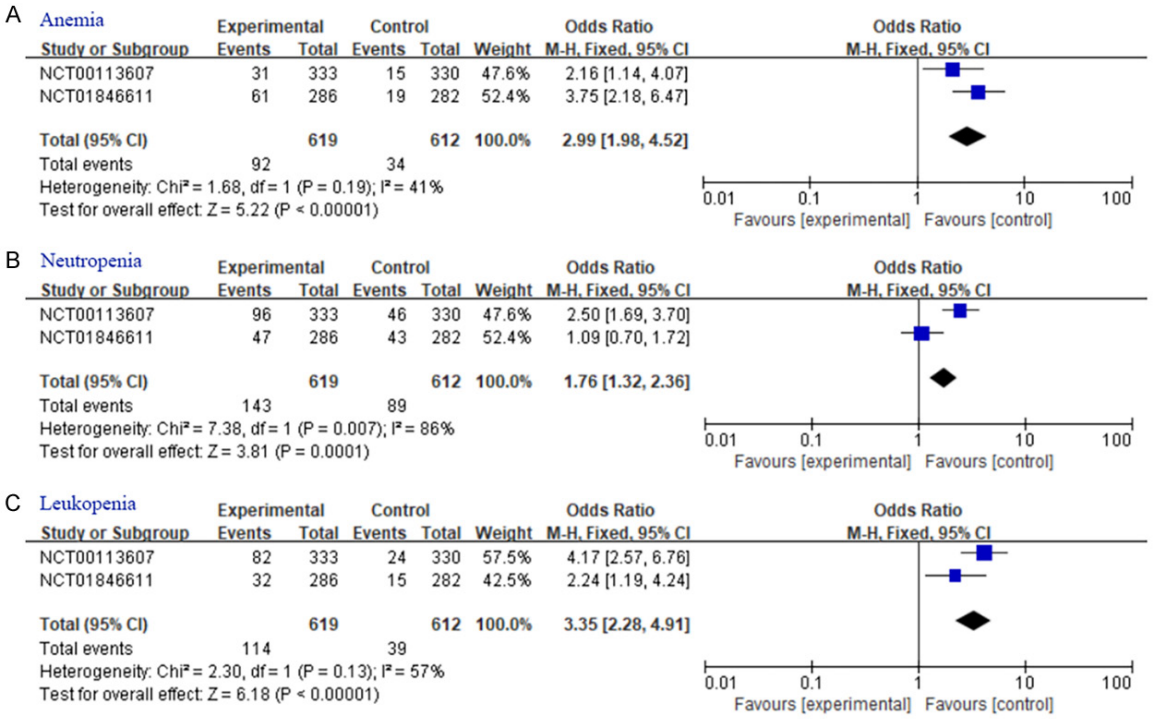


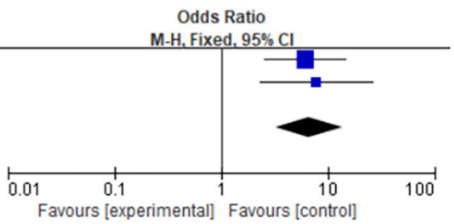
Figure 8. Forest plots of progression-free survival (PFS) for patients with *BRCA* mutations.



D Thrombocytopenia

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
NCT00113607	34	333	6	330	66.0%	6.14 [2.54, 14.83]
NCT01846611	22	286	3	282	34.0%	7.75 [2.29, 26.20]
Total (95% CI)		**619**		**612**	**100.0%**	**6.69 [3.28, 13.66]**
Total events	56		9			

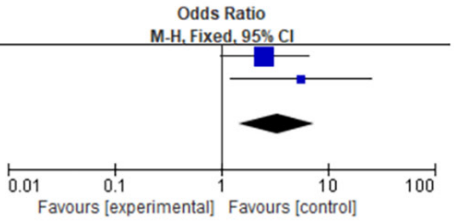
Heterogeneity: Chi² = 0.09, df = 1 (P = 0.76); I² = 0%
Test for overall effect: Z = 5.22 (P < 0.00001)



E Febrile neutropenia

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
NCT00113607	15	333	6	330	74.8%	2.55 [0.98, 6.65]
NCT01846611	11	286	2	282	25.2%	5.60 [1.23, 25.50]
Total (95% CI)		**619**		**612**	**100.0%**	**3.32 [1.49, 7.39]**
Total events	26		8			

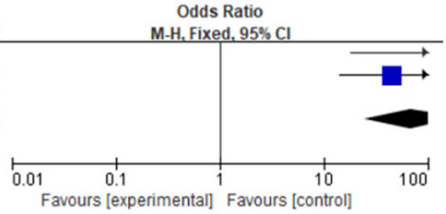
Heterogeneity: Chi² = 0.75, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 2.93 (P = 0.003)



F ALT increase

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
NCT00113607	95	333	1	330	26.1%	131.32 [18.18, 948.58]
NCT01846611	94	286	3	282	73.9%	45.53 [14.22, 145.84]
Total (95% CI)		**619**		**612**	**100.0%**	**67.96 [24.93, 185.26]**
Total events	189		4			

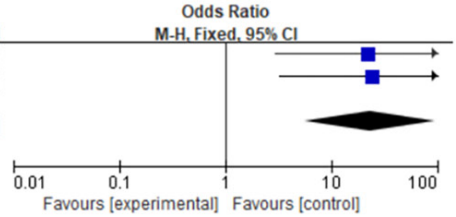
Heterogeneity: Chi² = 0.88, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 8.25 (P < 0.00001)



G AST increase

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
NCT00113607	21	333	1	330	50.4%	22.14 [2.96, 165.61]
NCT01846611	23	286	1	282	49.6%	24.57 [3.30, 183.25]
Total (95% CI)		**619**		**612**	**100.0%**	**23.35 [5.63, 96.75]**
Total events	44		2			

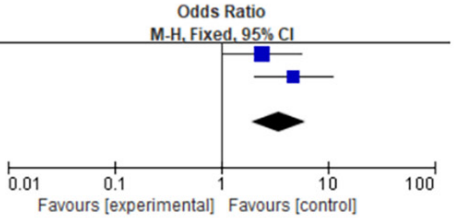
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 4.34 (P < 0.0001)



H Fatigue

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
NCT00113607	19	333	8	330	54.7%	2.44 [1.05, 5.64]
NCT01846611	31	286	7	282	45.3%	4.78 [2.07, 11.04]
Total (95% CI)		**619**		**612**	**100.0%**	**3.50 [1.94, 6.29]**
Total events	50		15			

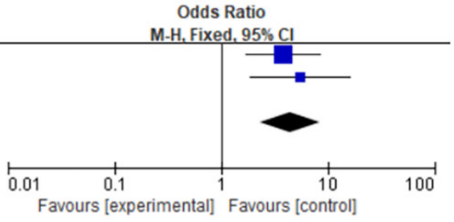
Heterogeneity: Chi² = 1.24, df = 1 (P = 0.26); I² = 20%
Test for overall effect: Z = 4.17 (P < 0.0001)



I Nausea

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
NCT00113607	29	333	8	330	66.3%	3.84 [1.73, 8.53]
NCT01846611	21	286	4	282	33.7%	5.51 [1.87, 16.26]
Total (95% CI)		**619**		**612**	**100.0%**	**4.40 [2.32, 8.36]**
Total events	50		12			

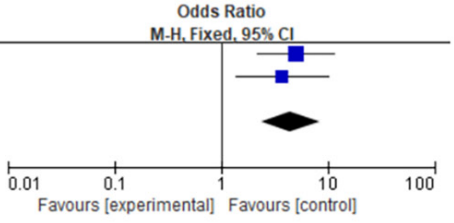
Heterogeneity: Chi² = 0.28, df = 1 (P = 0.60); I² = 0%
Test for overall effect: Z = 4.53 (P < 0.00001)



J Vomiting

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
NCT00113607	33	333	7	330	57.3%	5.08 [2.21, 11.65]
NCT01846611	18	286	5	282	42.7%	3.72 [1.36, 10.16]
Total (95% CI)		**619**		**612**	**100.0%**	**4.50 [2.37, 8.52]**
Total events	51		12			

Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 4.61 (P < 0.00001)



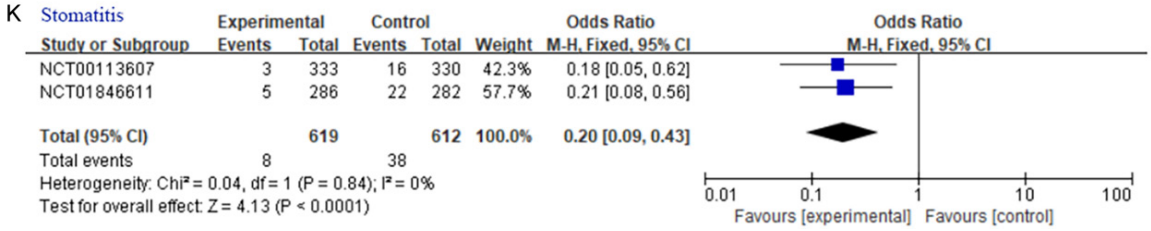
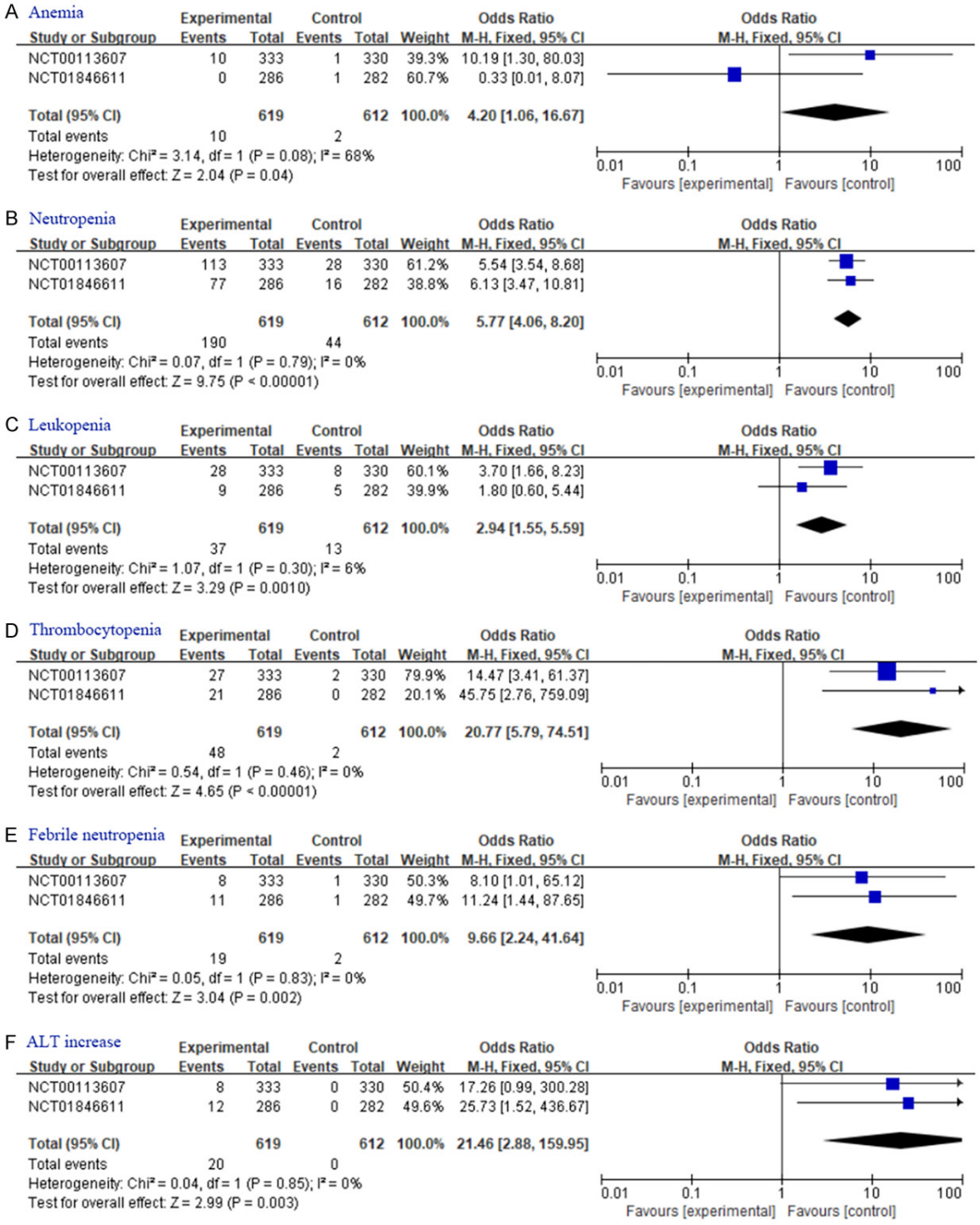


Figure 9. Forest plots of risk ratios for cumulative grade 3 toxicities.



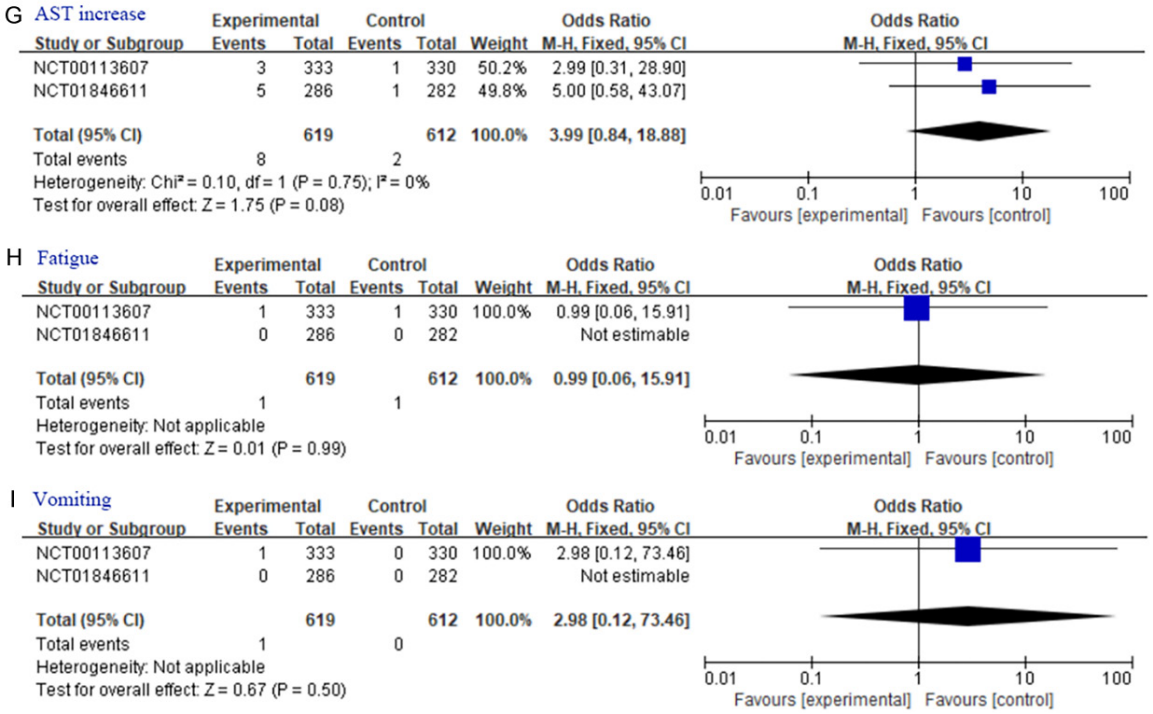


Figure 10. Forest plots of risk ratios for cumulative grade 4 toxicities.

however, subgroup analysis revealed that trabectedin combined with PLD improved OS in patients with *BRCA* mutation (HR, 0.49; 95% CI, [0.33-0.73]; *P* = 0.0004), and in patients with platinum partially sensitive relapses with PFI of 6-12 months (HR, 0.66; 95% CI, [0.52-0.84]; *P* = 0.0005). Compared with PLD alone, the OS of patients with recurrent ovarian cancer with *BRCA* gene mutation and/or PFI at 6-12 months after treatment with trabectedin combined with PLD was improved (*P* < 0.05).

The PFS conclusions of the two trials included in the study varied. The study with the test number NCT01846611 [24] demonstrated that trabectedin combined with PLD chemotherapy improved the PFS of patients compared with PLD alone, whereas the outcome of that with the test number NCT00113607 [19, 21] was different. After our meta-analysis, the results revealed that trabectedin combined with PLD chemotherapy improved PFS in recurrent ovarian cancer compared with PLD alone (HR, 0.86; 95% CI, [0.74-0.99]; *P* = 0.03). Subgroup analysis showed that compared to PLD alone, trabectedin + PLD chemotherapy improved PFS in patients with *BRCA* gene mutation (HR, 0.58; 95% CI, [0.40-0.58]; *P* = 0.004) and platinum-sensitive recurrent ovarian cancer (HR, 0.73; 95% CI, [0.56-0.95]; *P* = 0.02).

Trabectedin combined with PLD was more likely to cause grade 3-4 side effects than PLD alone. However, there were no deaths related to toxicity side effects in the two trials, indicating that trabectedin combined with PLD in the treatment of recurrent ovarian cancer increased the grade 3-4 toxicity and side effects; however, its safety was acceptable.

This meta-analysis had several limitations. Firstly, the main limitation was that it included only a few articles, which might have affected the research results. Secondly, the trial number NCT01846611 [24] includes patients with platinum-based secondary chemotherapy, whereas the patients included in NCT00113607 [22] are those who suffered relapse after the initial platinum chemotherapy, which constituted a source of potential bias. Thirdly, the two studies did not report further studies on platinum-resistant recurrent patients.

Conclusion

Through systematic reviews and meta-analyses of included studies, trabectedin plus PLD was

found to prolong OS and PFS in patients with *BRCA* mutation and/or platinum-sensitive recurrent ovarian cancer compared with PLD alone. Because of the small number of included studies, further evidence from larger RCTs is required in the future.

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Disclosure of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Abbreviations

PLD, pegylated liposomal doxorubicin; HRs, hazard ratios; RRs, risk ratios; Cis, confidence intervals; OS, overall survival; BRCA, breast-cancer-gene; PFS, progression-free survival; PFI, platinum-free survival interval; NCCN, national comprehensive cancer network; Bev, bevacizumab; TOP, topotecan; ORRs, objective response rates; DCR, disease control rate; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MEDLINE, Medical Literature Analysis and Retrieval System Online; EMBASE, Excerpta Medica Database; CENTRAL, Cochrane Library clinical controlled trials; PICOS, Participants, Intervention, Comparison and Outcomes, Study design; RCTs, randomized controlled trials; ACROBAT, Cochrane risk of bias tool analysis; ESGO, European Society of Medical Oncology; ESMO, European Society of Gynecological Oncology; HRD, homologous recombination defects; PARPi, poly (ADP-ribose) polymerase inhibitor.

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