The Impact of Pegylated Liposomal Doxorubicin in Recurrent Ovarian Cancer : An Updated Meta-Analysis of Randomized Clinical Trials

Xin-Ru Li
Chengdu University of Traditional Chinese Medicine
Yi Zhu
Sichuan Cancer Hospital and Institute
Guo-Nan Zhang (zhanggn@hotmail.com)
Sichuan Cancer Hospital https://orcid.org/0000-0002-2228-9197
Jian-Ming Huang
Sichuan Cancer Hospital and Institute
Li-Xia Pei
Chengdu University of TCM: Chengdu University of Traditional Chinese Medicine

Research Article

Keywords: Ovarian Neoplasms, Pegylated Liposomal Doxorubicin, Progression Free Survival, Overall Survival, Meta-analysis

Posted Date: February 22nd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-229950/v1

Version of Record: A version of this preprint was published on March 9th, 2021. See the published version at https://doi.org/10.1186/s13048-021-00790-4.

Abstract

Background: Pegylated Liposomal Doxorubicin (PLD) could improve the survival rate of patients with recurrent ovarian cancer in previous meta-analysis studies. The aim of the present meta-analysis was to further update the role of PLD in the treatment of recurrent ovarian cancer.

Methods: Literature search was performed by using the electronic databases Medicine, EMBASE, Web of Science, and Cochrane library until 27 July 2020. We only restricted the randomized clinical trials. Study specific hazard ratios and 95% confidence level (HR/95% CI), risk ratios and 95% confidence level (RR/95% CI), were pooled using a random effect model.

Results: 10 studies (12 trials) were included after screening of 940 articles. We categorized the eligible studies into two groups: the doublet regimens (four trials, 1767 patients) resulted that PLD plus carboplatin(carbo) provided superior progression free survival (PFS) (HR, 0.85; 95% CI, 0.74-0.97) and similar overall survival (OS) (HR, 1.00; 95% CI, 0.88-1.14) compared PAC plus carbo. PLD plus carboplatin was associated with significantly more anemia and Thrombocytopenia, other side effects well-tolerated. In platin resistant patients, the monotherapy regimens (eight trials, 1980 patients) resulted that PLD had similar PFS (HR, 1.02; 95% CI, 0.90–1.16) and OS (HR, 0.88; 95% CI, 0.77–1.01) to other monotherapies. PLD alone was more associated with mucositis/stomatitis and hand-foot syndrome, other side effects well-tolerated.

Conclusion: In platinum-sensitive recurrent ovarian cancer, PLD plus carbo is more effective than PAC plus carbo. In platinum-resistant or refractory recurrent ovarian cancer, PLD has similar survival to others monotherapies. For side effects, PLD plus carbo or monotherapy chemotherapy both were well-tolerated.

Introduction

Ovarian cancer is one of the most common gynecological malignancies, with the third highest incidence of gynecological tumors and the highest mortality rate. Because ovarian cancer is not easy to detect in the early stage, it is usually diagnosed as advanced stage and its 5-year relative survival rate is relatively low. The lifetime risk of ovarian cancer is approximately 1 in 75, and the likelihood of dying from this malignancy is 1 in 100 [1, 2]. Cytoreductive surgery followed by platinum-based chemotherapy remains the mainstay of treatment in ovarian cancer. Despite complete remission through the best upfront treatment, approximately 70% to 80% of patients experience a relapse within 5 years [3, 4]. So ovarian cancer is still a serious threat to women's health in the world.

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

PLD, an anthracycline chemotherapy derived from doxorubicin, and is the first FDA-approved cancer nanomedicine [7]. As early as in 2014, has been approved for the treatment of ovarian and breast cancer, multiple myeloma, and Kaposi sarcoma [8]. The 2017 NCCN Guidelines recommend that carbo combined with PLD be added as one of the initial chemotherapy regimens for ovarian cancer. Carbo combined with PLD is recommended for patients with recurrent platinum-sensitive ovarian cancer patients, and PLD monotherapy is recommended for relapsed platinum-resistant ovarian cancer patients. The 2018 NCCN Guidelines include PLD as a first-line chemotherapy regimen for ovarian cancer, and carboplatin/liposomal doxorubicin for advanced ovarian cancer patients (category 2A recommendation). The 2019 NCCN Guidelines recommend that PLD plus Bevacizumab is a potential treatment option for patients with platinum-resistant recurrent ovarian cancer. Clinical studies have shown that compared with other standard chemotherapy regimens, PLD has a non-inferior survival rate and is well-tolerated, especially with lower alopecia and neurotoxicity [9].

The previous studies [10, 11] clarified that PLD is effective and well tolerated in the treatment of ovarian cancer. Because these two meta-analysis are earlier and less trials included, we added the latest trials and performed an updated meta-analysis. this study results will help in the selection of chemotherapy regimens for recurrent ovarian cancer patients.

Methods

1. Search strategy

We conducted this meta-analysis framework under the guidance of PRISMA. Queries of literature were performed by using the electronic databases Medicine, EMBASE, Web of Science, and Cochrane library until 27 July 2020. The search MeSH terms and free words used were: 1) “Pegylated Liposomal Doxorubicin,” “Caelyx,” “Lipodox,” “Doxil” and 2) “ovarian cancer,” “ovarian neoplasm,” “ovarian carcinoma” and 3) “Randomized Controlled Trial.” In this study, language for the searching and inclusion studies were not limited. The detail of the search strategy is presented in the Supplementary Material 1. This study does not involve patient knowledge and ethics.

2. Eligibility criteria

The abstracts of all articles retrieved in the initial search were independently screened by two authors (X.R.L and L.X.P). Both processes were executed by independent reviewers according to the following criteria. The inclusion criteria were: 1) involved patients with histologically confirmed recurrent ovarian cancer; 2) included interventions were PLD alone versus other monotherapy or PLD plus carboplatin versus paclitaxel plus carboplatin; 3) involved outcomes measures were survival outcome and adverse events; 4) all studies were RCTs. The exclusion criteria were: 1) no PLD was performed; 2) no ovarian cancer patients were examined; 3) the study was conducted in pediatric population (<18 years old); 4) animal/laboratory study; 5) review articles, case reports, letters, commentaries, or conference proceedings; 6) recurrent ovarian cancer histology was not confirmed. Disagreements were discussed with a third author (Prof. G.N.Z) to achieve consensus.

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

3. Data Extraction

Data were extracted from the included studies. Data included: first author, journal, year of publication, number, age and characteristics of patients, study design, outcomes.

4. Statistical Analysis

For survival variables such as Progression Free Survival (PFS) and Overall Survival (OS), we used the hazard ratios (HR), and 95% CI, which are presented as forest plots. For categorical variables, we used the risk ratios (RR) and 95% CI, which are presented as forest plots. Heterogeneity across studies was evaluated using the I^2 metric and chi-square test. We used the random-effect model to calculate the summary estimate if heterogeneity existed (I^2>50%) across studies. Otherwise, the fix-effect model was used ($I^2 \leq 50\%$). If heterogeneity existed across studies, we performed subgroup analyses based on study design and analyzed the subgroup results. We used Egger's linear regression test, as well as Begg's funnel plot to assess potential publication bias existed across studies. All statistical testing was conducted using the Review Manager 5.3 (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and stata.15.0 (Stata-Corp, College Station, TX). All tests were two-sided with $P < 0.05$ considered statistically significant, except for heterogeneity test ($P < 0.1$) and publication bias ($P < 0.1$) in meta-analyses.

Results

1. Literature Search

A total of 940 articles were confirmed using our electronic database search. After removing duplicate articles and screening the studies titles and abstracts, 56 articles meeting the inclusion criteria underwent full-text assessment resulting in 10 relevant studies [13-22]. Flowchart of the selection procedure (Fig. 1).

2. Study Characteristics

In 2 studies treatment arms were evaluated separately: PLD plus carbo vs PAC plus carbo (four trials [13-16]: 851 PLD plus carbo and 916 PAC plus carbo). PLD vs other monotherapy (eight trials [17-22] : 963 PLD and 1,017 other monotherapy), Vergote2009 [19] was categorized into both trials: PLD vs Topotecan and PLD vs Canfosfamide; Kaye2012 [22] was categorized into both trials: PLD vs 200mg Olaparib and PLD vs 400mg Olaparib. All features of the included studies are demonstrated in Table.1. We assessed the study quality based on The Cochrane Collaboration's tool and the criteria specified in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions [12]Table.2. Each study was evaluated for potential bias and quality by two independent authors experienced. Disagreements were resolved by consensus.

3. Extraction of Data

3.1 Doublet Regimens overall analysis: PLD plus carbo vs PAC plus carbo

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

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

3.2 Monotherapy Regimens overall analysis: PLD vs Single agent

PLD was similar in PFS (HR,1.02; 95% CI,0.90–1.16; I^2=0%; p=0.72) and OS (HR,0.88; 95% CI, 0.77–1.01; I^2=0%; p =0.07) to other single agent. (Fig.3)

Grade 3-4 toxicities: PLD was associated with an significant increased risk of mucositis/stomatitis (RR, 0.10; 95% CI, 0.04–0.23; I^2=0%; p<0.01), and Hand-foot syndrome (RR, 0.03; 95% CI, 0.01–0.09; I^2=0%; p <0.01) compared with the other monotherapies. There were no difference risk of anemia(RR, 1.26; 95% CI, 0.86–1.83; I^2=0%; p=0.23), vomiting (RR, 0.97; 95% CI, 0.57–1.66; I^2=38%; p=0.91), fatigue/asthenia (RR, 1.09; 95% CI, 0.73–1.64; I^2=19%; p=0.66), thrombocytopenia (RR, 1.73; 95% CI, 0.93–3.24; I^2=4%; p=0.08) and neutropenia (RR, 1.32; 95% CI, 0.59–2.96; I^2=86%; p =0.50).(Fig.5)

3.3 Subgroup analysis

We perform neutropenia side effect subgroup analyze based on different drugs in Monotherapy Regimens (I^2=86%), one subgroup [19, 20] showed that Canfosfamide and Patupilone were lower risk than PLD (RR, 0.39; 95% CI, 0.21–0.72; I^2=33%; p<0.01), the other subgroup [17-19, 21] showed that Gemcitabine, Topotecan, LIFA and Olaparib were higher risk than PLD (RR, 2.26; 95% CI, 1.61–3.17; I^2=0%; p<0.01). And perform subgroup for the differences of bad toxic and side effects based on the different doses of PLD: In doublet regimens: anemia, 30mg/m^2 vs 45mg/m^2 PLD (I^2=0%); thrombocytopenia, 30mg/m^2 vs 45mg/m^2 PLD (I^2=0%). There were no difference in the incidence of adverse reactions at different doses of PLD. In monotherapy regimens: mucositis/stomatitis, 40mg/m^2 vs 50mg/m^2 PLD (I^2=60.5%); Hand-foot syndrome, 40mg/m^2 vs 50mg/m^2 PLD (I^2=30.2%). There were difference in the incidence of adverse reactions at different doses of PLD.

3.4 Publication bias

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

Discussion

To the best of our knowledge, this study is the most recently updated meta-analysis about PLD curative effect and side effects in recurrent ovarian cancer chemotherapy. The main results suggest that PLD is effective for the treatment of recurrent ovarian cancer, even better. The secondary indicators show that most patients well tolerated and has no serious adverse reactions.

1. Doublet Regimens

Because of studies results showed that platinum doublets of carbo plus PAC, carbo plus gemcitabine, and carbo plus PLD superior to single-agent platinum, and carbo plus PLD were as effective as carbo plus PAC in women with high-sensitive relapsed ovarian cancer [4, 23-25]. So we only selected and compared doublet regimens based on platinum in platinum-sensitive recurrent ovarian cancer. PLD plus carbo had superior in PFS and has no obvious different in OS. We found that in four doublet regimens trials, only the results of Pujade-Lauraine2010 and Gladieff 2012 showed that PFS in the PLD plus carbo group had significant superiors. This results may due to in Pujade-Lauraine2010, 90% of women received post-progression treatment and the proportion of women in the PAC plus carbo arm who received PLD as post-study therapy (68%) was significantly higher than the proportion of women in the PLD plus carbo arm who received PAC (43%;$P < 0.01$); this may have influenced OS HR in the direction of the PAC plus carbo arm [11]. However, in Gladieff 2012, OS was not counted due to overall survival data was immature, so there is no exact comparison between PFS and OS. There is another perspective, it is possible that tumor cells that survive treatment with PLD plus carbo maybe more aggressive or may be resistant to subsequent therapies. when the disease does recur, It may progress more quickly or maybe resistant to other therapies, thus negating any benefits for OS [10]. We also guess Bafaloukos 2010 And was phase II study that was not powered to assess OS and may affect the final result. But the specific reasons are not clear, and further research is needed.

We compared the different of PFS and OS based on different PLD doses. PLD 30mg/m^2 every 4weeks compared with PLD 45mg/m^2 every 4weeks, the results showed PFS and OS no significant difference. Therefore, we support PLD 30mg/m^2 every 4weeks can be used as the initial dose in PLD plus carbo doublet regimens.

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

Compared with Grade 3-4 severe toxicities, Hand-foot syndrome and mucositis/ stomatitis both mainly focused on low grade toxicities, the patient's adverse symptoms are mild. Anemia and thrombocytopenia both mainly focused on severe toxicities. Fortunately, the adverse incidence is not high (8.2% and 14.7%). We laterally compared the incidence of side effects at two different PLD doses (Grade 3-4 toxicity). For anemia, 30mg/m^2 vs 45mg/m^2 PLD (8.0% vs 9.5%). For thrombocytopenia, 30mg/m^2 vs 45mg/m^2 PLD (15.0% vs 12.0%). These two adverse reactions did not show significant dose-dependence of PLD, which may be because the combination of carbo reduced the toxic and side effects of PLD.

The updated meta-analysis results show that PLD plus carbo has a non-inferior survival rate and is well-tolerated. Hence, PLD plus carbo emerged as a favorable potion for platinum-sensitive patients in the recurrent setting.

2. Single Regimens

In platinum-resistant or refractory recurrent ovarian cancer, PLD has similar non-inferior survival results as other single agents. So platinum-resistant women are challenged with non-platinum drugs. Study showed that gemcitabine plus PLD is a very attractive combination given that they have different mechanisms of action and different toxicity profiles [28]. This combination does not reduce the effect of each other, but also increases the additive activity of the drug. This therapy was well tolerated by most platinum resistant ovarian cancer patients, and patients with higher levels of baseline deoxycytidine kinase had longer PFS. The usage recommended PLD 35 mg/m^2 on day 1, and gemcitabine 1000 mg/m^2 on days 1, 15 q4weks. But this study is a phase I b study need further study. Another study showed that Olaparib combined with PLD were well tolerated but did not result in significant prolongation of PFS or OS in platinum resistant or refractory ovarian cancer [29]. The 2019 NCCN Guidelines showed that PLD plus Bevacizumab is a potential treatment option for patients with platinum-resistant recurrent ovarian cancer. The 2020 NCCN Guidelines suggest that bevacizumab is effective in both platinum-sensitive and platinum-resistant recurrent ovarian cancer. Treatment of platinum-resistant or refractory recurrent ovarian cancer as a palliative care still need more potential chemotherapy options.

The mainly common adverse effect of monotherapy PLD were mucositis/stomatitis and Hand-foot syndrome. We laterally compared the incidence of side effects at two different PLD doses (Grade 3-4 toxicity). For mucositis/stomatitis, 40mg/m^2 vs 50mg/m^2 PLD (4.2% vs 10.2%). the result showed mucositis/stomatitis is a dose-dependent side effect of PLD. For Hand-foot syndrome, 40mg/m^2 vs 50mg/m^2 PLD (3.4% vs 17.6%). the result showed Hand-foot syndrome is also a significantly dose-dependent side effect of PLD.

This updated meta-analysis show that PLD is well-tolerated in 40mg/m^2 lower dose regimens, and which do not adversely affect survival compared with other single regimens, and confirm PLD as a good choice for women in whom monotherapy is a treatment option.

3. Strength and Limitation of PLD for the treatment of ovarian cancer

The most concerning potential side effect of doxorubicin and PLD is often cited as congestive heart failure. Doxorubicin is closely related to congestive heart failure. PLD's parent drug is doxorubicin, but PLD can effectively reduce cardiac toxicity. Studies show that PLD reduced incidence of cardiotoxicity by five-to six fold even in doses≥500 mg/m^2. It is because of pegylation, coating the liposome with a hydrophilic protective coating, allows a prolonged time of the drug in circulation due to its ability to evade immunologic elimination. Both lower plasma levels and improved ability to target tumor tissue allow for the sparing of cardiac toxicity with PLD [26]. One study surfaced that even with high cumulative doses of PLD up to 2500 mg, there were no significant incidences of cardiotoxicity by 2D strain on 3D left ventricular ejection fraction, so long-term use is safe [27]. So PLD had a cardioprotection, and is more beneficial for patients with poor heart function and elderly patients.

Recurrent studies showed that prolonged treatment with PLD has been associated with the development of secondary oral Mucosal squamous cell carcinoma in a number of case reports, but the specific mechanism of action is unknown [9]. Another trial showed that The cumulative doses of PLD in our patients before the development of squamous cell carcinoma were 1350mg/m^2 and 1142 mg/m^2 respectively, so reduce the amount dose, prolonged administration and regular oral cavity examinations along with complete skin examinations was necessary [30]. So we should use PLD dose as low as possible and prolonged administration to reduce the incidence of Hand-Foot Syndrome, thereby reducing the incidence of secondary oral Mucosal squamous cell carcinoma.

Conclusion

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

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

All the authors declare no competing interests.

Funding

This work was supported by National Natural Science Foundation of China (grant numbers 81902670), Sichuan Key Research and Development Project from Sichuan Provincial Science and Technology Department (grant numbers 2019YFS0424 and 2019YFS0036).

Author contributions

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

Acknowlegements

Not applicable.

References

1. Reid BM, Permuth JB, Sellers TA.Epidemiology of ovarian cancer: a review.Cancer Biology and Medicine2017;14:9-32.
2. Piao J, Lee EJ, Lee M.Association between pelvic inflammatory disease and risk of ovarian cancer: An updated meta-analysis.Gynecol Oncol2020.
3. Bookman MA, Okamoto A, Stuart G, Yanaihara N, Aoki D, Bacon M, et al.Harmonising clinical trials within the Gynecologic Cancer InterGroup: Consensus and unmet needs from the Fifth Ovarian Cancer Consensus Conference.Ann Oncol2017;28:viii30-viii35.
4. McGee J, Bookman M, Harter P, Marth C, McNeish I, Moore KN, et al.Fifth ovarian cancer consensus conference: Individualized therapy and patient factors.Ann Oncol2017;28:702-710.
5. Landrum LM, Brady WE, Armstrong DK, Moore KN, DiSilvestro PA, O'Malley DM, et al.A phase I trial of pegylated liposomal doxorubicin (PLD), carboplatin, bevacizumab and veliparib in recurrent, platinum-sensitive ovarian, primary peritoneal, and fallopian tube cancer: An NRG Oncology/Gynecologic Oncology Group study.Gynecol Oncol2016;140:204-209.
6. Buechel M, Herzog TJ, Westin SN, Coleman RL, Monk BJ, Moore KN.Treatment of patients with recurrent epithelial ovarian cancer for whom platinum is still an option.Ann Oncol2019;30:721-732.
7. Corrado G, Salutari V, Palluzzi E, Distefano MG, Scambia G, Ferrandina G.Optimizing treatment in recurrent epithelial ovarian cancer.Expert Rev Anticancer Ther2017;17:1147-1158.
8. Madrid Paredes A, Vallejo I, Carrasco M, Valencia C, Artime F, Calleja M.Prescription profile and impact after the pegylated liposomal doxorubicin shortage alert.European Journal of Hospital Pharmacy2015;22:A16.
9. Cannon TL, Lai DW, Hirsch D, Delacure M, Downey A, Kerr AR, et al.Squamous cell carcinoma of the oral cavity in nonsmoking women: A new and unusual complication of chemotherapy for recurrent ovarian cancer?Oncologist2012;17:1541-1546.
10. Gibson JM, Alzghari S, Ahn C, Trantham H, La-Beck NM.The role of pegylated liposomal doxorubicin in ovarian cancer: a meta-analysis of randomized clinical trials.The oncologist2013;18:1022-1031.
11. Lawrie TA, Bryant A, Cameron A, Gray E, Morrison J.Pegylated liposomal doxorubicin for relapsed epithelial ovarian cancer.The Cochrane database of systematic reviews2013;7:CD006910.
12. Rolim LC, da Silva EMK, Flumignan RLG, Abreu M, Dib SA.Cochrane Systematic Review of Acetyl-L-Carnitine for the Treatment of Diabetic Polyneuropathy.Eur J Vasc Endovasc Surg2019;58:e342-e343.
13. Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E, Gebski V, Heywood M, Vasey PA, et al.Pegylated liposomal doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinum-sensitive ovarian cancer in late relapse.J Clin Oncol2010;28:3323-3329.
14. Gladieff L, Ferrero A, De rauglaudre G, Brown C, Vasey P, Reinthaller A, et al.Carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in partially platinum-sensitive ovarian cancer patients: Results from a subset analysis of the CALYPSO phase III trial.Ann Oncol2012;23:1185-1189.
15. Mahner S, Meier W, Du Bois A, Brown C, Lorusso D, Dell'Anna T, et al.Carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in very platinum-sensitive ovarian cancer patients: Results from a subset analysis of the CALYPSO

phase III trial.Eur J Cancer2015;51:352-358.
16. Bafaloukos D, Linardou H, Aravantinos G, Papadimitriou C, Bamias A, Fountzilas G, et al.A randomized phase II study of carboplatin plus pegylated liposomal doxorubicin versus carboplatin plus paclitaxel in platinum sensitive ovarian cancer patients: A Hellenic Cooperative Oncology Group study.BMC Med2010;8:
17. Mutch DG, Orlando M, Goss T, Teneriello MG, Gordon AN, McMeekin SD, et al.Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer.J Clin Oncol2007;25:2811-2818.
18. Ferrandina G, Ludovisi M, Lorusso D, Pignata S, Breda E, Savarese A, et al.Phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in progressive or recurrent ovarian cancer.J Clin Oncol2008;26:890-896.
19. Vergote I, Finkler NJ, Hall JB, Melnyk O, Edwards RP, Jones M, et al.Randomized phase III study of canfosfamide in combination with pegylated liposomal doxorubicin compared with pegylated liposomal doxorubicin alone in platinum-resistant ovarian cancer.Int J Gynecol Cancer2010;20:772-780.
20. Colombo N, Kutarska E, Dimopoulos M, Bae DS, Rzepka-Gorska I, Bidzinski M, et al.Randomized, open-label, phase III study comparing patupilone (EPO906) with pegylated liposomal doxorubicin in platinum-refractory or -resistant patients with recurrent epithelial ovarian, primary fallopian tube, or primary peritoneal cancer.J Clin Oncol2012;30:3841-3847.
21. Banerjee S, Oza AM, Birrer MJ, Hamilton EP, Hasan J, Leary A, et al.Anti-NaPi2b antibody-drug conjugate lifastuzumab vedotin (DNIB0600A) compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer in a randomized, open-label, phase II study.Ann Oncol2018;29:917-923.
22. Kaye SB, Lubinski J, Matulonis U, Ang JE, Gourley C, Karlan BY, et al.Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer.Journal of clinical oncology : official journal of the American Society of Clinical Oncology2012;30:372-379.
23. Wilson MK, Pujade-Lauraine E, Aoki D, Mirza MR, Lorusso D, Oza AM, et al.Fifth ovarian cancer consensus conference of the gynecologic cancer intergroup: Recurrent disease.Ann Oncol2017;28:727-732.
24. Colombo N, Sessa C, du Bois A, Ledermann J, McCluggage WG, McNeish I, et al.ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease.Annals of oncology : official journal of the European Society for Medical Oncology2019;30:672-705.
25. Bergamini A, Pisano C, Di Napoli M, Arenare L, Della Pepa C, Tambaro R, et al.Cisplatin can be safely administered to ovarian cancer patients with hypersensitivity to carboplatin.Gynecol Oncol2017;144:72-76.
26. Gabizon AA, Patil Y, La-Beck NM.New insights and evolving role of pegylated liposomal doxorubicin in cancer therapy.Drug Resistance Updates2016;29:90-106.
27. Blank N, Laskov I, Kessous R, Kogan L, Lau S, Sebag IA, et al.Absence of cardiotoxicity with prolonged treatment and large accumulating doses of pegylated liposomal doxorubicin.Cancer Chemother Pharmacol2017;80:737-743.
28. Crespo G, Sierra M, Losa R, Berros JP, Villanueva N, Fra J, et al.Pegylated liposomal doxorubicin and gemcitabine in a fixed dose rate infusion for the treatment of patients with poor prognosis of recurrent ovarian cancer: A phase Ib study.Int J Gynecol Cancer2011;21:478-485.
29. McGuire WP, Penson RT, Gore M, Herraez AC, Peterson P, Shahir A, et al.Randomized phase II study of the PDGFRα antibody olaratumab plus liposomal doxorubicin versus liposomal doxorubicin alone in patients with platinum-refractory or platinum-resistant advanced ovarian cancer.BMC Cancer2018;18:
30. Pease DF, Peterson BA, Gilles S, Hordinsky MK, Bohjanen KA, Skubitz KM.Development of cutaneous squamous cell carcinoma after prolonged exposure to pegylated liposomal doxorubicin and hand–foot syndrome: a newly recognized toxicity.Cancer Chemother Pharmacol2019;84:217-221.

Tables

Table.1 Characteristics of included studies.

Study	Intervention	No.of participants	Age,years Median (range)	Type of trial	Patient characteristics	Pretreatment status	Main outcomes
Pujade-Lauraine 2010[14]	carbo(AUC5) + PLD 30 mg/m2 q4wks	466	60.5(24-82)	phase III randomized multicenter, open-label trial	PS ROC	After first-or second-line Platinum and taxane-based	PFS, OS, Toxicity
	carbo(AUC5) + PAC 175 mg/m2 q3wks	509	61(27-82)				
Gladieff2012[15]	carbo(AUC5) + PLD 30 mg/m2 q4wks	161	60(24-82)	phase III randomized non-inferiority trial	PS ROC	After first- or second-line platinum- and taxane-based	PFS, Toxicity
	carbo(AUC5) + PAC 175 mg/m2 q3wks	183	60(30-80)				
Mahner2014[16]	carbo(AUC5) + PLD 30 mg/m2 q4wks	131	60(30-80)	phase III randomized multicenter trial	PS ROC	Platinum and taxane-pretreated	PFS, OS, Toxicity
	carbo(AUC5) + PAC 175 mg/m2 q3wks	128	63(27-82)				
Bafaloukos2010[17]	carbo(AUC5) + PLD 45 mg/m2 q4wks	93	62(38-89)	phase II randomized multicenter	PS ROC	One cycle or more Of platinum-based	ORR, OS, Toxicity
	carbo(AUC5) + PAC 175 mg/m2 q3wks	96	63(37-81)				
Mutch2007[18]	PLD 50mg/m2 IVI q4wks	96	62(28-83)	phase III randomized multicenter open-label	PS ROC	Prior platinum-based ≤ 2 prior regimens allowed	PFS, OS, Toxicity
	Gemcitabine 1000mg/m2 D1,8 q3wks	99	59(38-85)				
Ferrandina2008[19]	PLD 40mg/m2 IVI q4wks	76	63(28-80)	phase III randomized multicenter	Partial PS and PR ROC	Failed first-line Platinum or paclitaxel	OS, Toxicity
	Gemcitabine 1000mg/m2 D1,5,8,15 q4wks	77	63(39-79)				
Vergote2009 [20]	PLD 50mg/m2 IVI q4wks	130	60(30-82)	phase III randomized multicenter	platinum-refractory or PR ROC	Failed one second-Line therapy with either topotecan or PLD	Toxicity
	Canfosfamide 1000mg/m2 q3wks	231	60(26-85)				
Vergote2009 [20]	PLD 50mg/m2 IVI q4wks	130	60(30-82)	phase III randomized multicenter	platinum-refractory or PR ROC	Failed one second-Line therapy with either	Toxicity
	Topotecan	87	60(30-				

	1.5mg/m2 D1-5 q3wks		82)			topotecan or PLD	
Colombo2012[21]	PLD 50mg/m2 IVI q4wks	417	59(23-84)	phase III randomized open-label	PR ROC	Failed≥4 cycles of platinum-based or discontinued	PFS, OS, Toxicity
	Patupilone 10mg/m2 IVI q3wks	412	59(25-87)				
Banerjee2018[22]	PLD 40mg/m2 IVI q4wks	48	62(52-86)	phase II randomized open-label	PR ROC	Progressed or relapsed < 6months with a platinum-based	PFS, Toxicity
	LIFA 2.4mg/kg q3wks	47	62(43-83)				
Kaye2012 [23]	PLD 50mg/m2 IVI q4wks	33	53(43-81)	phase II open-label randomized Multicenter	Partial PS and PR ROC	Recurred or progressed < 12 months with platinum-based	PFS, OS, Toxicity
	Olaparib 200mg bid continuously	32	58.5(45-77)				
Kaye2012 [23]	PLD 50mg/m2 IVI q4wks	33	53(43-81)	phase II open-label randomized Multicenter	Partial PS and PR ROC	Recurred or progressed < 12 months with platinum-based	PFS,OS, Toxicity
	Olaparib 400mg bid continuously	32	53.5(35-76)				

Note: OS, overall survival; PFS, progression-free survival; PS, platinum-sensitive; PR, Platinum-resistant; ROC, recurrent ovarian cancer.

Table.2 Risk of bias for included studies.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	other bias
Pujade-Lauraine2010[14]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Gladieff2012[15]	Low risk	Unclear risk	High risk	Low risk	Low risk	Low risk	Low risk
Mahner2014[16]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Bafaloukos2010[17]	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Mutch2007[18]	Low risk	Low risk	High risk	Unclear risk	Unclear risk	High risk	Low risk
Ferrandina2008[19]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Vergote2009[20]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Colombo2012[21]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Banerjee2018[22]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Kaye2012[23]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk

Figures

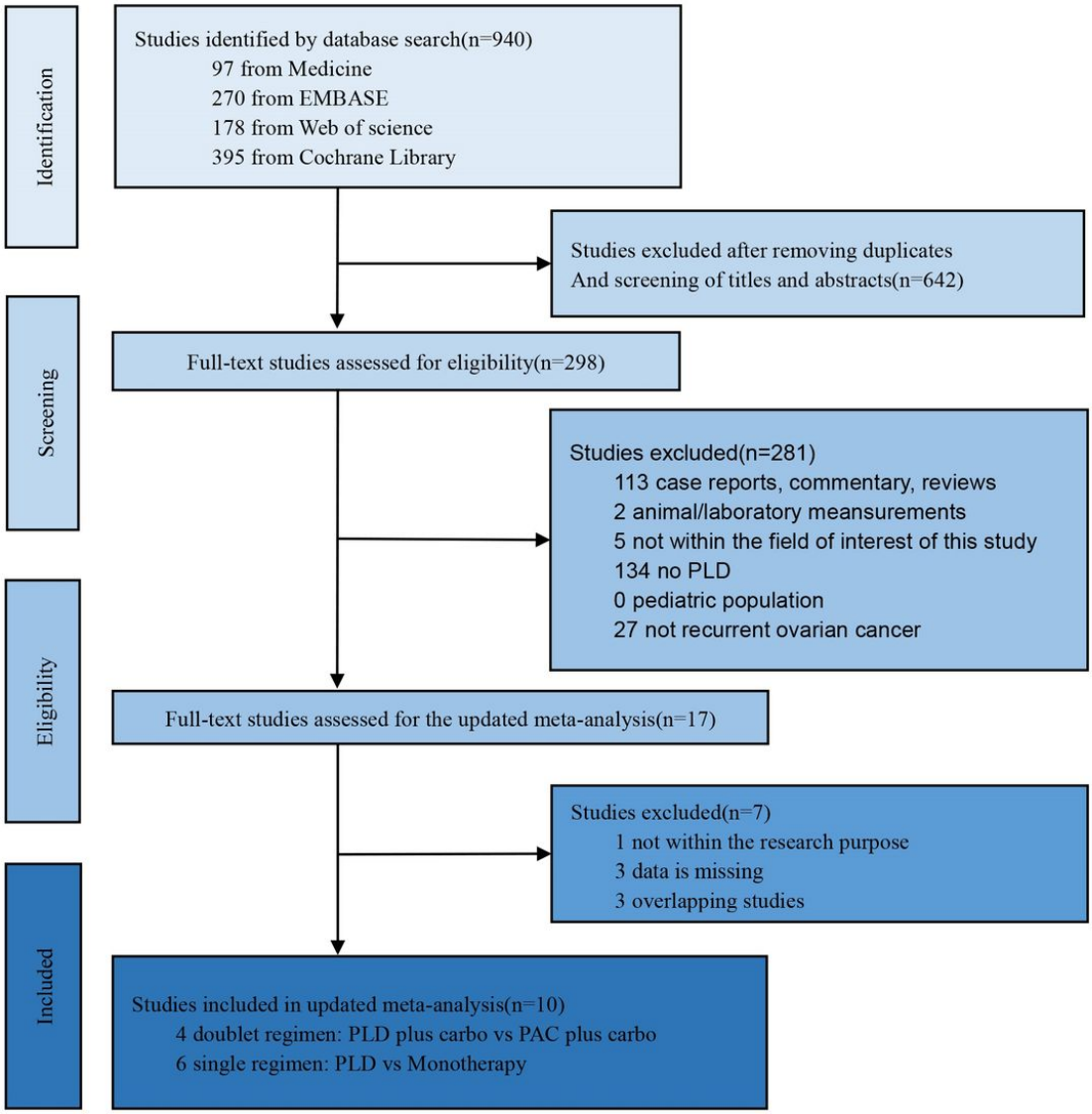

Figure 1

Study flow diagram of searches.

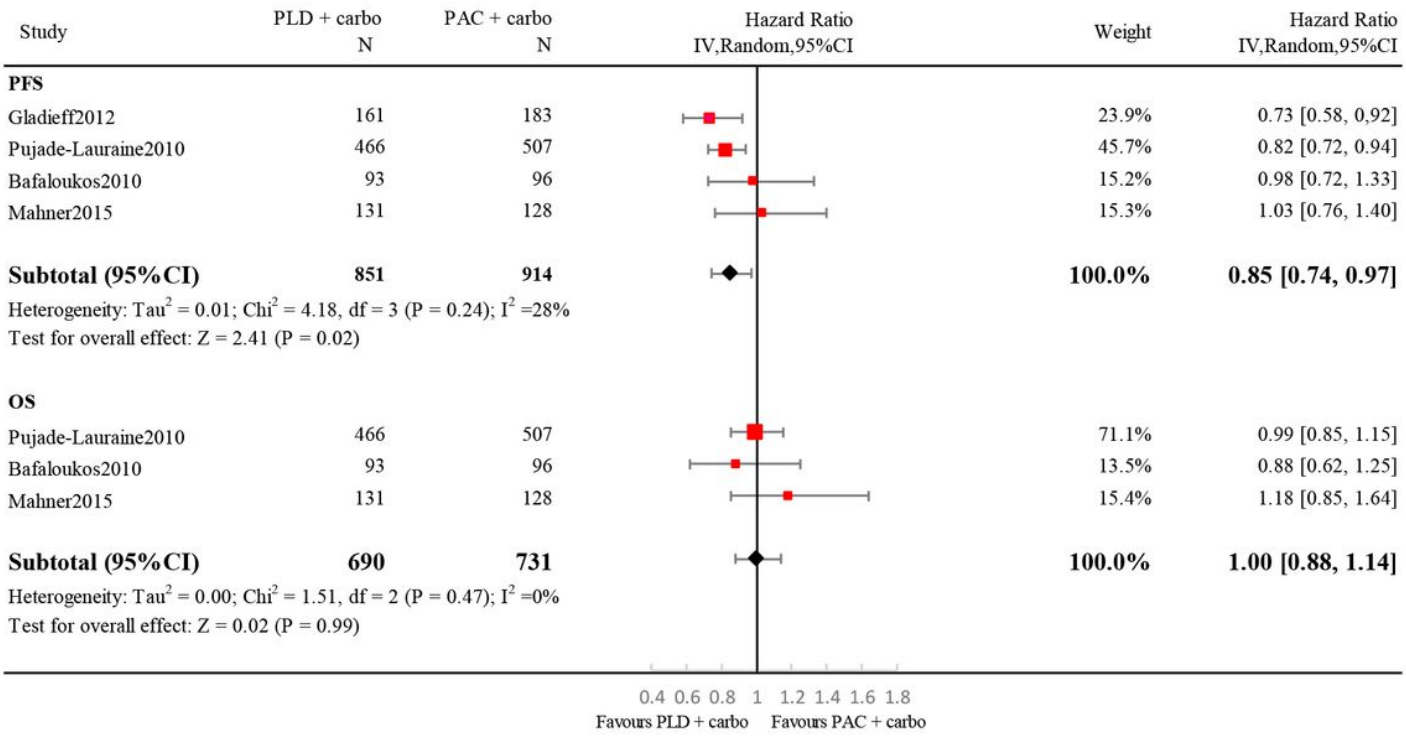

Figure 2

Forest plots of efficacy endpoints. Doublet regimens.

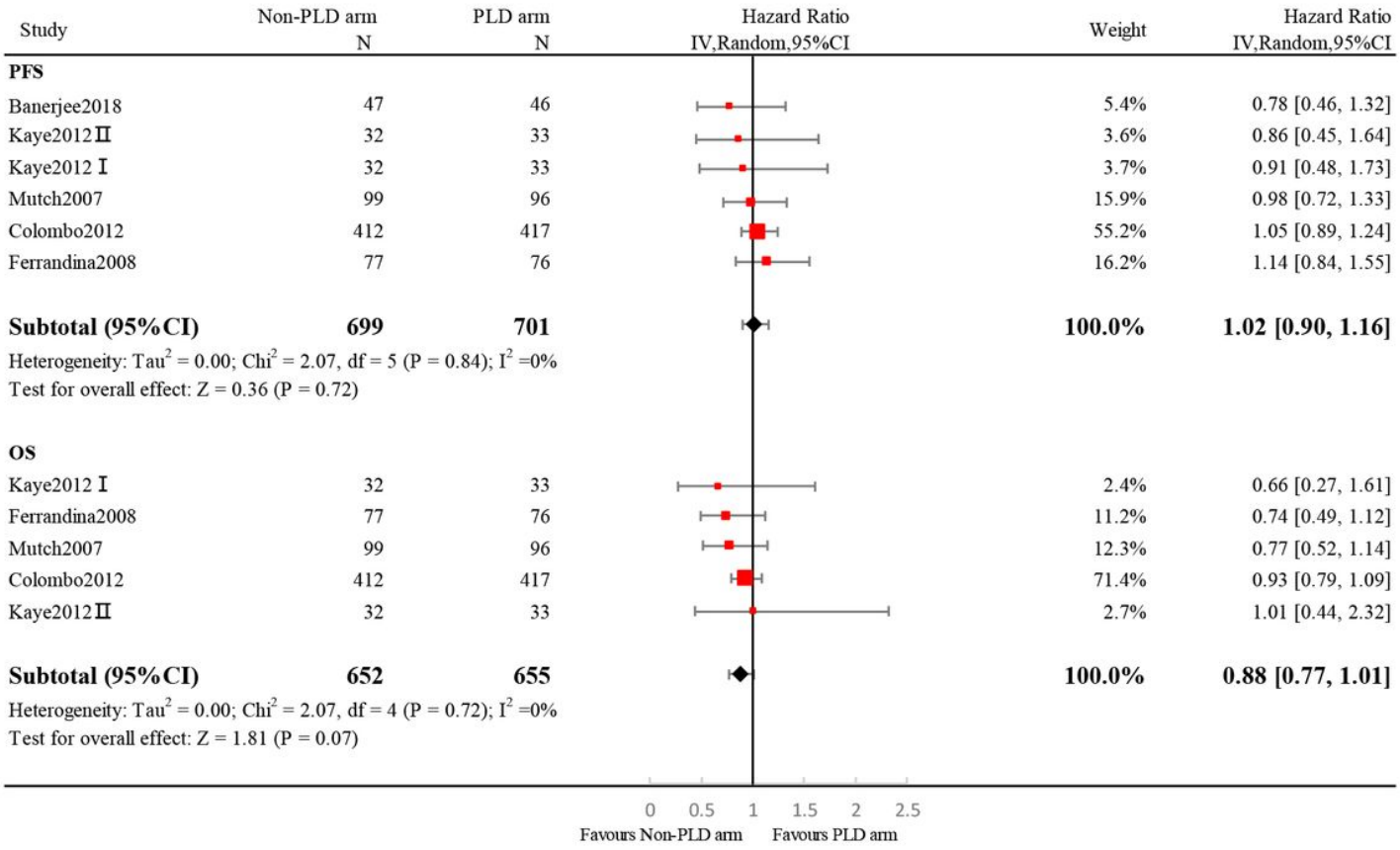

Figure 3

Forest plots of efficacy endpoints. Monotherapy regimens.

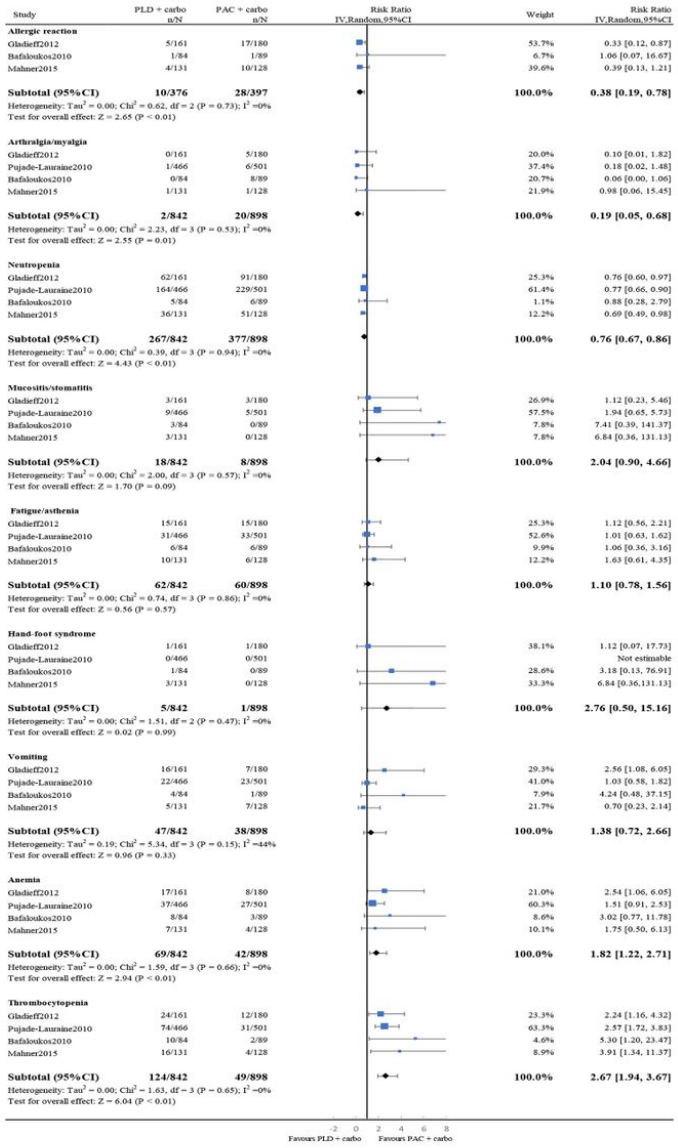

Figure 4

Forest plots of toxicity endpoints for the doublet regimens.

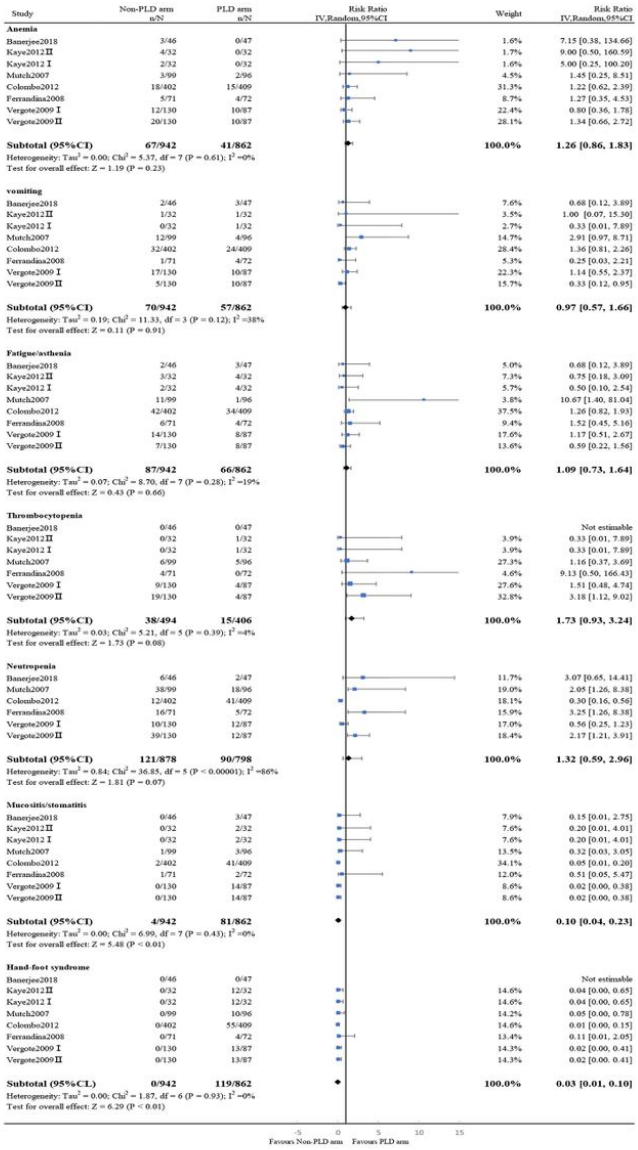

Figure 5

Forest plots of toxicity endpoints for the monotherapy regimens.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterial1.docx
- S2.jpg