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Weekly versus tri-weekly paclitaxel with carboplatin for first-line treatment in women with epithelial ovarian cancer (Review)

Ngoi NYL, Syn NLX, Goh RM, Goh BC, Huang RYJ, Soon YY, James E, Cook A, Clamp A, Tan DSP

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TABLE OF CONTENTS

ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 3
BACKGROUND 5
OBJECTIVES 6
METHODS 6
Figure 1. 9
Figure 2. 10
RESULTS 11
Figure 3. 13
Figure 4. 14
Figure 5. 16
DISCUSSION 18
AUTHORS' CONCLUSIONS 20
ACKNOWLEDGEMENTS 20
REFERENCES 21
CHARACTERISTICS OF STUDIES 25
DATA AND ANALYSES 34
Analysis 1.1. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 1: Progression-free survival 39
Analysis 1.2. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 2: Progression-free survival, subgroup analysis by residual disease 39
Analysis 1.3. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 3: Progression-free survival, subgroup analysis by FIGO stage 40
Analysis 1.4. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 4: Progression-free survival, subgroup analysis by ECOG status 41
Analysis 1.5. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 5: Progression-free survival, subgroup analysis by bevacizumab receipt 42
Analysis 1.6. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 6: Progression-free survival, subgroup analysis by age distribution 43
Analysis 1.7. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 7: Progression-free survival, subgroup analysis by carboplatin schedule 44
Analysis 1.8. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 8: Progression-free survival, subgroup analysis by histotype 44
Analysis 1.9. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 9: Overall Survival 45
Analysis 1.10. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 10: Overall survival, subgroup analysis by residual disease 45
Analysis 1.11. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 11: Overall survival, subgroup analysis by FIGO stage 46
Analysis 1.12. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 12: Overall survival, subgroup analysis by ECOG status 47
Analysis 1.13. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 13: Overall survival, subgroup analysis by bevacizumab receipt 47
Analysis 1.14. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 14: Overall survival, subgroup analysis by age distribution 48
Analysis 1.15. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 15: Overall survival, subgroup analysis by carboplatin schedule in dose-dense arm 48
Analysis 1.16. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 16: Overall survival, subgroup analysis by histotype 49
Analysis 1.17. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 17: Grade 3 or 4 neutropenia 49
Analysis 1.18. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 18: Febrile neutropenia 50

Analysis 1.19. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 19: Grade 3 or 4 anaemia 50
Analysis 1.20. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 20: Grade 3 or 4 leucopenia 50
Analysis 1.21. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 21: Grade 3 or 4 thrombocytopenia 51
Analysis 1.22. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 22: Grade 3 or 4 transaminitis 51
Analysis 1.23. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 23: Grade 3 or 4 fatigue 51
Analysis 1.24. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 24: Grade 3 or 4 myalgia 52
Analysis 1.25. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 25: Grade 3 or 4 arthralgia 52
Analysis 1.26. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 26: Grade 3 or 4 anorexia 52
Analysis 1.27. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 27: Grade 3 or 4 diarrhoea 53
Analysis 1.28. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 28: Grade 3 or 4 vomiting 53
Analysis 1.29. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 29: Grade ≥ 2 neuropathy 54
Analysis 1.30. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 30: Grade 3 or 4 neuropathy 55
Analysis 1.31. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 31: Any-grade alopecia 55
Analysis 1.32. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 32: Any-grade mucositis 56
Analysis 1.33. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 33: Grade 3 or 4 hypersensitivity 56
Analysis 1.34. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 34: Treatment discontinuation 56
Analysis 1.35. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 35: Dose modification 57
APPENDICES 57
HISTORY 59
CONTRIBUTIONS OF AUTHORS 59
DECLARATIONS OF INTEREST 59
SOURCES OF SUPPORT 60
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 60

[Intervention Review]

Weekly versus tri-weekly paclitaxel with carboplatin for first-line treatment in women with epithelial ovarian cancer

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ABSTRACT

Background

Epithelial ovarian cancer is the sixth most common cancer worldwide: 295,414 new cases were diagnosed in 2018, with 184,799 deaths. The lack of an effective screening strategy has led to the majority of women being diagnosed at an advanced stage. For these women, intravenous carboplatin combined with paclitaxel for six cycles is widely accepted as the standard first-line treatment for epithelial ovarian cancer, in combination with debulking surgery. However, there is conflicting evidence regarding the optimal dosing schedule of paclitaxel when combined with carboplatin in this setting.

Objectives

To compare the efficacy and tolerability of intravenous weekly paclitaxel with that of tri-weekly paclitaxel, in combination with intravenous carboplatin, as first-line treatment for epithelial ovarian cancer (defined as epithelial ovarian, primary peritoneal and fallopian tube cancer).

Search methods

We searched CENTRAL, MEDLINE, and Embase databases for relevant studies up to 15 November 2021, using keywords and MeSH terms. We additionally handsearched conference libraries, online clinical trial databases and screened through lists of retrieved references.

Selection criteria

We Included randomised controlled trials (RCTs) comparing weekly paclitaxel in combination with carboplatin versus tri-weekly paclitaxel in combination with carboplatin, for treatment of newly-diagnosed epithelial ovarian cancer.

Data collection and analysis

We used the hazard ratio (HR) to estimate the primary efficacy outcomes progression-free (PFS) and overall survival (OS). We used the risk ratio (RR) to estimate the primary toxicity outcome of severe neutropenia and secondary outcomes of quality of life (QoL) and treatment-related adverse events. Two review authors independently selected studies, extracted data, and assessed risk of bias, using standard Cochrane methodological procedures. We included individual participant data (IPD) from one of the included studies, ICON-8, provided

by the study team. We analysed data using a random-effects model in Review Manager 5.4 software. Additionally, we reconstructed IPD for PFS and OS data from published Kaplan-Meier curves from all studies and subsequently pooled these to analyse the two primary efficacy outcomes.

Main results

From 2469 records, we identified four eligible RCTs with data for 3699 participants. All eligible studies were included in the main meta-analysis and reported on PFS and OS.

There was likely a slight improvement in PFS when paclitaxel was dosed weekly compared to tri-weekly (HR 0.89, 95% confidence interval (CI) 0.81 to 0.98; 4 studies, 3699 participants; moderate-certainty evidence). We found little to no improvement in OS when paclitaxel was dosed weekly compared to tri-weekly (HR 0.92, 95% CI 0.79 to 1.06; 4 studies, 3699 participants; high-certainty evidence). There was likely little to no difference in high-grade (grade 3 or 4) neutropenia when paclitaxel was dosed weekly compared to tri-weekly (RR 1.11, 95% CI 0.86 to 1.43; 4 studies, 3639 participants; moderate-certainty evidence). However, weekly paclitaxel increased high-grade (grade 3 or 4) anaemia when compared to tri-weekly dosing (RR 1.57, 95% CI 1.12 to 2.20; 4 studies, 3639 participants; high-certainty evidence). There may be little to no difference in high-grade neuropathy when paclitaxel was dosed weekly compared to tri-weekly (RR 1.12, 95% CI 0.64 to 1.94; 4 studies, 3639 participants; low-certainty evidence). The overall risk of detection bias and performance bias was low for OS, but was unclear for other outcomes, as treatments were not blinded. The risk of bias in other domains was low or unclear.

We note that OS data were immature for three of the included studies (GOG-0262, ICON-8 and MITO-7).

Authors' conclusions

Weekly paclitaxel combined with carboplatin for first-line treatment of epithelial ovarian cancer likely improves PFS slightly (moderate-certainty evidence) but not OS (high-certainty evidence), compared to tri-weekly paclitaxel combined with carboplatin. However, this was associated with increased risk for high-grade anaemia, treatment discontinuation, dose delays and dose omissions (high- to low-certainty evidence). Our findings may not apply to women receiving bevacizumab in first-line therapy, those receiving treatment in the neo-adjuvant setting, or those with rare subtypes of clear cell or mucinous ovarian cancer.

PLAIN LANGUAGE SUMMARY

Does weekly dosing of paclitaxel improve survival, compared with tri-weekly dosing of paclitaxel in the initial treatment of ovarian cancer?

Background
Ovarian cancer is the sixth most common cancer worldwide. Treatment consists of a combination of surgery and chemotherapy (most commonly including paclitaxel and carboplatin), with the aim to reduce or delay the return of the cancer (known as progression-free survival (PFS)), and improve chances for cancer survival (known as overall survival (OS)). Several clinical trials (studies) have investigated whether the dosing schedule (timing) of paclitaxel affects these outcomes. However, the results from reported studies are conflicting.

The aim of the review
We reviewed the evidence about the effect of different schedules of paclitaxel on survival in women with newly-diagnosed ovarian cancer.

Study characteristics
The evidence is current up to 15 November 2021. We included four studies with a total of 3699 participants. All studies included were randomised controlled trials (clinical trials where people are randomly put into one of two or more treatment groups) of women aged 18 years or older with newly diagnosed ovarian cancer. The studies compared weekly versus tri-weekly dosing of paclitaxel, plus carboplatin.

Main findings
We found that, compared with tri-weekly paclitaxel dosing, weekly paclitaxel plus carboplatin likely slightly improves progression-free survival, although results in little to no difference in overall survival (high-certainty evidence).

For adverse effects, we found that weekly paclitaxel plus carboplatin likely results in little to no difference in severe low neutrophil count (a type of white blood cell that helps to fight infections) (moderate-certainty evidence); increases severe anaemia (haemoglobin level - an important component of red blood cells) (high-certainty evidence) and may result in little to no difference in severe damage to nerves (low-certainty evidence).

Conclusions
Weekly dosing of paclitaxel likely prolongs progression-free survival compared to tri-weekly dosing of paclitaxel, when combined with carboplatin in the initial treatment of ovarian cancer. However, this does not improve overall survival.

Summary of findings 1. Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment of ovarian cancer

Weekly paclitaxel plus carboplatin compared to Three-weekly paclitaxel plus carboplatin for first-line treatment of ovarian cancer

Patient or population: first-line treatment of ovarian cancer
Setting: Hospital
Intervention: Weekly paclitaxel plus carboplatin
Comparison: Three-weekly paclitaxel plus carboplatin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with tri-weekly paclitaxel plus carboplatin	Risk with Weekly paclitaxel plus carboplatin				
Progression-free survival (PFS) follow-up: range 22.3 months to 36.8 months	Study population		HR 0.89 (0.81 to 0.98)	3699 (4 RCTs)	⊕⊕⊕⊖ Moderate [1]	Weekly paclitaxel plus carboplatin likely improves progression-free survival slightly.
	177 per 1000	159 per 1000 (146 to 173)				
Overall survival (OS) follow-up: range 22.3 months to 76.8 months	Study population		HR 0.92 (0.79 to 1.06)	3699 (4 RCTs)	⊕⊕⊕⊕ High	Weekly paclitaxel plus carboplatin results in little to no difference in overall survival.
	67 per 1000	62 per 1000 (53 to 71)				
Haematological adverse event: Grade 3/4 neutropenia follow-up: range 22.3 months to 36.8 months	Study population		RR 1.11 (0.86 to 1.43)	3639 (4 RCTs)	⊕⊕⊕⊖ Moderate [2]	Weekly paclitaxel plus carboplatin likely results in little to no difference in Grade 3/4 neutropenia.
	534 per 1000	593 per 1000 (459 to 764)				
Haematological adverse event: Grade 3/4 anaemia follow-up: range 22.3 months to 36.8 months	Study population		RR 1.57 (1.12 to 2.20)	3639 (4 RCTs)	⊕⊕⊕⊕ High	Weekly paclitaxel plus carboplatin increases Grade 3/4 anaemia .
	158 per 1000	249 per 1000 (177 to 349)				
Neurological adverse event: Grade 3/4 neuropathy, not otherwise specified	Study population		RR 1.12 (0.64 to 1.94)	3639 (4 RCTs)	⊕⊕⊖⊖ Low [1 3]	Weekly paclitaxel plus carboplatin may result in little to no difference in Grade 3/4 neuropathy.
	40 per 1000	45 per 1000 (26 to 78)				

follow-up: range 22.3 months to 36.8 months				

*__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; **OR:** odds ratio; **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.

[1] Downgraded one level due to risk of bias (detection bias as patients and investigators were not blinded).
[2] Downgraded one level for severe statistical heterogeneity.
[3] Downgraded one level due to imprecision.

BACKGROUND

After surgery to remove the ovarian cancer, carboplatin and paclitaxel chemotherapy dosed every three weeks (tri-weekly) for six cycles is widely-accepted as standard first-line treatment for epithelial ovarian cancer. However, it is unclear if different dosing schedules for paclitaxel lead to differences in treatment effectiveness in prolonging time to cancer progression or death.

Description of the condition

Epithelial ovarian cancer is the sixth most common cancer worldwide: 295,414 new cases were diagnosed in 2018, with 184,799 deaths (Bray 2018). The lack of an effective screening strategy and the natural history of the disease contribute to the majority of women being diagnosed at an advanced stage. Epithelial ovarian, primary peritoneal and fallopian tube cancers are classified as a single disease entity due to their shared origin, similar natural history and similar prognosis (Labidi-Galy 2017). In combination with surgical removal of as much visible cancer as possible, intravenous carboplatin (area under curve (AUC) 5 mg/mL to 6 mg/mL) and paclitaxel (175 mg/m^2 to 180 mg/m^2) chemotherapy dosed tri-weekly remains the most widely-adopted approach to first-line therapy for advanced ovarian cancer, and results in a high rate of initial complete response. However, approximately 75% of women eventually relapse within the first two years of diagnosis, leading to only around 30% of women achieving long-term survival (Bukowski 2007; Jemal 2008). Recent studies have investigated the addition of intra-peritoneal paclitaxel and cisplatin, hyperthermic intraperitoneal chemotherapy (HIPEC) (van Driel 2018), as well as novel systemic therapies such as bevacizumab (Tewari 2019) or poly-ADP ribose polymerase inhibitors (PARPi), or both (Gonzalez-Martin 2019; Moore 2018) for the treatment of advanced ovarian cancer, with encouraging results.

Description of the intervention

Intravenous carboplatin and paclitaxel, dosed tri-weekly, remains the widely-accepted standard first-line chemotherapeutic approach for women with epithelial ovarian cancer (Baird 2010). The National Comprehensive Cancer Network has classified carboplatin plus paclitaxel tri-weekly, or carboplatin plus paclitaxel tri-weekly with bevacizumab, as preferred regimens. Other recommended regimens include carboplatin plus paclitaxel weekly, paclitaxel weekly with carboplatin tri-weekly, carboplatin plus docetaxel and carboplatin plus liposomal doxorubicin (National Comprehensive Cancer Network 2021). Similarly, the Gynecologic Cancer InterGroup (GCIG) epithelial ovarian cancer consensus conference statement has listed acceptable front-line regimens to be carboplatin plus paclitaxel tri-weekly, paclitaxel weekly with carboplatin tri-weekly, intraperitoneal cisplatin plus paclitaxel, or carboplatin plus paclitaxel tri-weekly with bevacizumab (Karam 2017).

How the intervention might work

The basis for weekly paclitaxel chemotherapy as a dose-intensification measure arose from the Norton-Simon Regression Hypothesis (Simon 2006). Based on this theory, the rate of tumour regrowth between treatments is proportional to the rate of tumour growth. Administering the same or higher cumulative drug dose over a shorter period of time may potentate tumour-cell kill by minimising the opportunity for tumour regrowth between cycles of chemotherapy. Furthermore, paclitaxel has also been described to have an anti-angiogenic effect when administered weekly (Browder 2000), given that endothelial cell proliferation and migration recovers within four days of chemotherapy administration, and more frequent dosing of chemotherapy is required to sustain angiogenesis inhibition (Browder 2000). Finally, weekly dosing of chemotherapy is potentially less myelosuppressive and may be better tolerated by people with cancer.

Accordingly, weekly dosing of paclitaxel or carboplatin, or both has been shown to be effective and well-tolerated in other cancer types, such as breast cancer (Sparano 2015) and non-small cell lung cancer (Ramalingam 2006), and has been successfully incorporated into treatment paradigms in these cancers. In breast cancer, dose-dense adjuvant therapy for both anthracyclines and taxanes has been shown to be superior to chemotherapy dosed at tri-weekly intervals, in terms of progression-free survival (PFS) and overall survival (OS) (Citron 2003). Weekly paclitaxel has also been repeatedly shown to confer survival benefit over tri-weekly paclitaxel dosing in both the adjuvant and metastatic settings in breast cancer treatment (Sparano 2015).

Why it is important to do this review

The first randomised phase III trial to demonstrate a survival benefit from weekly paclitaxel in epithelial ovarian cancer was JGOG-3016, which found that weekly paclitaxel, dosed at 80 mg/m^2,was associated with improvements in PFS and OS when compared to tri-weekly paclitaxel, dosed at 175 mg/m^2, even at long-term follow-up. However, three other randomised phase III trials have failed to confirm this benefit in the intention-to-treat population (GOG-0262; ICON-8; MITO-7).

Aside from efficacy outcomes, dose-dense and tri-weekly carboplatin and paclitaxel therapy have other potential differences in terms of described toxicity, effect on quality of life (QoL) and cost-effectiveness (Lee 2018). Acknowledging the limitations of direct cross-trial comparison, toxicity outcomes appeared to differ between trials. In JGOG-3016, dose-dense weekly paclitaxel 80 mg/m^2 was associated with an increase in premature therapy discontinuation compared to control and an increased incidence of treatment delays. Yet, chemotherapy completion rates on the weekly chemotherapy arms of MITO-7 and ICON-8 were higher compared to control. High grade anaemia was more frequent in women receiving weekly paclitaxel in both the JGOG-3016 and GOG-0262 studies, compared to respective controls, but was markedly lower in the ICON-8 study, which recruited a predominantly white European population. In the GOG-0262 study, weekly paclitaxel was associated with higher rates of grade 2 or higher sensory neuropathy compared to control, whereas no differences were observed between groups in the JGOG-3016 and ICON-8 studies compared to respective control.

In light of differing conclusions amongst these studies, and the potential benefits of weekly paclitaxel therapy, further research is warranted to clarify the role of weekly paclitaxel, in combination with carboplatin, for epithelial ovarian cancer treatment. A systematic review of individualised participant data is important to determine the treatment effect of weekly paclitaxel dosing in combination with carboplatin compared to standard therapy for first-line epithelial ovarian cancer treatment.

OBJECTIVES

To compare the efficacy and tolerability of intravenous weekly paclitaxel with that of tri-weekly paclitaxel, in combination with intravenous carboplatin, as first-line treatment for epithelial ovarian cancer (defined as epithelial ovarian, primary peritoneal and fallopian tube cancer).

METHODS

Criteria for considering studies for this review

Types of studies

We considered only randomised controlled trials (RCTs) as studies in this review and meta-analysis.

Types of participants

We included studies of adult women, 18 years or older, with newly diagnosed epithelial ovarian cancer, International Federation of Gynecology and Obstetrics (FIGO) Stage I to IV.

Types of interventions

The intervention was carboplatin, area under curve (AUC) to a total dose of 5 mg/mL/min to 6 mg/mL/min per cycle, combined with weekly paclitaxel, including metronomic (similar cumulative dosage) or dose-dense (increased cumulative dosage) paclitaxel. We defined the control therapy as carboplatin AUC 5 mg/mL to 6 mg/mL, combined with paclitaxel 175 mg/m^2 to 180 mg/m^2, dosed every three weeks. Other chemotherapeutic agents, including cisplatin, molecular therapies (such as those which target the epidermal growth factor receptor) and immunotherapy were allowed, but must have been given in both intervention and control groups.

Types of outcome measures

Primary outcomes

Primary efficacy outcomes of interest were progression-free survival (PFS) and overall survival (OS).

- PFS, defined as time from randomisation to disease progression or death from any cause.
- OS, defined as time from randomisation to death from any cause.
- The primary toxicity outcome of interest was the risk of severe neutropenia, defined as grade 3 or 4 neutropenia classified according to Common Terminology Criteria for Adverse Events (CTCAE) version 2.0, 3.0 and 4.0 (CTCAE 2018).

Secondary outcomes

- Adverse events, classified according to CTCAE version 2.0, 3.0 and 4.0. We extracted and grouped grades of toxicity as:
  - haematological: anaemia, thrombocytopenia, leucopenia, haemorrhage;
  - cardiac: bradycardia, atrial fibrillation;
  - neurological: peripheral and central;
  - skin: nail disorders, alopecia, stomatitis, mucositis, allergy;
  - gastrointestinal: diarrhoea, anorexia, nausea, vomiting, liver dysfunction, proctitis.
- Quality of life (QoL), measured using a scale that has been validated through reporting of norms in a peer-reviewed publication, such as the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Ovarian 28 (EORTC-OV28) or the Functional Assessment of Cancer - Ovarian (FACT-O) questionnaire.

Search methods for identification of studies

We adapted the search strategy from the *Cochrane Handbook for Systemic Reviews of Interventions* (Lefebvre 2021). We did not apply any language or date restrictions, and considered both full-text and abstract publications.

Electronic searches

We searched the following electronic databases.

- The Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group's Trial Register (searched 15 November 2021)
- Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 11) in the Cochrane Library (searched 15 November 2021)
- MEDLINE Ovid (1946 to 15 November 2021)
- Embase (1980 to week 45, 2021)

The CENTRAL, MEDLINE and Embase search strategies are presented in Appendix 1Appendix 2, and Appendix 3, respectively.

Searching other resources

We identified all relevant articles on PubMed and carried out a further search for newly published articles using the 'related articles' feature. We searched references of retrieved articles for relevant articles.

To identify ongoing trials, we searched trials registries at: www.clinicaltrials.gov and www.cancer.gov/clinicaltrials. If searches identified ongoing trials without published data, we planned to contact the principal investigators to request the relevant data. We handsearched the citation lists of included studies, key textbooks and previous systematic reviews to identify further reports of trials. We also performed a handsearch of the reports of conferences in the following sources: Gynecologic Oncology (Annual Meeting of the American Society of Gynaecologic Oncologists), International Journal of Gynaecologic Cancer (Annual Meeting of the International Gynaecologic Cancer Society), Annual Meeting of European Society of Medical Oncology (ESMO), Annual Meeting of the American Society of Clinical Oncology (ASCO), European Society of Gynaecological Oncology (ESGO).

Data collection and analysis

Selection of studies

We downloaded all titles and abstracts retrieved by electronic searching into a reference management database and removed any duplicates (www.mendeley.com/). Two review authors (NLS, RMG) independently examined the remaining references and excluded any studies which did not meet the inclusion criteria. We obtained full-text copies of potentially relevant references. Two review authors (NLS, NYN) independently assessed the eligibility of the retrieved papers and resolved any disagreements through discussion, consulting a third review author (DST) if necessary. During the course of screening the literature, we documented the overall number of studies identified, as well as the excluded studies

and reasons for exclusion. Where available directly from the trial study team, we obtained individual participant data (IPD).

Data extraction and management

We used the full-text versions of the identified eligible studies to retrieve the data for analysis. The study team from one study provided IPD directly to the review authors (ICON-8). We performed data extraction according to the guidelines proposed by Cochrane (Li 2021).Two review authors (NLS, RMG) independently extracted study characteristics and outcome data from included studies onto a pre-piloted data collection form. A second review author (NYN) double-checked that the data were entered correctly by comparing the data presented with the study reports. The extracted data included the following information.

- 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, including ethnicity
  - Age
  - Comorbidities
  - Other baseline characteristics, e.g. stage, grade, histotype
- Intervention details
  - Choice, dose intensity and frequency of platinum agent
  - Dose and frequency of paclitaxel
  - Route of paclitaxel administration
  - Details of radiotherapy and debulking surgery if applicable
  - Details of targeted therapy if applicable
- Risk of bias in study
- Duration of follow-up
- Outcomes: for each outcome, we extracted the outcome definition and unit of measurement (if relevant).
- Results: we extracted the number of participants allocated to each intervention group, the total number analysed for each outcome, and the number of missing participants. We collected the following types of data.
  - For time-to-event data (survival and disease progression), we extracted the log of the hazard ratio (log (HR)) and its standard error from trial reports. If these were not reported, we attempted to estimate the log (HR) and its standard error using the methods of Parmar 1998.
  - For dichotomous outcomes (e.g. adverse events), we extracted the number of women in each treatment arm who experienced the outcome of interest and the number of women assessed at endpoint, in order to estimate a risk ratio.
  - For continuous outcomes, we extracted the final value and standard deviation of the outcome of interest and the number of women assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference between treatment arms and its standard error.

Assessment of risk of bias in included studies

We assessed the risk of bias of included studies using the Cochrane risk of bias tool, which assesses the explicit reporting of the following individual elements for RCTs (Higgins 2011).

- Selection bias: random sequence generation and allocation concealment
- Performance bias: blinding of participants and personnel (women and treatment providers)
- Detection bias: blinding of outcome assessment
- Attrition bias: incomplete outcome data
- Reporting bias: selective reporting of outcomes

Two review authors (NLS, RMG) applied the risk of bias tool independently and resolved any differences by discussion or by appeal to a third review author (NYN). We judged each item to be at high, low or unclear risk of bias, as set out in the criteria provided by Higgins 2011, and provided a quote from the study report or a statement, or both, as justification for the judgement for each item in the risk of bias table. These results are summarised in both a risk of bias graph and a risk of bias summary diagram. When interpreting treatment effects and meta-analyses, we took into account the risk of bias for the studies that contributed to that outcome. Please see Appendix 4 for the full risk of bias criteria.

Measures of treatment effect

For time-to-event data, we described the treatment effect using a hazard ratio (HR) with corresponding 95% confidence intervals (CI). For each study, we used IPD if available from the study team. If IPD were not available, we extracted information about time-to-event outcomes using the methods described by Guyot 2012.

For dichotomous outcomes, we analysed data based on the number of events and the number of women assessed in the intervention and comparison groups, which we then used to calculate the risk ratio (RR) and corresponding 95% CI.

For continuous outcomes, we analysed data based on the mean, standard deviation (SD) and number of women assessed for both the intervention and comparison groups to calculate mean difference (MD) between treatment arms with a 95% CI. If a trial reported the MD without giving the data for each group separately, we used this to report the study results. If more than one study measured the same outcome using different tools, we calculated the standardised mean difference (SMD) and 95% CI using the inverse variance method in RevMan 5 (Review Manager 2020).

Unit of analysis issues

The unit of analysis was the individual participant. For studies that had multiple treatment groups, we divided the 'shared' comparison group into the number of treatment groups and treated the split comparison group as independent comparisons.

Dealing with missing data

We dealt with missing data as suggested in the Chapter 10.12, Cochrane Handbook for Systematic Reviews (Higgins 2021), whereby we contacted study authors to obtain missing data (participant, outcome, or summary data). We did not impute any missing outcome data for any of the outcomes. We reported on the levels of loss to follow-up and assessed this as a source of potential

bias. The potential impact of missing data on the conclusions of this review are discussed.

Assessment of heterogeneity

We assessed the degree of heterogeneity between studies. Where we considered studies to be similar enough (in terms of participants, settings, intervention and outcome measures) to allow pooling of data using meta-analysis, we assessed the degree of heterogeneity by visual inspection of forest plots, by estimation of the percentage heterogeneity between studies which cannot be ascribed to sampling variation (I^2 statistic) (Higgins 2003), by a formal statistical test of the significance of the heterogeneity (Chi^2) (Deeks 2001) and, where possible, by subgroup analyses. When using the I^2 statistic to quantify possible heterogeneity, substantial heterogeneity was detected by $I^2 > 50\%$. A low P value ($P < 0.10$) in the Chi^2 test indicated heterogeneity. If there was evidence of substantial clinical, methodological or statistical heterogeneity across included studies we did not report pooled results from meta-analysis but instead used a narrative approach to data synthesis. We considered pooling results through meta-analysis even when there was substantial heterogeneity, if the direction of effect appeared to be consistent across studies.

Assessment of reporting biases

In a meta-analysis of more than 10 studies, funnel plots corresponding to the primary outcome would be examined to assess the potential for small study effects such as publication bias. Funnel plot asymmetry would be assessed visually, and exploratory analyses would be performed to investigate any asymmetry found (Sterne 2011). As our review only included four studies, this was not possible.

Data synthesis

As sources of variation are likely between studies, we pooled the study results using the random-effects model in Review Manager 2020, with inverse variance for meta-analysis (DerSimonian 1986). For time-to-event data, we pooled hazard ratios using the generic inverse variance facility of Review Manager 2020.

For dichotomous outcomes, we calculated the RRs as appropriate for each study then pooled them. For continuous outcomes, we pooled the MDs between the treatment arms at the end of follow-up when all studies measured the outcome on the same scale; otherwise we pooled the SMDs.

We only undertook meta-analyses when we felt them to be meaningful, that is, if the treatments, participants and the underlying clinical question were similar enough for pooling to make sense. We planned to report any skewed data as medians and interquartile ranges.

Reconstruction and synthesis of individual participant data

We reconstructed participant-level survival data from published Kaplan-Meier curves using validated algorithms by Guyot and colleagues (Freeman 2020; Guyot 2012; Papadimitropoulou 2020; Song 2020; Syn 2020; Wei 2017). However, we did not have to reconstruct the data from the ICON-8 study because the ICON-8 investigators provided the original participant-level survival time. Briefly, we downloaded, preprocessed, and digitised raster images of survivor curves to obtain their step function, including the timings of the steps (Guyot 2012). We used additional information such as number-at-risk tables and total number of events, when reported, to further improve the calibration of the reconstruction algorithm (Guyot 2012). We then recovered time-to-event information on individual women by solving the inverted Kaplan-Meier product-limit equations (Guyot 2012). Side-by-side comparisons of reconstructed and original curves demonstrated that the algorithms robustly recovered participant-level survival time from published studies.

We analysed time-to-event endpoints of PFS and OS using both the one-stage method of Guyot 2012 (i.e. using reconstructed or original individual participant data, as shown in the Kaplan Meier plots in Figure 1 and Figure 2), and a two-stage approach (i.e. the prespecified inverse variance-weighted meta-analyses, as shown in the forest plots (Analysis 1.1 and Analysis 1.9). For one-stage meta-analyses, we used the Kaplan-Meier method to calculate OS. We carried out the one-stage meta-analyses using Cox-proportional hazards models, which address between-study heterogeneity using a variety of approaches (Bowden 2011; Debray 2013; de Jong 2020; Smith 2005). We regarded the shared-frailty model to be the most robust approach, as it most explicitly incorporates a (gamma-distributed) random-effects term to account for between-study heterogeneity. As sensitivity analysis, we also employed stratified Cox models, which adjust for inter-study heterogeneity by allowing participants from a particular study share a baseline hazard specific to that study (Bowden 2011; Debray 2013; de Jong 2020; Smith 2005). As a final sensitivity analysis, we also fitted marginal Cox models, which assume that no heterogeneity exists among studies. We calculated median follow-up using the reverse Kaplan-Meier method (Schemper 1996), and one-stage meta-analyses were conducted in Stata version 16·1 (Stata 2019).

Figure 1. PRISMA Flow Diagram

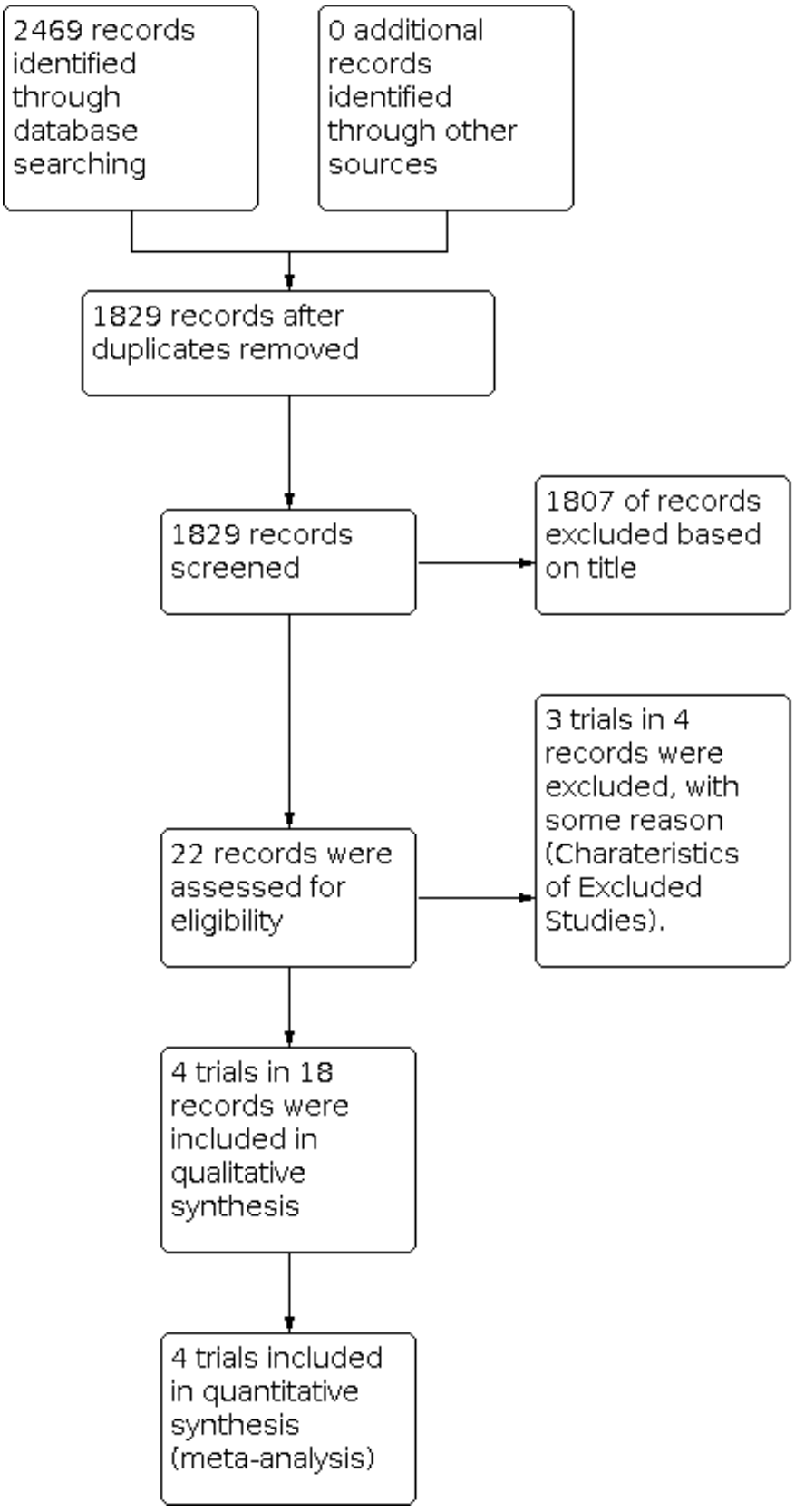
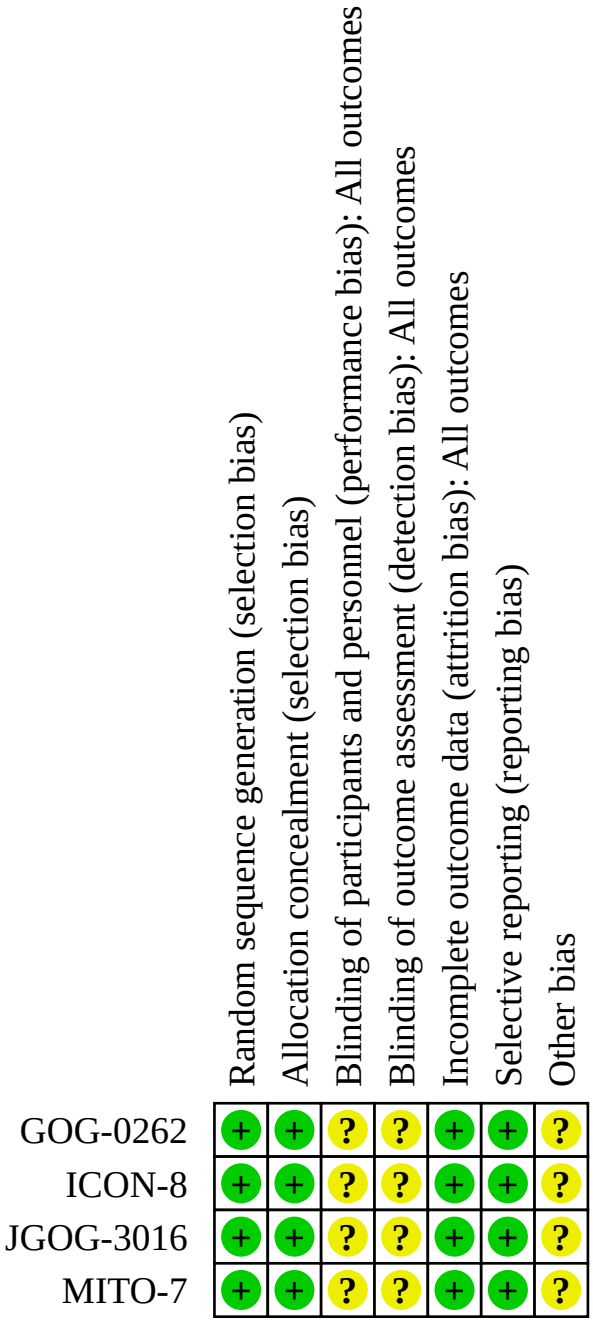


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses for the following factors.

- Studies conducted in Asia or with a majority of Asian women versus studies conducted in Western countries or with a majority of white women
- Metronomic (similar cumulative dosage) versus dose-dense (increased cumulative dosage) dosing schedule

- Targeted therapy versus no targeted therapy
- Completeness of debulking surgery, residual disease < 1 cm versus residual disease > 1cm
- Intraperitoneal route (injection into the peritoneum (body cavity)) of administration versus non-intraperitoneal

We considered factors such as age, stage, type of intervention, length of follow-up and risk of bias status in the interpretation of any heterogeneity.

Sensitivity analysis

If we had identified sufficient studies, we would have assessed the robustness of primary outcome data by analyses of the type of publication (e.g. full-text publication or abstract) and maturity of results. We would have performed sensitivity analyses for studies with unclear or high risk of bias.

Summary of findings and assessment of the certainty of the evidence

We used the GRADEprofiler software to assist with the preparation of the summary of findings table (GRADEpro GDT). The summary of findings table presents the review's main findings in a table format, and provide key information about the best estimate of the magnitude of the effect, in relative terms, and absolute differences for each relevant comparison of alternative management strategies, numbers of participants and studies addressing each important outcome, and the rating of the overall confidence in effect estimates for the comparisons in an outcome-specific manner.

We assessed the certainty of evidence as 'high', 'moderate', 'low' or 'very low' using the GRADE approach (GRADE Working Group 2004; Schünemann 2021), which evaluates studies on five domains: study limitations (risk of bias), consistency, imprecision, indirectness and publication bias. Two review authors (NLS, RMG) independently rated the certainty for each outcome. They resolved any disagreements by appeal to a third (NYN) or fourth review author (DST) if necessary.

The outcomes included in the summary of findings table are:

- progression-free survival;
- overall survival;
- haematological adverse events: neutropenia;
- haematological adverse events: anaemia;
- neurological adverse events.

RESULTS

Description of studies

Overall, we identified 2469 potentially relevant records up to November 2021. Of these, we screened 1829 records after removing duplicates, and excluded 1807 records that did not fulfil our predefined inclusion criteria. We retrieved the remaining 22 publications as full-text or abstract publications for more detailed evaluation. Of these references, we excluded three studies (reported in four references). In total, we identified four eligible studies reported in 18 references, which included a total of 3699 women, and formally included them in this review.

Results of the search

The PRISMA flow diagram is shown in Figure 1.

Included studies

This review included four studies (GOG-0262; ICON-8; JGOG-3016; MITO-7). The ICON-8 study team supplied Individual participant data, and we extracted the data for all other studies from publications. All studies were fully published, with full-text data available (Characteristics of included studies).

Design

Of the four studies, three were two-armed RCTs (GOG-0262; JGOG-3016; MITO-7), and one was a three-armed RCT (ICON-8). One study recruited women between 2003 and 2005 (JGOG-3016), whereas three studies (GOG-0262; ICON-8; MITO-7) recruited women between the period of 2008 to 2014.

Participants

A total of 3717 women with newly diagnosed epithelial ovarian cancer were recruited across all studies (GOG-0262: 692 women, ICON-8: 1566 women, JGOG-3016: 637 women, MITO-7: 822 women), and we included 3699 women in this review. In two studies, women with FIGO stages II to IV were eligible (GOG-0262; JGOG-3016), and in the remaining two studies women with FIGO stages IC to IV were eligible (MITO-7; ICON-8). In the GOG-0262 study, women with stage II disease must have had no residual lesions larger than 1 cm in the greatest dimension. In the ICON8 study, women with stage IC-IIA disease must have had mandatory high-risk histological subtype. Amongst all studies, the majority of women presented with advanced stage (FIGO III-IV) disease (GOG-0262: stage III 67%, stage IV 30%; ICON-8: stage III 58%, stage IV 16%, JGOG-3016: stage III 66%, stage IV 16%, MITO-7: stage III 59%, stage IV 24%).

After primary or interval debulking surgery, the amount of residual disease was described in four studies (GOG-0262: absence of residual macroscopic disease = 24%, not fully assessed = 13%; ICON-8: residual < 1 cm in size = 28%, residual disease > 1cm in size = 14%, inoperable disease = 2%; JGOG-3016: residual disease > 1 cm = 54%, residual disease < 1cm in size = 46%, MITO-7: absence of macroscopic residual disease = 28%, residual disease ≤ 1cm = 12%, residual disease > 1 cm = 23%, inoperable disease = 25%).

The median age of women recruited in three studies was between 57 and 62 years (JGOG-3016: 57 years, MITO-7: 59.5 years, ICON-8: 61 years). The median age of women recruited was not stated in GOG-0262 however, 46% of women were described as being of age < 60 years. Three studies reported the distribution of participants' performance status (PS) by the Eastern Cooperative Oncology Group (ECOG) scale (Oken 1982). The majority of women were of excellent performance status (ECOG 0 to 1) in three studies (ICON-8: 92%, JGOG-3016: 90%, MITO-7: 97%). The distribution of participants' performance status was not described in GOG-0262 however, all women had ECOG PS of 0 to 2.

The histological subtype of epithelial ovarian cancer amongst women recruited was predominantly serous for all four studies (GOG-0262: 88%, ICON-8: 72%, JGOG-3016: 56%, MITO-7: 70%).

Location

The included studies were conducted in different geographic regions. Recruitment for GOG-0262 took place in the USA, Canada and South Korea, while ICON-8 recruited from the UK, Australia, New Zealand, Mexico, Ireland and South Korea. JGOG-3016 recruited women exclusively from Japan, while the MITO-7 study recruited women from Italy and France. The ethnicity of recruited women was reported by two studies: JGOG-3016 recruited exclusively Japanese women, while 85% of women on GOG-0262 were non-Hispanic White.

Intervention

Women in the included studies were treated with varying schedules of carboplatin combined with paclitaxel as front-line treatment for epithelial ovarian cancer. The included studies utilised the following regimens.

- GOG-0262 - intravenous carboplatin AUC 6 mg/mL + paclitaxel 175 mg/m^2 +/- bevacizumab 15 mg/kg every three weeks versus intravenous carboplatin AUC 6 mg/mL +/- bevacizumab 15 mg/kg every three weeks + paclitaxel 80 mg/m^2 weekly for six cycles
- ICON-8 - intravenous carboplatin AUC 5 mg/mL or 6 mg/mL + paclitaxel 175 mg/m^2 every three weeks versus intravenous carboplatin AUC 5 mg/mL or 6 mg/mL every three weeks + paclitaxel 80 mg/m^2 weekly versus intravenous carboplatin AUC 2 mg/mL + paclitaxel 60 mg/m^2 weekly for six cycles
- JGOG-3016 - intravenous carboplatin AUC 6 mg/mL + paclitaxel 180 mg/m^2 every three weeks versus intravenous carboplatin AUC 6 mg/mL every three weeks + paclitaxel 80 mg/m^2 weekly for six cycles
- MITO-7 - intravenous carboplatin AUC 6 mg/mL + paclitaxel 175 mg/m^2 every three weeks versus intravenous carboplatin AUC 2 mg/mL + paclitaxel 60 mg/m^2 weekly for six cycles

None of the women received bevacizumab or targeted therapy in the ICON-8, JGOG-3016 and MITO-7 studies, while 84% of women also received bevacizumab in the GOG-0262 study.

Outcomes

Primary outcome measures

All studies analysed PFS, which was defined similarly amongst included studies as the time from date of randomisation to death or disease progression. The median follow-up for PFS outcomes was 28.5 months (range 22.3 to 36.8 months) in the four included studies (GOG-0262; ICON-8; JGOG-3016; MITO-7). All studies analysed OS, and the median observation times for OS were 76.8 months (JGOG-3016), 28 months (GOG-0262), 36.8 months (ICON-8), and 22.3 months (MITO-7). No P values were available for the analyses of OS in three studies, as these analyses remained immature with fewer events occurring than were prespecified (GOG-0262ICON-8; MITO-7). All studies measured and reported toxicity and safety.

Secondary outcome measures

All studies reported quality of life, adverse events and treatment discontinuation.

Quality of life measures

Three studies utilised the Functional Assessment of Cancer Therapy (FACT)-Ovary (FACT-O) questionnaire (Basen-Engquist 2001) for assessing changes to women' quality of life (QoL) while receiving study treatments (JGOG-3016; GOG-0262; MITO-7). The ICON-8 study assessed quality of life measures using the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ)-C30 (Aaronson 1993), QLQ-OV28 (Greimel 2003), and EuroQol Group EQ5D (EuroQol 1990) tools. The time points for assessing QoL differed amongst included studies. In the GOG-0262 study, assessments were performed at baseline, prior to cycle four, three weeks after cycle six, 36 weeks after cycle one and 63 weeks after cycle one. In the ICON-8 study, QoL assessment was performed at baseline, before each chemotherapy cycle and then six-weekly until nine months, three-monthly until two years and six-monthly until five years. In the JGOG-3016 study, QoL assessment was performed at baseline, after cycles three and six and at 12 months after randomisation. In the ICON-8 study, QoL assessment was performed at baseline, before each chemotherapy cycle and then every six weeks until nine months, every three months until two years and every six months until five years. In the MITO-7 study, QoL assessment was performed at baseline, then every week for nine weeks.

Toxicity

Three studies scored toxicity using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (GOG-0262; ICON-8; MITO-7), whereas the JGOG-3016 study used CTCAE version 2.0 (CTCAE 2018).

Excluded studies

We excluded three studies after evaluation of their full-text publications. The reasons for their exclusion were as follows.

- We excluded the Shen 2005 study due to concerns regarding its reported methods. Under 1:1 randomisation, it would be expected that 50% of the total 125 women to be allocated to each arm on this study. However, the study reported having 51 and 74 women in each arm, respectively. This was very unlikely to be due to chance. Under the exact binomial test, the chance of having 51 and 74 women in each arm, assuming 1:1 randomisation, is 0.86%
- The Du 2015 study was not suitably informative, as it did not report the number of death events, making it impossible to accurately extract PFS and OS events from reported data. Furthermore, severity of toxicity was not reported using CTCAE criteria, so this could not be analysed with the included studies.
- One study utilised carboplatin AUC 2 mg/mL + paclitaxel 60 mg/m^2 weekly on days 1, 8 and 15 of a four-week cycle as an intervention arm. The review authors agreed that the dose-intensity of paclitaxel on this regimen was too low for it to be included (Falandry 2021).

Excluded studies are described further in Characteristics of excluded studies.

Ongoing studies

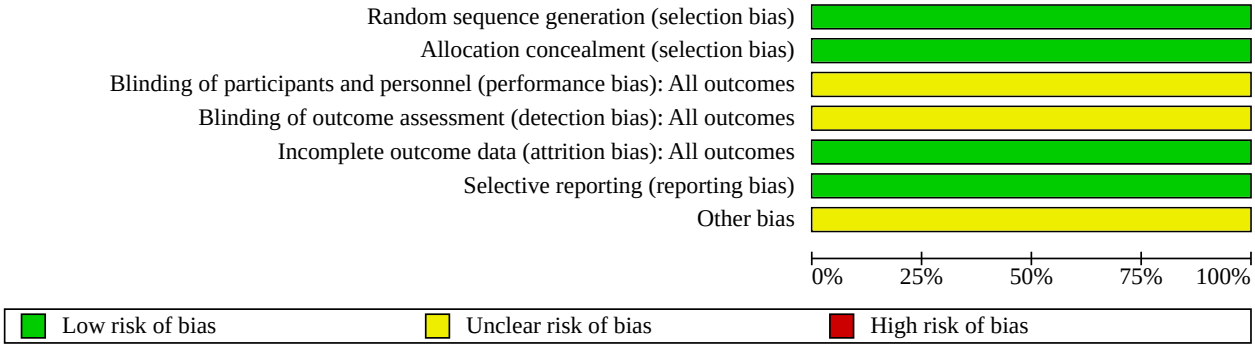
We identified one relevant ongoing study. ICON8B (CRUK/13/023) is an international RCT randomising women with newly-diagnosed advanced ovarian, fallopian tube or primary peritoneal cancer to one of two arms; group B1: intravenous carboplatin, paclitaxel and bevacizumab every three weeks for 18 weeks followed by bevacizumab continuing alone for approximately 11 months, or group B2: intravenous carboplatin every three weeks, paclitaxel

every week and bevacizumab every three weeks for 18 weeks followed by bevacizumab continuing alone for approximately 11 months. This study has completed recruitment. However, study results have not yet been reported and are expected to be released in 2023.

Risk of bias in included studies

The risk of bias assessments for included studies are summarised in Characteristics of included studies, Figure 2 and Figure 3.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

All studies used central allocation to allocate women to treatment. All studies which described central allocation utilised a computer-generated central minimisation procedure to ensure that equal numbers of women received each study treatment based on prespecified stratification factors (low risk of bias). All studies utilised disease status with respect to cytoreduction procedure and participant performance status as stratification factors. Three studies used disease stage as an additional stratification factor (GOG-0262; ICON-8; JGOG-3016). Only one study stratified EOC histotype into subgroups 'serous/others' versus 'clear cell/mucinous' (JGOG-3016). As the GOG-0262 study allowed women to opt for bevacizumab therapy, the decision whether to use bevacizumab therapy was an additional stratification factor for this study.

Blinding

None of the studies blinded participants and investigators to the allocated treatment. OS outcomes would not be influenced by the presence or absence of blinding, therefore performance and detection bias for this outcome would be low. However, the lack of blinding may affect other study outcomes such as PFS and QoL. Therefore, we judged all studies to be 'unclear' for this domain.

Incomplete outcome data

Three studies described missing outcome data in detail (ICON-8; JGOG-3016; MITO-7). Missing outcome data numbers were balanced across groups in JGOG-3016 and MITO-7, but were higher in group 2 of ICON-8 compared to groups 1 and 3 (12 women lost to follow-up or withdrawn compared to four and five women each in groups 1 and 3, respectively). GOG-0262, ICON-8 and JGOG-3016 analysed all randomised women, whereas MITO-7 excluded women who had withdrawn consent immediately after randomisation. As the absolute numbers of women who had missing data was small, and detailed descriptions were provided in three of four studies, it is unlikely that the missing data introduced bias to the main meta-analysis. Thus, we assessed attrition bias to be 'low'.

Selective reporting

All studies reported prespecified primary outcomes (GOG-0262: PFS; ICON-8: PFS, OS; JGOG-3016: PFS; MITO-7: PFS, QoL). Therefore, the risk of reporting bias was low.

Other potential sources of bias

We did not identify any other potential sources of bias.

Effects of interventions

See: **Summary of findings 1** Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment of ovarian cancer

Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment

Primary outcome

Progression free survival (PFS)

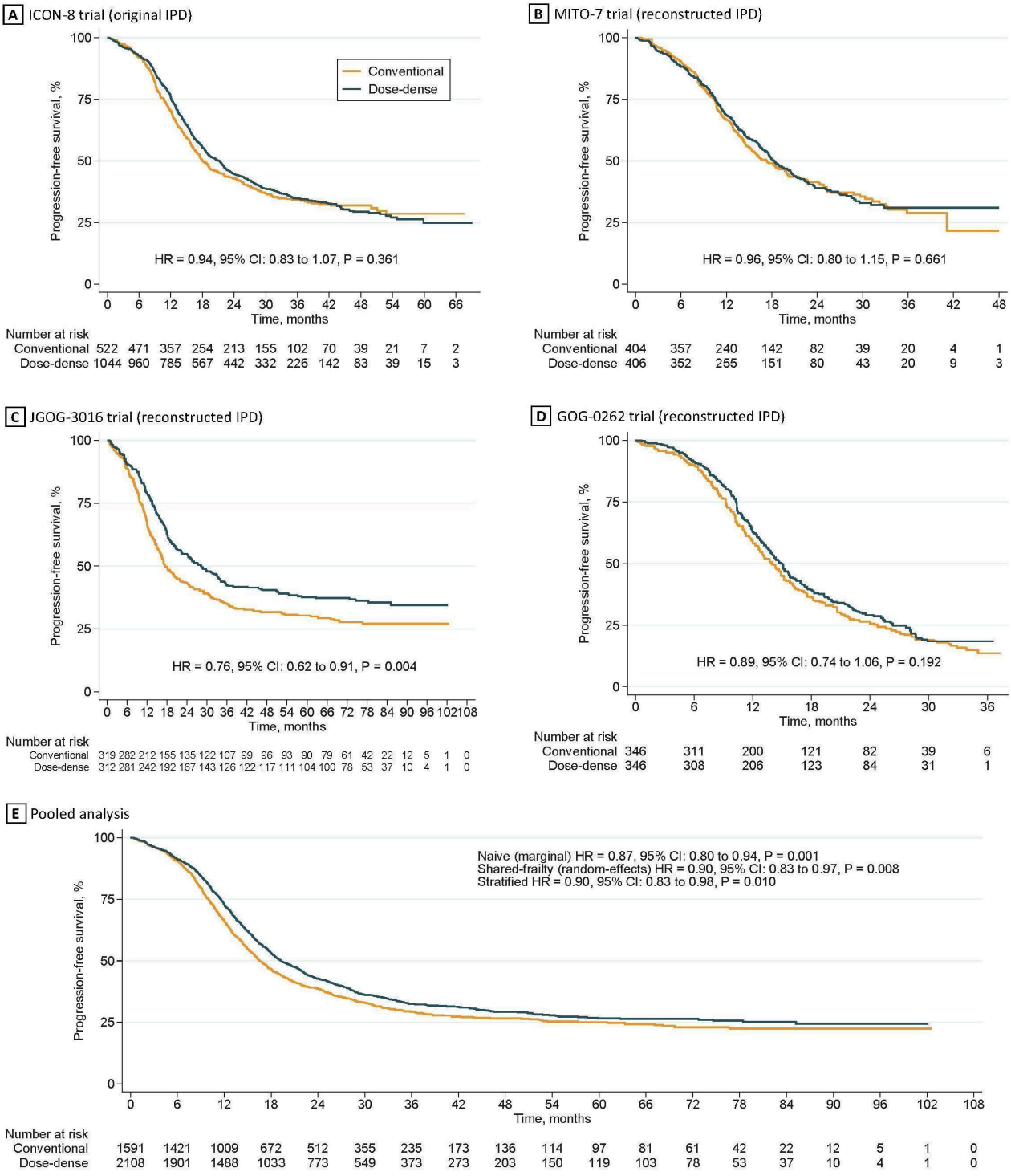
Participants

All studies provided information on this outcome, and this analysis included 3639 participants..

Results

The main analysis showed a significant difference in PFS between weekly and tri-weekly paclitaxel dosing (HR 0.89, 95% CI 0.81 to 0.98; P = 0.02; 4 studies, 3699 participants; moderate-certainty evidence; Analysis 1.1; Summary of findings 1). This indicates that weekly paclitaxel reduces the hazard rate of progression or death by 11% (with 95% confidence that the true effect size is between 2% and 19%). There was low heterogeneity between studies (Chi^2 = 4.37, P = 0.22, I^2 = 31%). Figure 4 shows sensitivity analysis that utilised IPD from one study; improved PFS for weekly versus tri-weekly paclitaxel was evident. Shared-frailty (random-effects) HR for PFS of weekly versus tri-weekly paclitaxel dosing was 0.90 (95% CI 0.83 to 0.97; P = 0.0076; Figure 4E).

Figure 4.



Subgroup analysis

The test for subgroup differences showed no statistical difference when the following subgroup analyses were conducted.

- Residual disease (P = 0.74; absent: one study; ≤1cm: three studies; > 1cm: three studies; no surgery performed: one study; Analysis 1.2).
- FIGO stage of disease (P = 0.91; stage I or II: three studies; stage III or IV: two studies; stage I: one study; stage II: two studies; stage III: three studies; stage IV: three studies; Analysis 1.3).

- ECOG performance status (P = 0.78; ECOG 0 or 1: two studies; ECOG 2, 3 or 4: four studies; ECOG 0: three studies; ECOG 1: three studies; ECOG 2: three studies; Analysis 1.4).
- Bevacizumab receipt (P = 0.15; no bevacizumab received: three studies; bevacizumab received: one study; Analysis 1.5).
- Age distribution (P = 0.67; < 60 years: two studies; ≥ 60 years: three studies; < 70 years: three studies; ≥ 70 years: two studies; Analysis 1.6).
- Epithelial ovarian cancer histotype (P = 0.30; serous: two studies; non-serous: two studies; Analysis 1.8). It is noted that the JGOG-3016 study stratified histology into the following subgroups: serous/others versus clear-cell/mucinous. We have included the JGOG-3016 data in this subgroup analysis assuming that the proportion of other histologies in the serous/others subgroup is small.

The test for subgroup differences showed a statistical difference when the following subgroup analysis was conducted.

- Carboplatin dosing (P = 0.04; weekly carboplatin dosing: two studies; tri-weekly carboplatin dosing: three studies; Analysis 1.7).

There was low heterogeneity (I^2 = 36%) between results from studies within the tri-weekly carboplatin subgroup. However, since the number of studies included in the analysis was small, we do not have enough evidence to confidently conclude that there is a true subgroup effect.

Overall survival (OS)

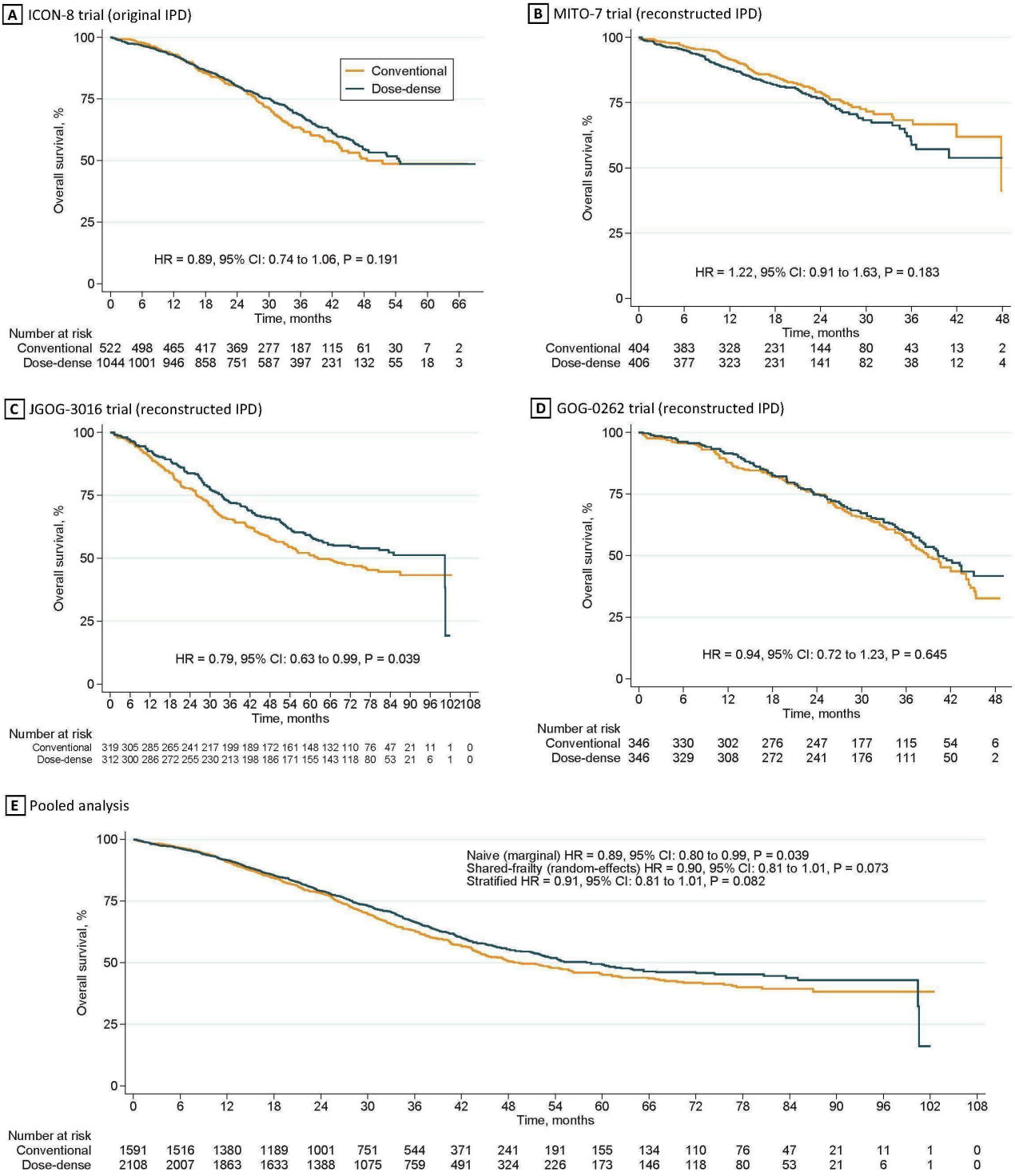
Participants

All studies provided information on this outcome, and this analysis included 3699 participants.

Results

The main analysis showed no significant difference in OS between weekly and tri-weekly paclitaxel dosing (HR 0.92, 95% CI 0.79 to 1.06; P = 0.25; 4 studies, 3699 participants; high-certainty evidence; Analysis 1.9; Summary of findings 1). There was low heterogeneity between studies (Chi^2 = 4.86, P = 0.18, I^2 = 38%). On sensitivity analysis that utilised IPD from one study (Figure 5), no significant difference in OS for weekly versus tri-weekly paclitaxel was evident. The shared-frailty (random-effects) HR of weekly versus tri-weekly paclitaxel dosing was 0.90 (95% CI 0.81 to 1.01; P = 0.073; Figure 5E). However, it is worth noting that the upper limit of the 95% CI of the shared-frailty HR was approaching statistical significance.

Figure 5.



Subgroup analysis

The test for subgroup differences showed no statistical difference when the following subgroup analyses were conducted.

- Residual disease (P = 0.92; ≤ 1cm: one study; > 1cm: one study; Analysis 1.10).
- FIGO stage of disease (P = 0.79; stage I or II: two studies; stage I: one study; stage II: two studies; stage III, two studies; stage IV: two studies; Analysis 1.11).
- ECOG performance status (P = 0.70; ECOG 0 or 1: two studies; ECOG 2, 3 or 4: two studies; Analysis 1.12).

- Bevacizumab receipt (P = 0.90; no bevacizumab received: three studies; mixed population of women who received/did not receive bevacizumab: one study; Analysis 1.13).
- Age distribution (P = 0.69; age < 60 years: one study; age ≥ 60: one study; Analysis 1.14).
- Carboplatin dosing (P = 0.30; weekly carboplatin dosing: two studies; tri-weekly carboplatin dosing: two studies; Analysis 1.15).
- Epithelial ovarian cancer histotype (P = 0.71; serous: two studies; non-serous: two studies; Analysis 1.16).

Neutropenia

Participants

All studies reported on this outcome, and this analysis included 3639 participants.

Results

We did not observe any difference in grade 3 or 4 neutropenia between weekly and tri-weekly paclitaxel dosing (RR 1.11, 95% CI 0.86 to 1.43; P = 0.41; 4 studies, 3699 participants; moderate-certainty evidence; Analysis 1.17; Summary of findings 1). There was a high degree of heterogeneity between studies (Chi^2 = 73.70, P < 0.00001, I^2 = 96%).

Secondary outcome:

Adverse events

Participants

All four studies (3639 participants) reported the following high grade (grade 3 or 4) acute adverse events: thrombocytopenia, vomiting and diarrhoea. Three studies (2956 participants) reported high grade fatigue (ICON-8; JGOG-3016; MITO-7). Two studies (2365 participants) reported any-grade alopecia, acute high-grade transaminitis, anorexia and mucositis (ICON-8; MITO-7). These studies also reported acute high-grade leucopenia (ICON-8; MITO-7). Two studies (2157 participants) reported acute high-grade myalgia, arthralgia and hypersensitivity (ICON-8; JGOG-3016).

Results

We noted a difference between weekly and tri-weekly paclitaxel for the following adverse events, favouring tri-weekly paclitaxel.

- Anaemia (452 versus 248 events; RR 1.57, 95% CI 1.12 to 2.20; P = 0.002; 4 studies, 3639 participants; high-certainty evidence; Analysis 1.19; Summary of findings 1). There was a high degree of heterogeneity between studies (Chi^2 = 14.47, P = 0.002, I^2 = 79%).
- Treatment discontinuation (190 versus 98 events; RR 1.86, 95% CI 1.42 to 2.42; P<0.00001; 3 studies, 2108 participants; Analysis 1.34).
- Dose delays (1081 versus 516 events; RR 1.57, 95% CI 2.21 to 2.03; P = 0.0006; 3 studies, 3050 participants; Analysis 1.35). We observed a high level of heterogeneity between studies (Chi^2 = 21.27, P<0.0001, I^2 = 91%).
- Dose omissions (465 versus 78 events; RR 2.98, 95% CI 2.40 to 3.70; P<0.00001; 1 study, 1566 participants; Analysis 1.35).

We did not note any differences between weekly and tri-weekly paclitaxel for the following adverse events.

- Febrile neutropenia (Analysis 1.18)
- Grade 3 or 4 leucopenia (Analysis 1.20)
- Grade 3 or 4 thrombocytopenia (Analysis 1.21)
- Grade 3 or 4 transaminitis (Analysis 1.22)
- Grade 3 or 4 fatigue (Analysis 1.23)
- Grade 3 or 4 myalgia (Analysis 1.24)
- Grade 3 or 4 arthralgia (Analysis 1.25)
- Grade 3 or 4 anorexia (Analysis 1.26)
- Grade 3 or 4 diarrhoea (Analysis 1.27)
- Grade 3 or 4 vomiting (Analysis 1.28)
- Grade 2 or higher neuropathy, not otherwise specified (Analysis 1.29)
- Grade 2 or higher sensory neuropathy (Analysis 1.29)
- Grade 2 or higher motor neuropathy (Analysis 1.29)
- Grade 3 or 4 neuropathy, not otherwise specified (Analysis 1.30)
- Grade 3 or 4 sensory neuropathy (Analysis 1.30)
- Grade 3 or 4 motor neuropathy (Analysis 1.30)
- Any-grade alopecia (RR 0.87, 95% CI 0.65-1.17; P = 0.36; 2 studies, 2330 participants; Analysis 1.31)
- Any-grade mucositis (Analysis 1.32)
- Grade 3 or 4 hypersensitivity (Analysis 1.33)
- Dose reductions (Analysis 1.35).

Quality of Life

Participants

A total of 3346 participants were evaluated for participant-reported QoL outcomes across four studies (GOG-0262 560 participants; ICON-8 1540 participants; JGOG-3016: 637 participants, MITO-7: 609 participants).

Results

QoL analysis described by three of the four studies appeared to be concordant in suggesting no clinically significant deterioration in QoL analysis overall when paclitaxel was dosed weekly compared to tri-weekly.

In the GOG-0262 study (560 participants), after adjusting for potential confounders, weekly paclitaxel was associated with lower FACT-OTrial Outcome Index (TOI) scores (suggesting lower QoL) during the period of assessment, compared to those receiving paclitaxel tri-weekly. However, the maximal decrease in FACT-O TOI score was only 2.7 points (97.5% CI, -5.44 to 0.02, P = 0.02), occurring after cycle six of chemotherapy; we did not consider this to be clinically significant. However, participant-reported neurotoxicity (peripheral neuropathy in particular), was higher amongst women receiving weekly compared to tri-weekly paclitaxel, and this persisted during the study period.

In the ICON-8 study (1540 participants), cross-sectional comparison between study groups showed marginally lower global health scores for weekly paclitaxel dosing groups compared to the tri-weekly paclitaxel dosing group. This difference was statistically significant until nine months after randomisation, but was deemed to be clinically insignificant. At the nine-month follow-up after randomisation, we did not note any further differences between the three treatment groups with cross-sectional analysis. This likely reflects slower improvements in QoL for women receiving weekly paclitaxel regimens compared to tri-weekly dosing; however, eventual recovery for all groups was likely to be similar by nine

months. Slightly worse fatigue and peripheral neuropathy were reported by women receiving weekly paclitaxel compared to tri-weekly dosing. In particular, peripheral neuropathy for women receiving weekly paclitaxel was reported to be more gradual in onset, but more prolonged beyond the end of treatment, compared to tri-weekly dosing in this study.

In the JGOG-3016 study (637 participants), we did not observe any difference in overall QoL between weekly paclitaxel and standard chemotherapy groups at 12 months after randomisation. However, QoL by the FACT-Taxane subscale was lower in the weekly paclitaxel dosing group compared to standard chemotherapy group (P = 0.02). This reflects the worse neurotoxicity reported by women in the weekly paclitaxel group, which negatively impacted upon QoL.

In comparison, the MITO-7 study (609 participants) reported no deterioration of QoL by overall FACT-O scoring for women receiving weekly paclitaxel compared to tri-weekly dosing, including for the FACT-Taxane neurotoxicity subscale. In all QoL analyses, weekly paclitaxel was favoured in treatment-by-time interaction (P < 0.0001). This difference compared to the prior two studies may reflect the lower cumulative dose of paclitaxel when dosed weekly in the MITO-7 study (180 mg/m^2 per cycle), compared to the GOG-0262, JGOG-3016, and ICON-8 studies (240 mg/m^2 per cycle), although the precise mechanism for paclitaxel neurotoxicity is still not fully understood.

Subgroup analysis

We could not conduct subgroup analyses for the secondary outcome of QoL due to heterogeneity in the available data.

DISCUSSION

Summary of main results

In this systematic review and meta-analysis, we analysed the efficacy and toxicity profile of weekly paclitaxel compared to tri-weekly paclitaxel when combined with carboplatin for the first-line treatment of ovarian cancer. The results are summarised in the Summary of findings 1.

Moderate-certainty evidence found that dosing paclitaxel weekly improved PFS, compared to tri-weekly dosing; this was consistent on aggregate data meta-analysis, as well as on pooled IPD meta-analysis. Moderate-evidence found no difference in the risk for grade 3 or 4 neutropenia or febrile neutropenia between both dosing schedules. Low-certainty evidence found no difference in the risk for grade 3 or 4 neuropathy between both dosing schedules. However, high-certainty evidence found an increased risk of grade 3 or 4 anaemia with weekly paclitaxel and no improvement in OS, compared to tri-weekly paclitaxel dosing.

We used a qualitative synthesis to assess QoL due to heterogeneity in the QoL instruments used by the studies, assessment time points and outcome reporting. We found no clinically significant deterioration in QoL for participants receiving weekly compared to tri-weekly paclitaxel.

Overall completeness and applicability of evidence

All studies included in the main analysis were published in full. Reliable conclusions could be drawn from the primary outcome measure of PFS, which had mature data reported by all studies included in the main analysis. It is worth noting that the GOG-0262 and MITO-7 studies were statistically powered solely for their PFS endpoint and relatively few OS events were included at the time of study publication. However, this would not affect the reliability of the OS conclusions drawn from our meta-analysis. All studies reported toxicity outcomes in detail, providing sufficient data for us to draw conclusions. We were not able to reliably analyse certain a priori subgroup analyses determined at the time of protocol writing, such as ethnicity (Asian participants versus non-Asian participants) and the receipt of targeted therapy (addition of targeted therapy versus no addition of targeted therapy), as there was only one study each reporting data on these subgroups (GOG-0262; JGOG-3016).

For the secondary outcome of QoL, we synthesised the data qualitatively as QoL outcome reporting amongst including studies was heterogenous. Missing data, in terms of standard deviation, standard error, 95% confidence intervals at specific time points, as well as measures of uncertainty versus dispersion, led to difficulties in aggregating the data in a quantitative meta-analysis. Furthermore, heterogeneity existed in terms of the reporting timeframe of QoL assessment, e.g. end of the cycle versus number of weeks after randomisation, as well as the QoL instrument scales and subscales utilised by included studies. We also observed differences in the reporting of central tendencies. Therefore, we undertook qualitative synthesis of QoL data instead of the planned meta-analysis.

Histological subtype

Epithelial ovarian cancer is a heterogenous disease with well-defined distinct histological subtypes, which are associated with different clinico-pathological features, response to chemotherapy and prognosis. We did not impose any restrictions based on histological subtype when including studies for analysis. All four included studies recruited a majority of women with high-grade serous subtype epithelial ovarian cancer (GOG-0262: 88%, ICON-8: 68%, JGOG-3016: 56%, MITO-7: 70%), whereas other histological types, such as clear cell or mucinous cancer, were less well-represented.

Ethnicity

Survival amongst women with epithelial ovarian cancer has been observed to vary by ethnicity and country. A recent population-based study of 7914 women diagnosed with epithelial ovarian cancer showed an improved five-year disease specific survival for Asian women compared to Caucasian women (54.1% versus 46.1%, P = 0.001) (Fuh 2019). Possible pharmacogenetic differences between ethnic groups has often been cited as the likely reason underlying observed differences in treatment response and toxicity outcomes. Ethnic differences in the distribution of genotypes of enzymes required for paclitaxel metabolism have been described (Gandara 2009), though the precise mechanisms for how these pharmacogenetic variations impact upon clinical outcomes has yet to be fully elucidated. In our study, subgroup analysis by ethnicity was not possible as only one study recruited an all-Japanese population (JGOG-3016), and the remaining three studies did not report on outcomes by ethnic group.

Role of bevacizumab

The addition of bevacizumab to first-line tri-weekly carboplatin and paclitaxel is well recognised as an option for first-line therapy of

epithelial ovarian cancer (National Comprehensive Cancer Network 2021). Two RCTs have demonstrated improvements in PFS when bevacizumab is added to tri-weekly carboplatin and paclitaxel (Oza 2015; Tewari 2019). The role of bevacizumab addition in women receiving weekly paclitaxel combined with carboplatin in first-line therapy of epithelial ovarian cancer is poorly established. In the GOG-0262 study, 84% of enrolled women received bevacizumab, and in the 16% of women (112 participants) who did not receive bevacizumab, weekly paclitaxel was associated with longer PFS compared to tri-weekly dosing (14.2 versus 10.3 months, HR 0.62). In the present meta-analysis, the test for subgroup differences indicates no statistically significant subgroup effect (P = 0.15), suggesting that bevacizumab does not modify the effect of weekly paclitaxel dosing in comparison to tri-weekly dosing. However, only one study contributed data to the subgroup of participants who had received bevacizumab (GOG-0262): 80 participants), meaning that the analysis may not be able to detect subgroup differences. It is interesting to note that the pooled effect estimates for participants not receiving bevacizumab favours weekly paclitaxel dosing. As such, these results should not be applied to women receiving bevacizumab in first-line therapy.

Neoadjuvant therapy

Only the ICON-8 study has published prospective data from a post-hoc exploratory analysis comparing objective responses (by Response Evaluation Criteria in Solid Tumours (RECIST) or GCIG criteria between weekly paclitaxel and tri-weekly paclitaxel dosing when combined with tri-weekly carboplatin in this setting (Morgan 2021). This study did not observe any difference in the rate of RECIST complete or partial response, nor of complete cytoreduction, between weekly and tri-weekly paclitaxel groups. Contrary to this, other retrospective studies have suggested that paclitaxel 80 mg/m^2 weekly combined with carboplatin tri-weekly facilitates higher rates of pathological complete response and complete resection with no residual disease in women undergoing interval debulking surgery after neoadjuvant chemotherapy (Becker 2016; Ebata 2016). In the present meta-analysis, only one of the included studies reported data on PFS and OS according to timing of surgery (interval versus primary debulking surgery) (ICON-8). As such, these results may not be applicable to women receiving neoadjuvant therapy.

Cost-effectiveness

Cost-effectiveness of weekly versus tri-weekly paclitaxel dosing in combination with carboplatin was not an a priori analysis planned at the time of protocol writing for this systematic review. However, we note that two studies have published cost-effectiveness analyses of weekly versus tri-weekly paclitaxel dosing based on results of the GOG-0262 (Seagle 2017) and JGOG-3016 (Dalton 2012) studies. The first study by Dalton and colleagues utilised a Markov decision model (Briggs 1998) to estimate an acceptable incremental cost-effectiveness ratio (ICER) per progression-free life-year saved (PFLYS), using survival estimates from the JGOG-3016 study and costs of drugs, growth colony-stimulating factors and transfusions from Medicare reimbursement data. Costs reported by Dalton 2012 were updated to the year of equivalence (2021) using readily available on-line tools (Inflation Tool 2021). Despite the higher costs per cycle of chemotherapy for weekly paclitaxel compared with tri-weekly paclitaxel dosing (US dollar (USD) 1008 per cycle versus USD 618 per cycle), leading to an ICER of USD 6707 per PFLYS for weekly paclitaxel, weekly paclitaxel was cost-effective in this economic model when using a maximum ICER of USD 100,000 per life-year saved as a cost-effective threshold (Dalton 2012).

A second cost-effectiveness analysis performed by Seagle and colleagues similarly described robust cost-effectiveness for weekly paclitaxel versus tri-weekly paclitaxel in combination with carboplatin for first-line treatment of advanced epithelial ovarian cancer when using survival estimates, discontinuation and complication rates from the GOG-0262 study (Seagle 2017). This analysis utilised a three-state Markov decision model with a 21 day cycle length and 28 month time-horizon. Costs reported by Seagle 2017 were updated to the year of equivalence (2021) using readily available on-line tools (Inflation Tool 2021). Costs of chemotherapy, complications and surveillance were taken from Medicare or institutional data. Based on this analysis, the ICER for weekly paclitaxel was found to be USD 8714 (95% CI USD 8219 to USD 11016) per PFLYS, and 99.8% of ICER estimates met a more stringent willingness-to-pay of USD 50,000 per PFLYS (Seagle 2017).

Quality of the evidence

The certainty (quality) of evidence was determined using the tool developed by the GRADE Working Group (GRADEpro GDT). The certainty of evidence was high for OS reported in the main analysis. The certainty of evidence was downgraded by one level to moderate for PFS reported in the main analysis, as absence of blinding may lead to detection bias or performance bias. The certainty of evidence for treatment-related high-grade neutropenia was moderate. The lack of blinding was not likely to influence this outcome and sufficient events were reported; however, we downgraded it for severe statistical heterogeneity. The certainty of evidence was high for high-grade anaemia, as the lack of blinding would not influence this outcome, and a large number of events were reported. The certainty of evidence was low for high-grade neuropathy, not otherwise specified. We downgraded this by two levels due to imprecision, as well as the absence of blinding which may lead to detection or performance bias.

Potential biases in the review process

Every reasonable effort was made to reduce and to address potential bias by ensuring that all relevant studies were identified, all relevant data could be obtained as far as possible, and that the review process did not introduce further bias.

Firstly, we only included RCTs in this review. Furthermore, we conducted searches for all relevant studies, including unpublished studies and studies that were not yet fully-published. The search strategy also considered studies that were published in a non-English language. We handsearched all important conference proceedings up to the latest issue. Thus, the likelihood that relevant studies were not identified is thought to be small. During the analysis of this review, we performed all relevant processes in duplicate. Finally, as three authors were leading researchers on one of the included studies (ICON-8), these authors were not involved in decisions regarding inclusion of their study or data extractions.

However, this review is limited by the small number of included studies, which precluded the generation of a funnel plot to exclude publication bias. Furthermore, formal IPD were only provided by one out of the four included studies (ICON-8) . However, where IPD were not available for the other studies (GOG-0262; JGOG-3016;

MITO-7), we used the method of Guyot 2012 to reconstruct IPD survival time and censoring status. The reconstruction proved to be very accurate. When comparing survival curves obtained from reconstructed survival data for all studies with those obtained after incorporating formal IPD from ICON-8, the number-at-risk tables were found to be nearly identical, and the compared hazard ratios based on reconstructed survival data were accurate to two or even three decimal places.

Agreements and disagreements with other studies or reviews

Marchetti 2018 has performed a similar systematic review comparing dose-dense weekly paclitaxel with standard tri-weekly paclitaxel in combination with carboplatin for first-line epithelial ovarian cancer treatment, including the same four studies as our present analysis. However, in the report by Marchetti 2018, no benefit for dose-dense weekly paclitaxel over standard tri-weekly paclitaxel was demonstrated. Specifically, there was no significant increase in PFS for women receiving weekly paclitaxel compared to tri-weekly dosing (HR 0.92, 95% CI 0.81 to 1.04, P = 0.20). Our present meta-analysis differs from the report by Marchetti 2018 due to the incorporation of IPD from the ICON-8 study. The ICON-8 study was a three-arm study, whereby two of the three arms utilised weekly paclitaxel combined with carboplatin. In the published data, the ICON-8 investigators did not report the HR for weekly paclitaxel (incorporating both weekly paclitaxel groups, i.e. group 2 + group 3) compared to tri-weekly paclitaxel (group 1). Therefore, in the report by Marchetti 2018, authors approximated the HR for PFS of weekly paclitaxel versus tri-weekly paclitaxel (HR 1.02, 95% CI 0.94 to 1.10), using summary statistics from the ICON-8 publication and methods of Tierney 2007. As our report has the benefit of IPD from the ICON-8 investigators, we were able to calculate the true HR for PFS of weekly paclitaxel (group 2 + group 3) versus tri-weekly paclitaxel (group 1), which was 0.94 (95% CI 0.83 to 1.06). This led to a difference in PFS outcome in our report. Furthermore, the report by Marchetti 2018 was limited by the lack of fully mature OS data, as well as the lack of QoL data from ICON-8 at the time of publication. In terms of toxicity, the meta-analysis published by Marchetti 2018 agreed with our report on more frequent severe acute anaemia (grade 3 to 4) when paclitaxel is dosed weekly, as well as no difference in terms of high grade neutropenia or febrile neutropenia.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this meta-analysis are based on four studies (GOG-0262; ICON-8; JGOG-3016; MITO-7), which included 3699 women with ovarian cancer. It provides moderate-certainty evidence that weekly paclitaxel combined with carboplatin slightly improves progression-free survival (PFS) compared to tri-weekly paclitaxel combined with carboplatin in women receiving first-line treatment for ovarian cancer. However, high-certainty evidence also suggests that weekly paclitaxel with carboplatin leads to little or no improvement in overall survival compared to standard tri-weekly dosing. In addition, high-certainty evidence suggest that women receiving weekly paclitaxel combined with carboplatin suffered increase risk for severe anaemia. There was also increased risk for treatment discontinuation, dose delays and dose omissions observed on subgroup analysis. Moderate- and low-certainty evidence, respectively, suggest no increased risk for severe neutropenia or severe neuropathy with this approach.

Implications for research

Evolving treatment paradigms in the first-line treatment of ovarian cancer, specifically in advanced stage disease, have led to the introduction of maintenance poly-ADP ribose polymerase inhibitors (PARPi) after the completion of first-line tri-weekly carboplatin and paclitaxel, based on improvements in PFS on randomised studies (Gonzalez-Martin 2019). It remains unclear if the introduction of additional agents, such as bevacizumab or PARPi maintenance therapy after first-line chemotherapy, will dilute any potential PFS benefits retrieved from increasing paclitaxel dose-intensity during chemotherapy.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

GOG-0262

Study characteristics	
Methods	Randomisation • A randomised controlled trial • Women were randomised 1:1 to two arms - weekly paclitaxel with tri-weekly carboplatin, versus tri-weekly paclitaxel with tri-weekly carboplatin Recruitment period • September 2010 to February 2012 Median follow-up time • 28 months
Participants	Eligibility criteria

GOG-0262 *(Continued)*

- Women > 18 years old with histologic diagnosis of epithelial ovarian cancer, peritoneal primary carcinoma or fallopian tube cancer
- FIGO stage III with more than 1 cm residual disease or FIGO stage IV, defined surgically at the completion of initial abdominal surgery and with appropriate tissue available for histologic evaluation
- Eligible histologic epithelial cell types: serous, endometrioid, clear cell, mucinous adenocarcinoma, undifferentiated carcinoma, mixed epithelial carcinoma, transitional cell carcinoma, malignant Brenner's Tumor, or adenocarcinoma not otherwise specified
- Adequate bone marrow function, renal functional, hepatic function, neurologic function
- ECOG performance status of 0 to 2
- Entered within 12 weeks of diagnostic/staging surgery
- Provide informed consent
- No current diagnosis of borderline epithelial ovarian tumour, or recurrent invasive epithelial ovarian, primary peritoneal or fallopian tube cancer treated with surgery
- No prior radiotherapy to any portion of the abdominal cavity or pelvis
- No prior chemotherapy for any abdominal or pelvic tumour
- No targeted therapy or hormonal therapy for management of their epithelial ovarian, fallopian tube or peritoneal primary cancer
- No synchronous primary endometrial cancer or past history of primary endometrial cancer unless all of the following conditions are met: stage not greater than I to A, grade 1 or 2, no more than superficial myometrial invasion, without vascular or lymphatic invasion; no poorly differentiated subtypes, including papillary serous, clear cell or other FIGO grade 3 lesions
- No other invasive malignancy with evidence of the other cancer present within the last 5 years, with the exception of non-melanoma skin cancer
- No acute hepatitis or active infection
- No clinically significant cardiovascular disease
- Not be pregnant or nursing
- No prior therapy with any anti-VEGF drug, including bevacizumab
- No medical history or conditions which in the opinion of the investigator would jeopardize participation in the trial

Women recruited to each arm

- Total of 692 women were enrolled. 346 women were recruited to each arm and included in the efficacy analysis.

Locations

- USA, Canada, South Korea

Median age

- Not described

Ethnicity

- 85% non-Hispanic White

Disease stage (FIGO classification)

- Stage II 3%, Stage III 67%, Stage IV 30%

Histological subtype

- Serous subtype 88%

Interventions	Weekly paclitaxel combined with carboplatin • Intravenous paclitaxel 80 mg/m^2 over 1 hour, on days 1, 8 and 15 of a 21-day cycle • Intravenous carboplatin (AUC 6 mg/ml/min), on day 1 of the cycle • Both of the above drugs were given for 6 cycles.

GOG-0262 *(Continued)*

	tri-weekly paclitaxel combined with carboplatin • Intravenous paclitaxel 175 mg/m^2 over 3 hours, on day 1 of a 21-day cycle • Intravenous carboplatin (AUC 6) on day 1 of the cycle • Both of the above drugs were given for 6 cycles. Intravenous bevacizumab was optional and provided to women who chose to receive it. Women were prospectively stratified according to whether they elected to receive bevacizumab at the time of randomisation. • Women receiving bevacizumab were administered intravenous bevacizumab 15 mg/kg on day 1 of a 21-day cycle.
Outcomes	Outcomes from the registered protocol of the study that are considered in the review • PFS • OS • Response Rate (RR) • Toxicity • Quality of Life
Notes	This trial was funded by the National Cancer Institute and Genentech.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence was generated using a minimisation program.
Allocation concealment (selection bias)	Low risk	Random allocation was performed at a central site.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The risk of bias for the outcome of OS was objective and thus low. This trial was open-label with no blinding of participants and personnel, so the risk of bias was high for other outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The risk of bias for the outcome of OS was objective and thus low. This trial was open-label with no blinding of participants and personnel, so the risk of bias was high for other outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	CONSORT diagram was provided. There were no missing outcome data.
Selective reporting (reporting bias)	Low risk	All prespecified primary and secondary outcomes were reported.
Other bias	Unclear risk	No information provided.

ICON-8

Study characteristics

Methods	Randomisation

ICON-8 *(Continued)*

	• Women were randomised 1:1:1 to one of three arms: tri-weekly paclitaxel plus tri-weekly carboplatin, weekly paclitaxel plus tri-weekly carboplatin, weekly paclitaxel plus weekly carboplatin. Recruitment period • 6 June 2011 to 28 November 2014 Median follow-up time • 36.8 months
Participants	Eligibility criteria • Women aged 18 years or older • FIGO (1988 classification) stage IC to IV cancer, with mandatory high-risk histological subtype for women with stage IC to IIA disease • ECOG performance status of 0 to 2 • Life expectancy longer than 12 weeks • Adequate haematological, renal and hepatic function • Started chemotherapy within 8 weeks of surgery • No previous systemic therapy for epithelial ovarian cancer and not planned to receive maintenance therapy after completion of protocol therapy • Provided written informed consent to join the trial Women recruited to each arm • 1566 women were recruited in total. 522 women were included in group 1, 523 in group 2, and 521 in group 3. Locations • UK, Australia, New Zealand, Mexico, South Korea, and Republic of Ireland. Median age • 62 years Ethnicity • Not described Disease stage (FIGO classification) • 72% FIGO stage IIIC or higher Histological subtype • High-grade serous subtype 69%.
Interventions	tri-weekly paclitaxel combined with tri-weekly carboplatin • Intravenous paclitaxel 175 mg/m^2, on day 1 of a 21-day cycle • Intravenous carboplatin (AUC 5 or 6 mg/ml/min) on day 1 of the cycle • Both of the above drugs were given for 6 cycles. Weekly paclitaxel combined with tri-weekly carboplatin • Intravenous paclitaxel 80 mg/m^2, on days 1, 8 and 15 of a 21-day cycle • Intravenous carboplatin (AUC 5 or 6 mg/ml/min), on day 1 of the cycle • Both of the above drugs were given for 6 cycles. Weekly paclitaxel combined with weekly carboplatin

ICON-8 *(Continued)*

	• Intravenous paclitaxel 80 mg/m^2, on days 1, 8 and 15 of a 21-day cycle. • Intravenous carboplatin (AUC 2 mg/ml/min), on days 1, 8 and 15 of a 21-day cycle. • Both of the above drugs were given for 6 cycles.
Outcomes	Outcomes from the registered protocol of the study that are considered in the review: • PFS • OS • Safety • Quality of life
Notes	This trial was funded by Cancer Research UK, Medical Research Council, Health Research Board in Ireland, Irish Cancer Society, Cancer Australia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Women were randomly assigned using the Medical Research Council Clinical Trials Unit (MRCCTU) at University College London (UCL) randomisation telephone service, using the method minimisation.
Allocation concealment (selection bias)	Low risk	Women were randomly assigned using the Medical Research Council Clinical Trials Unit (MRCCTU) at University College London (UCL) randomisation telephone service, using the method minimisation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The risk of bias for the outcome of OS was objective and thus low. This trial was open-label with no blinding of participants and personnel, so the risk of bias was high for other outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The risk of bias for the outcome of OS was objective and thus low. This trial was open-label with no blinding of participants and personnel, so the risk of bias was high for other outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	CONSORT diagram provided. The numbers of women lost to follow-up were detailed and were few in number (group 1: 4, group 2: 12, group 5).
Selective reporting (reporting bias)	Low risk	All prespecified primary and secondary outcomes were reported.
Other bias	Unclear risk	No information provided.

JGOG-3016

Study characteristics

Methods	Randomisation • Women were randomised 1:1 to one of two arms: tri-weekly paclitaxel plus tri-weekly carboplatin, weekly paclitaxel plus tri-weekly carboplatin. Recruitment period • April 2003 to December 2005

JGOG-3016 *(Continued)*

	Median follow-up time • 76.8 months
Participants	Eligibility criteria • Women had histologically or cytologically proven diagnosis of stage II to IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer • No previous chemotherapy • Aged 20 years or older • ECOG performance status of 0 to 3 • Adequate organ function • Provide written informed consent • Women with ovarian tumour with a low malignant potential, or synchronous or metachronous (within 5 years) malignant disease other than carcinoma in situ, were excluded. Women recruited to each arm • 637 women were enrolled; however,only 631 eligible women had data included in the intention-to-treat analysis • 312 women were randomised to weekly paclitaxel plus carboplatin, while 319 women were randomised to tri-weekly paclitaxel plus carboplatin Location • Japan Median age • Not described Ethnicity • All women enrolled were Japanese. Disease stage (FIGO classification) • Stage II 18% • Stage III 66% • Stage IV 16% Histological subtype • High-grade serous subtype 56%.
Interventions	Weekly paclitaxel combined with tri-weekly carboplatin • Intravenous paclitaxel over 1 hour, on days 1, 8 and 15 of a 21-day cycle • Intravenous carboplatin (AUC 6 mg/ml/min) over 1 hour, on day 1 of the cycle. • Both of the above drugs were given for 6 cycles. Women with measurable lesions who had a partial response or complete response received three additional cycles of chemotherapy. tri-weekly paclitaxel combined with tri-weekly carboplatin • Intravenous paclitaxel 180 mg/m^2 over 3 hours, on day 1 of a 21-day cycle. • Intravenous carboplatin (AUC 6 mg/ml/min) over 1 hour, on day 1 of the cycle. • Both of the above drugs were given for 6 cycles. Women with measurable lesions who had a partial response or complete response received three additional cycles of chemotherapy.
Outcomes	Outcomes from the registered protocol of the study that are considered in the review: • PFS

JGOG-3016 *(Continued)*

- OS
- RR
- Adverse events

Notes	Note that the JGOG 3016 study stratified histology into the following subgroups: 'Serous/others' versus 'clear-cell/mucinous'. This trial was funded by Japanese Gynecologic Oncology Group, Bristol-Myers Squibb.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was by telephone or fax from a central registration centre located at University of Toyama (Toyama, Japan), and the random allocation table was computer-generated by use of the SAS PROC PLAN.
Allocation concealment (selection bias)	Low risk	Randomisation was by telephone or fax from a central registration centre located at University of Toyama (Toyama, Japan), and the random allocation table was computer-generated by use of the SAS PROC PLAN.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The risk of bias for the outcome of OS was objective and thus low. This trial was open-label with no blinding of participants and personnel, so the risk of bias was high for other outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The risk of bias for the outcome of OS was objective and thus low. This trial was open-label with no blinding of participants and personnel, so the risk of bias was high for other outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 2 women were lost to follow-up, and this was detailed in the CONSORT diagram.
Selective reporting (reporting bias)	Low risk	All prespecified primary and secondary outcomes were reported.
Other bias	Unclear risk	No information provided.

MITO-7

Study characteristics

Methods	Randomisation • Women were randomised 1:1 to one of two arms: tri-weekly paclitaxel plus tri-weekly carboplatin, weekly paclitaxel plus weekly carboplatin. Recruitment period • 20 November 2008 to 1 March 2012 Median follow-up time • 21.6 months
Participants	Eligibility criteria

MITO-7 *(Continued)*

- Women aged 18 years or older.
- Cytological or histological diagnosis of epithelial ovarian, fallopian tube, or peritoneal cancer
- FIGO stage IC–IV disease
- ECOG performance status 0 to 2
- Life expectancy of at least 3 months
- Women with clinically relevant heart disease or other concurrent disorders that were a contraindication to treatment drugs were excluded.
- No previous chemotherapy
- Adequate bone marrow, kidney, and liver function
- Provide written informed consent
- Women who had previous or concomitant other malignant disease (except non- melanoma skin cancer or in-situ carcinoma of the uterine cervix) were excluded.

Women recruited to each arm

- 822 women were enrolled.
- 409 women were randomised to tri-weekly paclitaxel plus tri-weekly carboplatin. 413 women were randomised to weekly paclitaxel plus weekly carboplatin.

Locations

- Italy and France

Median age

- 59 years for tri-weekly treatment group. 60 years for weekly treatment group.

Ethnicity

- No information provided.

Disease stage (FIGO classification)

- Stage IC 7%
- Stage II 8%
- Stage III 60%
- Stage IV 25%

Histological subtype

- Serous subtype 70%

Interventions

Weekly paclitaxel combined with weekly carboplatin

- Intravenous paclitaxel 60 mg/m^2 over 1 hour, on days 1, 8 and 15 of a 21-day cycle
- Intravenous carboplatin (AUC 2 mg/ml/min) over 30 mins on days 1, 8 and 15 of the cycle
- Both of the above drugs were given for 18 consecutive weeks.

tri-weekly paclitaxel combined with tri-weekly carboplatin

- Intravenous paclitaxel 175 mg/m^2 over 3 hours, on day 1 of a 21-day cycle
- Intravenous carboplatin (AUC 6 mg/ml/min) over 30 mins, on day 1 of the cycle
- Both of the above drugs were given for 6 cycles.

Outcomes

Outcomes from the registered protocol of the study that are considered in the review:

- Quality of life
- PFS
- OS
- Objective RR

MITO-7 *(Continued)*	
	• Toxic effects
Notes	Efficacy analyses were performed on the basis of modified intention to treat. Women who withdrew consent immediately after randomisation were excluded. This trial declared no funding.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The study used a computer-based minimisation procedure to randomly allocate participants. Randomisation was done centrally at the Clinical Trials Unit of the National Cancer Institute in Napoli, Italy.
Allocation concealment (selection bias)	Low risk	The study used a computer-based minimisation procedure to randomly allocate participants. Randomisation was done centrally at the Clinical Trials Unit of the National Cancer Institute in Napoli, Italy.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The risk of bias for the outcome of OS was objective and thus low. This trial was open-label with no blinding of participants and personnel, so the risk of bias was high for other outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The risk of bias for the outcome of OS was objective and thus low. This trial was open-label with no blinding of participants and personnel, so the risk of bias was high for other outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 12 women were lost to follow-up and this was detailed in the CONSORT diagram.
Selective reporting (reporting bias)	Low risk	All prespecified primary and secondary outcomes were reported.
Other bias	Unclear risk	No information provided.

AUC: area under curve; CONSORT:Consolidated Standards of Reporting Trials ; ECOG:Eastern Cooperative Oncology Group; FIGO: International Federation of Gynecology and Obstetrics; GOG:Gynecologic Oncology Group; OS: overall survival; PFS: progression-free survival; RR: response rate

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

Study	Reason for exclusion
Du 2015	• Severity of adverse events were not reported. • Number of progression-free survival events in each arm were not reported.
Falandry 2021	• The weekly paclitaxel arm on this trial utilised weekly carboplatin (AUC 2) and paclitaxel 60 mg/m^2 weekly on days 1, 8 and 15 of a 28-day cycle. • The review authors agreed that the dose-intensity of paclitaxel on this regimen was too low for it to be included.
Shen 2005	• Process of randomisation was not described. • Under 1:1 randomisation, we expected 50% of the total 125 included women to be allocated to each arm. However, the trial reported 51 and 74 women in each arm, respectively. We felt that this

Study	Reason for exclusion
	was very unlikely to be due to chance as under the exact binomial test, the chances of having 51 and 74 women in each arm assuming 1:1 randomisation is 0.86%

AUC: area under curve

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

ICON8B

Study name	ICON8B is an international trial of weekly chemotherapy and bevacizumab for women with ovarian cancer, fallopian tube cancer or primary peritoneal cancer
Methods	Randomised controlled trial
Participants	Eligibility criteria • Are female and at least 18 years old • Have been diagnosed with epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer • Have a cancer that is staged as high risk • Are well enough to be up and about for at least half the day • Have satisfactory blood test results • Are willing to use reliable contraception during the trial and for 6 months afterwards
Interventions	Group B1 • 6 cycles of carboplatin once every 3 weeks, paclitaxel once every 3 weeks and bevacizumab once every 3 weeks, followed by 12 cycles of bevacizumab once every 3 weeks. Group B3 • 6 cycles of carboplatin once every 3 weeks, paclitaxel once every week (on days 1, 8 and 15 of a 3 weekly cycle) and bevacizumab once every 3 weeks, followed by 12 cycles of bevacizumab once every 3 weeks.
Outcomes	• Progression-free survival • Overall survival • Toxic effects • Quality of life
Starting date	Recruitment took place between 6 June 2011 and 8 May 2020.
Contact information	mrcctu.icon8and8b@ucl.ac.uk
Notes	www.icon8trial.org/patients/icon8b-trial-summary/

DATA AND ANALYSES

Comparison 1. Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Progression-free survival	4		Hazard Ratio (IV, Random, 95% CI)	0.89 [0.81, 0.98]
1.2 Progression-free survival, subgroup analysis by residual disease	3		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
1.2.1 Absent	1		Hazard Ratio (IV, Random, 95% CI)	1.02 [0.70, 1.49]
1.2.2 ≤ 1 cm	3		Hazard Ratio (IV, Random, 95% CI)	0.84 [0.63, 1.13]
1.2.3 > 1 cm	3		Hazard Ratio (IV, Random, 95% CI)	0.82 [0.62, 1.08]
1.2.4 No surgery	1		Hazard Ratio (IV, Random, 95% CI)	0.97 [0.70, 1.34]
1.3 Progression-free survival, subgroup analysis by FIGO stage	4		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
1.3.1 Stage I or II	3		Hazard Ratio (IV, Random, 95% CI)	0.91 [0.66, 1.27]
1.3.2 Stage I	1		Hazard Ratio (IV, Random, 95% CI)	1.98 [0.23, 16.91]
1.3.3 Stage II	2		Hazard Ratio (IV, Random, 95% CI)	0.78 [0.55, 1.10]
1.3.4 Stage III	3		Hazard Ratio (IV, Random, 95% CI)	0.89 [0.80, 1.00]
1.3.5 Stage IV	3		Hazard Ratio (IV, Random, 95% CI)	0.91 [0.77, 1.09]
1.3.6 Stage III or IV	2		Hazard Ratio (IV, Random, 95% CI)	0.93 [0.84, 1.03]
1.4 Progression-free survival, subgroup analysis by ECOG status	4		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
1.4.1 ECOG 0 or 1	2		Hazard Ratio (IV, Random, 95% CI)	0.86 [0.70, 1.07]
1.4.2 ECOG 2, 3, or 4	4		Hazard Ratio (IV, Random, 95% CI)	0.84 [0.64, 1.11]
1.4.3 ECOG 0	3		Hazard Ratio (IV, Random, 95% CI)	0.90 [0.79, 1.02]
1.4.4 ECOG 1	3		Hazard Ratio (IV, Random, 95% CI)	0.98 [0.86, 1.12]
1.4.5 ECOG 2	3		Hazard Ratio (IV, Random, 95% CI)	0.93 [0.60, 1.42]
1.5 Progression-free survival, subgroup analysis by bevacizumab receipt	3		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
1.5.1 No bevacizumab	3		Hazard Ratio (IV, Random, 95% CI)	0.81 [0.66, 1.00]
1.5.2 Received bevacizumab	1		Hazard Ratio (IV, Random, 95% CI)	0.99 [0.83, 1.18]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6 Progression-free survival, subgroup analysis by age distribution	3		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
1.6.1 < 60 years	2		Hazard Ratio (IV, Random, 95% CI)	0.85 [0.71, 1.02]
1.6.2 >/= 60 years	3		Hazard Ratio (IV, Random, 95% CI)	0.83 [0.70, 0.97]
1.6.3 < 70 years	3		Hazard Ratio (IV, Random, 95% CI)	0.92 [0.82, 1.04]
1.6.4 >/= 70 years	2		Hazard Ratio (IV, Random, 95% CI)	0.81 [0.61, 1.07]
1.7 Progression-free survival, subgroup analysis by carboplatin schedule	4		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
1.7.1 Tri-weekly carboplatin	3		Hazard Ratio (IV, Random, 95% CI)	0.86 [0.77, 0.98]
1.7.2 Weekly carboplatin	2		Hazard Ratio (IV, Random, 95% CI)	1.00 [0.93, 1.08]
1.8 Progression-free survival, subgroup analysis by histotype	2		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
1.8.1 Serous	2		Hazard Ratio (IV, Random, 95% CI)	0.82 [0.62, 1.08]
1.8.2 Non-serous	2		Hazard Ratio (IV, Random, 95% CI)	0.99 [0.78, 1.25]
1.9 Overall Survival	4		Hazard Ratio (IV, Random, 95% CI)	0.92 [0.79, 1.06]
1.10 Overall survival, subgroup analysis by residual disease	1		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
1.10.1 Absent	0		Hazard Ratio (IV, Random, 95% CI)	Not estimable
1.10.2 ≤ 1 cm	1		Hazard Ratio (IV, Random, 95% CI)	0.76 [0.49, 1.19]
1.10.3 > 1 cm	1		Hazard Ratio (IV, Random, 95% CI)	0.74 [0.57, 0.97]
1.10.4 No surgery	0		Hazard Ratio (IV, Random, 95% CI)	Not estimable
1.11 Overall survival, subgroup analysis by FIGO stage	2		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
1.11.1 Stage I or II	2		Hazard Ratio (IV, Random, 95% CI)	0.74 [0.46, 1.17]
1.11.2 Stage I	1		Hazard Ratio (IV, Random, 95% CI)	1.27 [0.17, 9.59]
1.11.3 Stage II	2		Hazard Ratio (IV, Random, 95% CI)	0.66 [0.41, 1.06]
1.11.4 Stage III	2		Hazard Ratio (IV, Random, 95% CI)	0.84 [0.72, 0.99]
1.11.5 Stage IV	2		Hazard Ratio (IV, Random, 95% CI)	0.89 [0.70, 1.13]

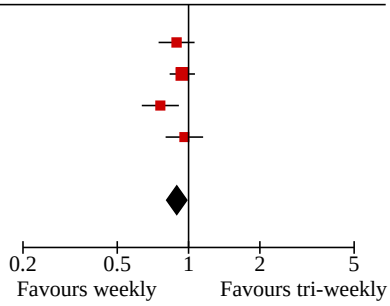
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.12 Overall survival, subgroup analysis by ECOG status	2		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
1.12.1 ECOG 0 or 1	2		Hazard Ratio (IV, Random, 95% CI)	0.86 [0.74, 0.99]
1.12.2 ECOG 2, 3 or 4	2		Hazard Ratio (IV, Random, 95% CI)	0.80 [0.59, 1.09]
1.13 Overall survival, subgroup analysis by bevacizumab receipt	4		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
1.13.1 No bevacizumab	3		Hazard Ratio (IV, Random, 95% CI)	0.92 [0.76, 1.12]
1.13.2 Mixed population of participants who did/did not receive bevacizumab	1		Hazard Ratio (IV, Random, 95% CI)	0.94 [0.72, 1.23]
1.14 Overall survival, subgroup analysis by age distribution	1		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
1.14.1 < 60 years	1		Hazard Ratio (IV, Random, 95% CI)	0.77 [0.56, 1.05]
1.14.2 >/= 60 years	1		Hazard Ratio (IV, Random, 95% CI)	0.84 [0.61, 1.16]
1.15 Overall survival, subgroup analysis by carboplatin schedule in dose-dense arm	4		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
1.15.1 Weekly carboplatin	2		Hazard Ratio (IV, Random, 95% CI)	1.01 [0.75, 1.35]
1.15.2 Tri-weekly carboplatin	3		Hazard Ratio (IV, Random, 95% CI)	0.87 [0.76, 0.99]
1.16 Overall survival, subgroup analysis by histotype	2		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
1.16.1 Serous	2		Hazard Ratio (IV, Random, 95% CI)	0.84 [0.72, 0.98]
1.16.2 Non-serous	2		Hazard Ratio (IV, Random, 95% CI)	0.89 [0.68, 1.15]
1.17 Grade 3 or 4 neutropenia	4	3639	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.86, 1.43]
1.18 Febrile neutropenia	4	3639	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.56, 1.36]
1.19 Grade 3 or 4 anaemia	4	3639	Risk Ratio (M-H, Random, 95% CI)	1.57 [1.12, 2.20]
1.20 Grade 3 or 4 leucopenia	2	2365	Risk Ratio (M-H, Random, 95% CI)	1.65 [0.29, 9.23]
1.21 Grade 3 or 4 thrombocytopenia	4	3639	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.61, 1.54]
1.22 Grade 3 or 4 transaminitis	2	2330	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.48, 3.85]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.23 Grade 3 or 4 fatigue	3	2956	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.76, 2.18]
1.24 Grade 3 or 4 myalgia	2	2157	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.04, 1.34]
1.25 Grade 3 or 4 arthralgia	2	2157	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.07, 1.26]
1.26 Grade 3 or 4 anorexia	2	2330	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.13, 5.87]
1.27 Grade 3 or 4 diarrhoea	4	3639	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.77, 2.15]
1.28 Grade 3 or 4 vomiting	4	3639	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.62, 1.33]
1.29 Grade ≥ 2 neuropathy	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.29.1 Not otherwise specified	3	3013	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.43, 1.42]
1.29.2 Sensory neuropathy	2	2214	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.64, 1.87]
1.29.3 Motor neuropathy	2	2214	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.69, 1.73]
1.30 Grade 3 or 4 neuropathy	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.30.1 Not otherwise specified	4	3639	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.64, 1.94]
1.30.2 Sensory neuropathy	3	2840	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.79, 1.77]
1.30.3 Motor neuropathy	3	2840	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.67, 2.49]
1.31 Any-grade alopecia	2	2330	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.65, 1.17]
1.32 Any-grade mucositis	2	2330	Risk Ratio (M-H, Random, 95% CI)	3.55 [0.37, 34.17]
1.33 Grade 3 or 4 hypersensitivity	2	2157	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.44, 1.59]
1.34 Treatment discontinuation	3	2108	Risk Ratio (M-H, Random, 95% CI)	1.86 [1.42, 2.42]
1.35 Dose modification	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.35.1 Dose delay	3	3050	Risk Ratio (M-H, Random, 95% CI)	1.57 [1.21, 2.03]
1.35.2 Dose reduction	2	2367	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.38, 1.58]
1.35.3 Dose omission	1	1566	Risk Ratio (M-H, Random, 95% CI)	2.98 [2.40, 3.70]

Analysis 1.1. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 1: Progression-free survival

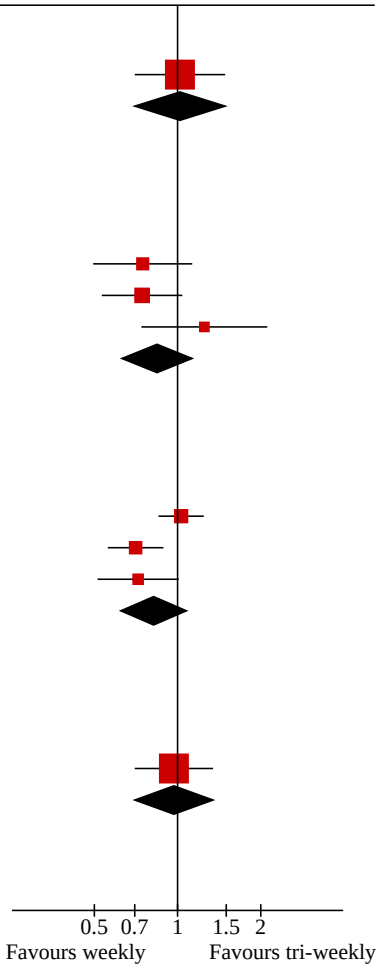
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
GOG-0262	-0.1165	0.0892	22.4%	0.89 [0.75 , 1.06]
ICON-8	-0.0609	0.0627	35.1%	0.94 [0.83 , 1.06]
JGOG-3016	-0.2744	0.0919	21.4%	0.76 [0.63 , 0.91]
MITO-7	-0.0408	0.093	21.1%	0.96 [0.80 , 1.15]
Total (95% CI)			**100.0%**	**0.89 [0.81 , 0.98]**

Heterogeneity: Tau² = 0.00; Chi² = 4.37, df = 3 (P = 0.22); I² = 31%
Test for overall effect: Z = 2.31 (P = 0.02)
Test for subgroup differences: Not applicable



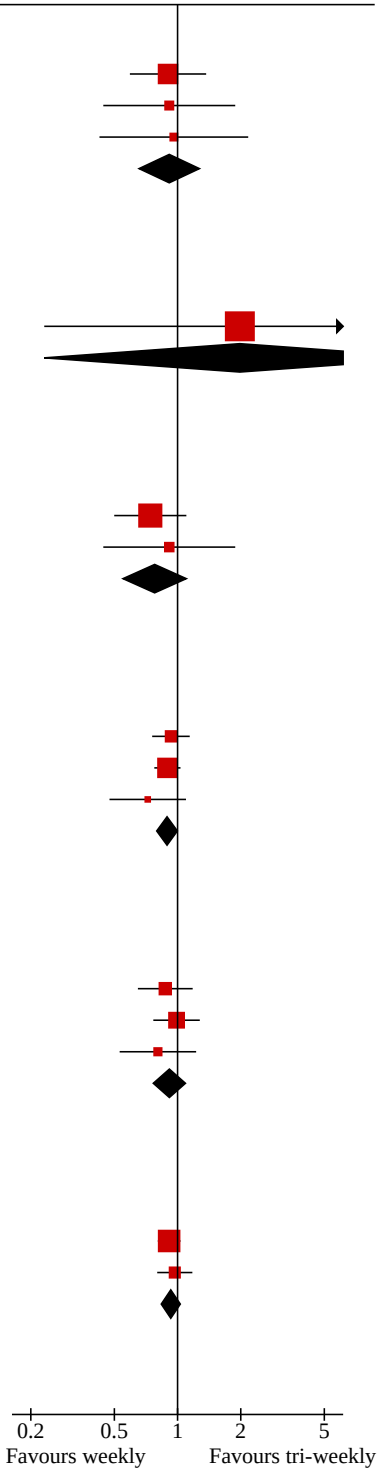
Analysis 1.2. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 2: Progression-free survival, subgroup analysis by residual disease

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.2.1 Absent				
MITO-7	0.0198	0.1921	100.0%	1.02 [0.70 , 1.49]
Subtotal (95% CI)			**100.0%**	**1.02 [0.70 , 1.49]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.10 (P = 0.92)				
1.2.2 ≤ 1 cm				
GOG-0262	-0.2904	0.2105	33.3%	0.75 [0.50 , 1.13]
JGOG-3016	-0.2957	0.1711	43.0%	0.74 [0.53 , 1.04]
MITO-7	0.2231	0.2675	23.7%	1.25 [0.74 , 2.11]
Subtotal (95% CI)			**100.0%**	**0.84 [0.63 , 1.13]**
Heterogeneity: Tau² = 0.02; Chi² = 2.99, df = 2 (P = 0.22); I² = 33%				
Test for overall effect: Z = 1.15 (P = 0.25)				
1.2.3 > 1 cm				
GOG-0262	0.0296	0.0962	38.1%	1.03 [0.85 , 1.24]
JGOG-3016	-0.3496	0.1183	34.8%	0.70 [0.56 , 0.89]
MITO-7	-0.3285	0.1727	27.1%	0.72 [0.51 , 1.01]
Subtotal (95% CI)			**100.0%**	**0.82 [0.62 , 1.08]**
Heterogeneity: Tau² = 0.04; Chi² = 7.40, df = 2 (P = 0.02); I² = 73%				
Test for overall effect: Z = 1.43 (P = 0.15)				
1.2.4 No surgery				
MITO-7	-0.0305	0.1664	100.0%	0.97 [0.70 , 1.34]
Subtotal (95% CI)			**100.0%**	**0.97 [0.70 , 1.34]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.18 (P = 0.85)				
Test for subgroup differences: Chi² = 1.26, df = 3 (P = 0.74), I² = 0%				



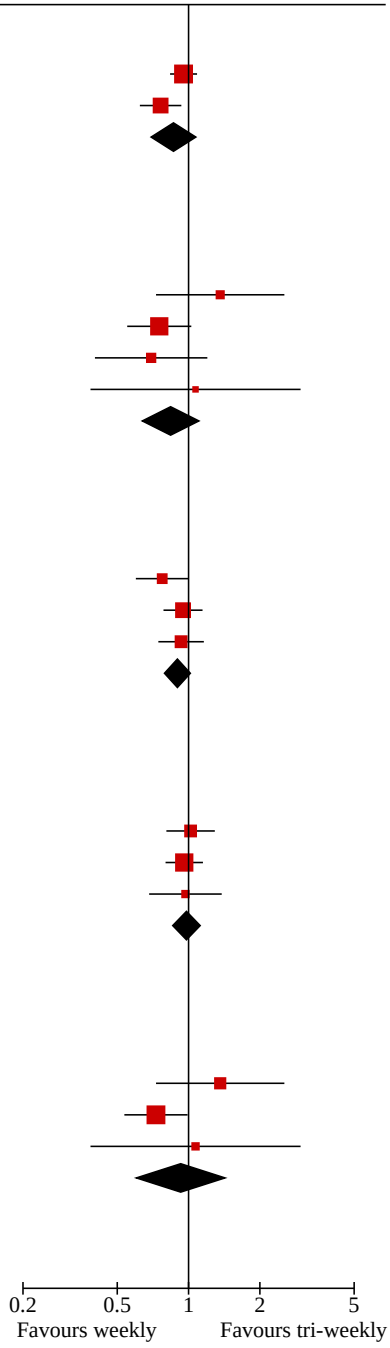
Analysis 1.3. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 3: Progression-free survival, subgroup analysis by FIGO stage

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.3.1 Stage I or II				
ICON-8	-0.1047	0.2134	62.6%	0.90 [0.59 , 1.37]
JGOG-3016	-0.091	0.3691	20.9%	0.91 [0.44 , 1.88]
MITO-7	-0.0408	0.4161	16.5%	0.96 [0.42 , 2.17]
Subtotal (95% CI)			**100.0%**	**0.91 [0.66 , 1.27]**
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 2 (P = 0.99); I² = 0%				
Test for overall effect: Z = 0.54 (P = 0.59)				
1.3.2 Stage I				
ICON-8	0.683	1.0945	100.0%	1.98 [0.23 , 16.91]
Subtotal (95% CI)			**100.0%**	**1.98 [0.23 , 16.91]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.62 (P = 0.53)				
1.3.3 Stage II				
ICON-8	-0.2991	0.2018	77.0%	0.74 [0.50 , 1.10]
JGOG-3016	-0.091	0.3691	23.0%	0.91 [0.44 , 1.88]
Subtotal (95% CI)			**100.0%**	**0.78 [0.55 , 1.10]**
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.62); I² = 0%				
Test for overall effect: Z = 1.42 (P = 0.16)				
1.3.4 Stage III				
GOG-0262	-0.0726	0.105	30.3%	0.93 [0.76 , 1.14]
ICON-8	-0.1115	0.0732	62.4%	0.89 [0.77 , 1.03]
JGOG-3016	-0.3271	0.214	7.3%	0.72 [0.47 , 1.10]
Subtotal (95% CI)			**100.0%**	**0.89 [0.80 , 1.00]**
Heterogeneity: Tau² = 0.00; Chi² = 1.15, df = 2 (P = 0.56); I² = 0%				
Test for overall effect: Z = 2.00 (P = 0.05)				
1.3.5 Stage IV				
GOG-0262	-0.1347	0.1532	34.5%	0.87 [0.65 , 1.18]
ICON-8	-0.0111	0.13	47.9%	0.99 [0.77 , 1.28]
JGOG-3016	-0.2157	0.214	17.7%	0.81 [0.53 , 1.23]
Subtotal (95% CI)			**100.0%**	**0.91 [0.77 , 1.09]**
Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 2 (P = 0.67); I² = 0%				
Test for overall effect: Z = 1.00 (P = 0.32)				
1.3.6 Stage III or IV				
ICON-8	-0.0926	0.0633	70.7%	0.91 [0.81 , 1.03]
MITO-7	-0.0305	0.0983	29.3%	0.97 [0.80 , 1.18]
Subtotal (95% CI)			**100.0%**	**0.93 [0.84 , 1.03]**
Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 1 (P = 0.60); I² = 0%				
Test for overall effect: Z = 1.40 (P = 0.16)				
Test for subgroup differences: Chi² = 1.56, df = 5 (P = 0.91), I² = 0%				



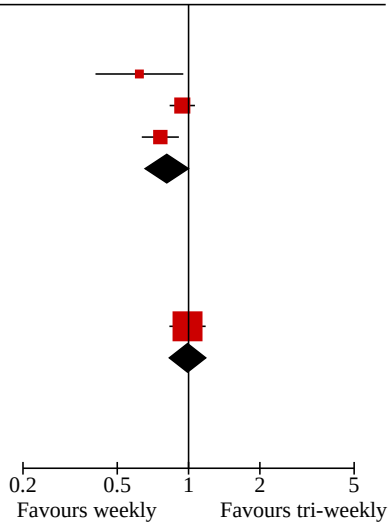
Analysis 1.4. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 4: Progression-free survival, subgroup analysis by ECOG status

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.4.1 ECOG 0 or 1				
ICON-8	-0.0487	0.0669	56.1%	0.95 [0.84 , 1.09]
JGOG-3016	-0.2718	0.1028	43.9%	0.76 [0.62 , 0.93]
Subtotal (95% CI)			**100.0%**	**0.86 [0.70 , 1.07]**
Heterogeneity: Tau² = 0.02; Chi² = 3.31, df = 1 (P = 0.07); I² = 70%				
Test for overall effect: Z = 1.32 (P = 0.19)				
1.4.2 ECOG 2, 3, or 4				
GOG-0262	0.3075	0.3182	17.4%	1.36 [0.73 , 2.54]
ICON-8	-0.2848	0.1589	53.6%	0.75 [0.55 , 1.03]
JGOG-3016	-0.3638	0.2787	22.0%	0.70 [0.40 , 1.20]
MITO-7	0.0677	0.5209	6.9%	1.07 [0.39 , 2.97]
Subtotal (95% CI)			**100.0%**	**0.84 [0.64 , 1.11]**
Heterogeneity: Tau² = 0.01; Chi² = 3.43, df = 3 (P = 0.33); I² = 13%				
Test for overall effect: Z = 1.25 (P = 0.21)				
1.4.3 ECOG 0				
GOG-0262	-0.2562	0.1307	24.0%	0.77 [0.60 , 1.00]
ICON-8	-0.054	0.0968	43.8%	0.95 [0.78 , 1.15]
MITO-7	-0.0726	0.1128	32.2%	0.93 [0.75 , 1.16]
Subtotal (95% CI)			**100.0%**	**0.90 [0.79 , 1.02]**
Heterogeneity: Tau² = 0.00; Chi² = 1.70, df = 2 (P = 0.43); I² = 0%				
Test for overall effect: Z = 1.69 (P = 0.09)				
1.4.4 ECOG 1				
GOG-0262	0.0198	0.1201	32.0%	1.02 [0.81 , 1.29]
ICON-8	-0.042	0.0927	53.7%	0.96 [0.80 , 1.15]
MITO-7	-0.0305	0.1799	14.3%	0.97 [0.68 , 1.38]
Subtotal (95% CI)			**100.0%**	**0.98 [0.86 , 1.12]**
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 2 (P = 0.92); I² = 0%				
Test for overall effect: Z = 0.30 (P = 0.76)				
1.4.5 ECOG 2				
GOG-0262	0.3075	0.3182	29.6%	1.36 [0.73 , 2.54]
ICON-8	-0.3169	0.1567	55.9%	0.73 [0.54 , 0.99]
MITO-7	0.0677	0.5209	14.5%	1.07 [0.39 , 2.97]
Subtotal (95% CI)			**100.0%**	**0.93 [0.60 , 1.42]**
Heterogeneity: Tau² = 0.06; Chi² = 3.34, df = 2 (P = 0.19); I² = 40%				
Test for overall effect: Z = 0.35 (P = 0.73)				
Test for subgroup differences: Chi² = 1.75, df = 4 (P = 0.78), I² = 0%				

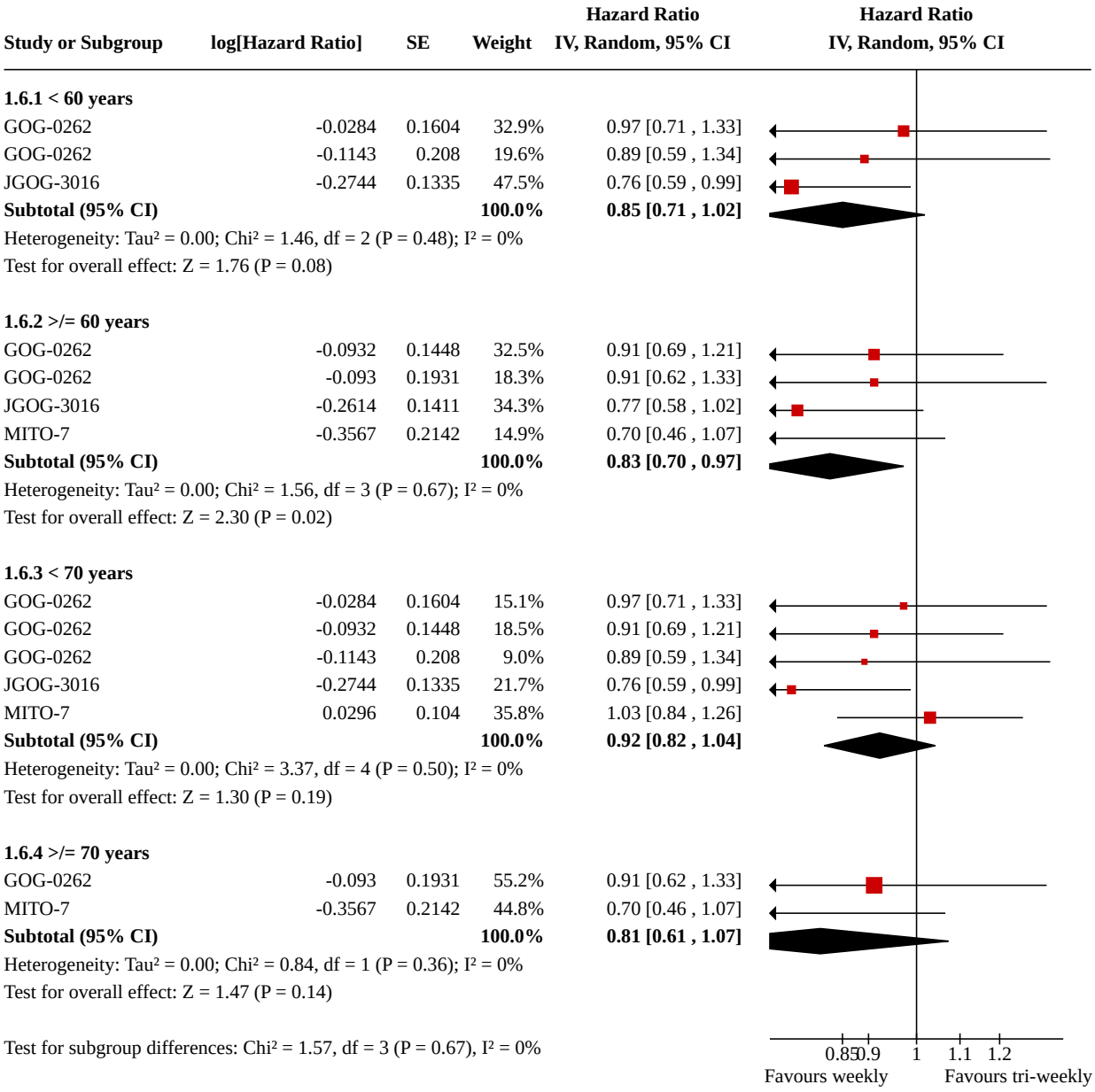


Analysis 1.5. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 5: Progression-free survival, subgroup analysis by bevacizumab receipt

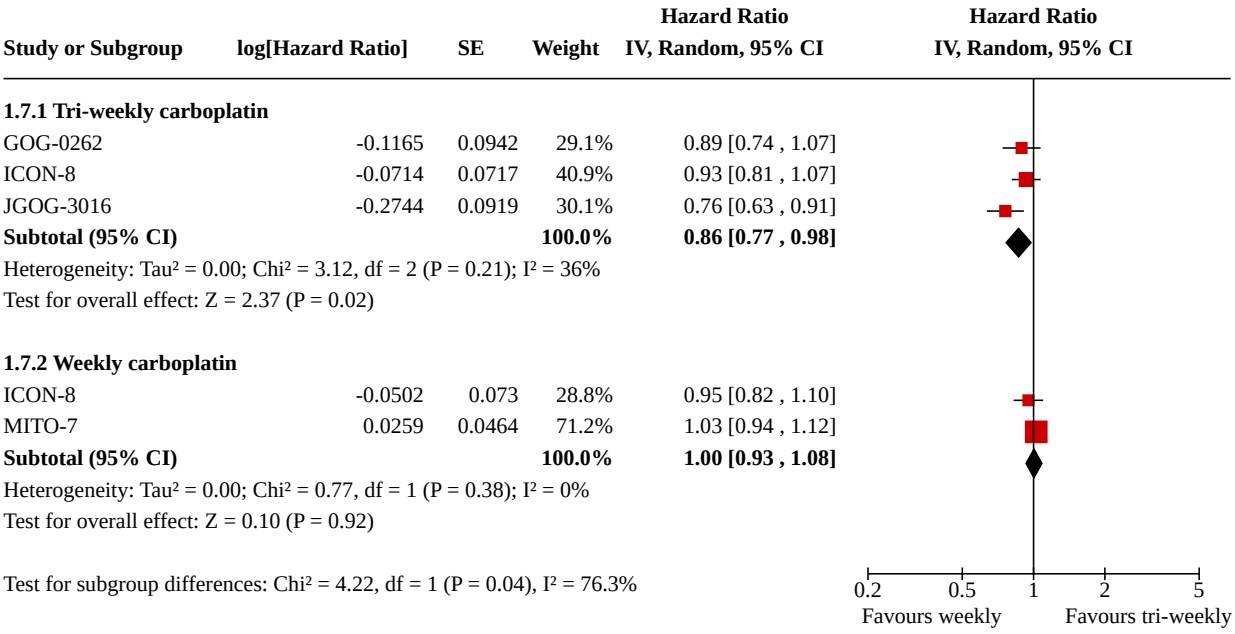
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.5.1 No bevacizumab				
GOG-0262	-0.478	0.2177	16.6%	0.62 [0.40 , 0.95]
ICON-8	-0.0609	0.0627	45.1%	0.94 [0.83 , 1.06]
JGOG-3016	-0.2744	0.0919	38.3%	0.76 [0.63 , 0.91]
Subtotal (95% CI)			**100.0%**	**0.81 [0.66 , 1.00]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 6.12$, df = 2 (P = 0.05); $I^2 = 67\%$				
Test for overall effect: Z = 1.98 (P = 0.05)				
1.5.2 Received bevacizumab				
GOG-0262	-0.0101	0.0899	100.0%	0.99 [0.83 , 1.18]
Subtotal (95% CI)			**100.0%**	**0.99 [0.83 , 1.18]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.11 (P = 0.91)				
Test for subgroup differences: $Chi^2 = 2.09$, df = 1 (P = 0.15), $I^2 = 52.1\%$				



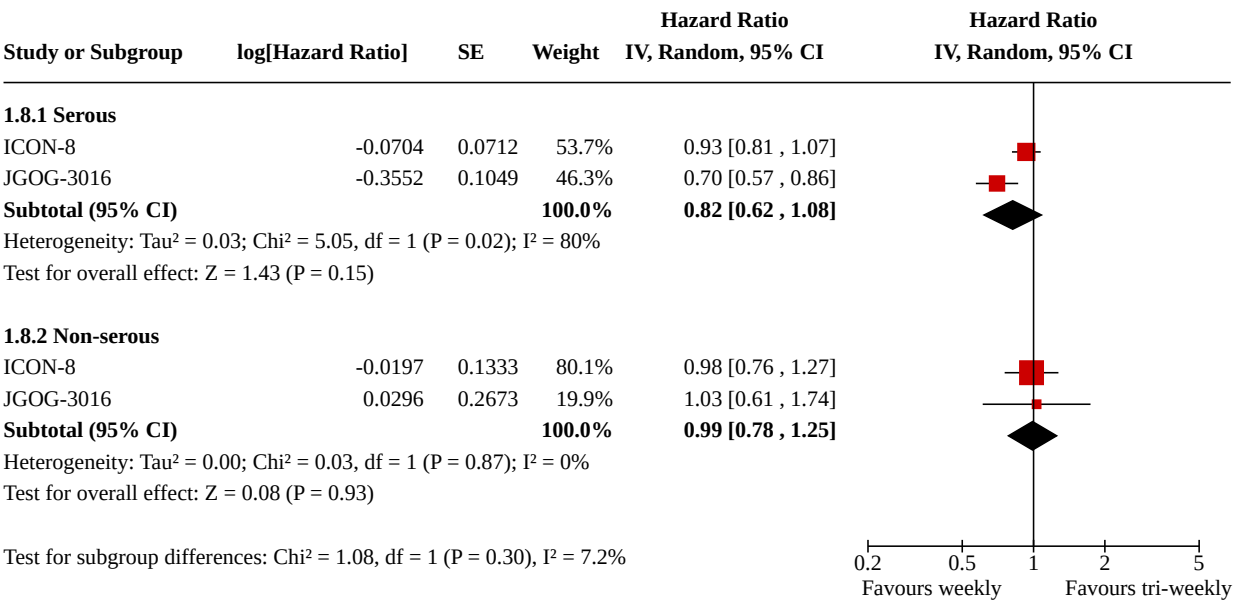
Analysis 1.6. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 6: Progression-free survival, subgroup analysis by age distribution



Analysis 1.7. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 7: Progression-free survival, subgroup analysis by carboplatin schedule



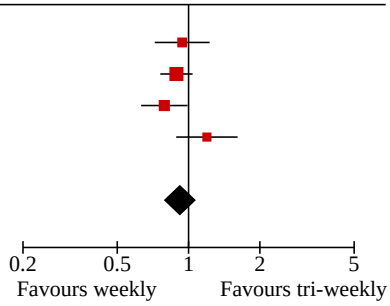
Analysis 1.8. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 8: Progression-free survival, subgroup analysis by histotype



Analysis 1.9. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 9: Overall Survival

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
GOG-0262	-0.0619	0.136	20.3%	0.94 [0.72 , 1.23]
ICON-8	-0.1178	0.0801	37.0%	0.89 [0.76 , 1.04]
JGOG-3016	-0.2357	0.1151	25.3%	0.79 [0.63 , 0.99]
MITO-7	0.1781	0.1521	17.3%	1.19 [0.89 , 1.61]
Total (95% CI)			**100.0%**	**0.92 [0.79 , 1.06]**

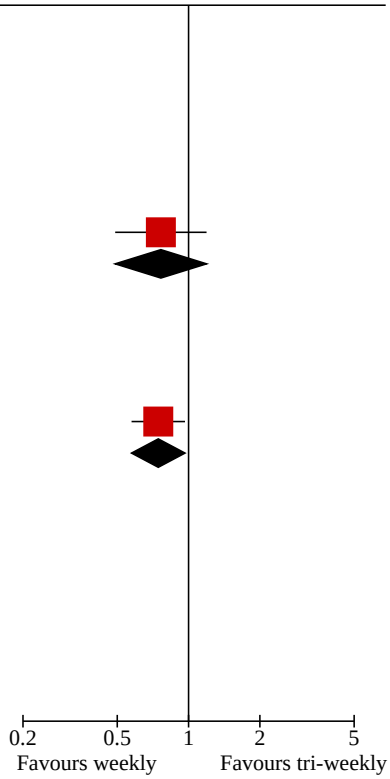
Heterogeneity: Tau² = 0.01; Chi² = 4.86, df = 3 (P = 0.18); I² = 38%
Test for overall effect: Z = 1.15 (P = 0.25)
Test for subgroup differences: Not applicable



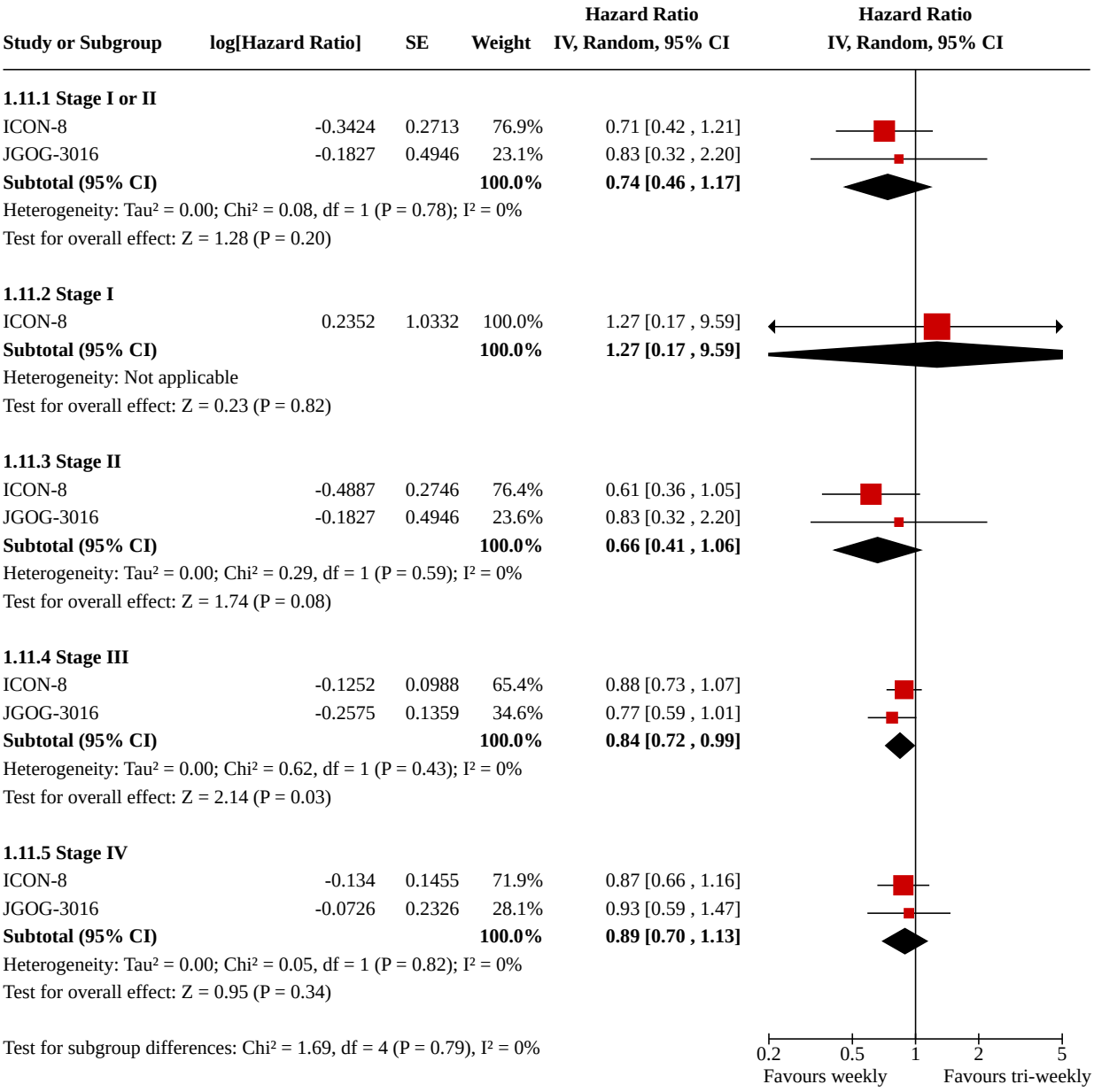
Analysis 1.10. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 10: Overall survival, subgroup analysis by residual disease

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.10.1 Absent				
Subtotal (95% CI)				**Not estimable**
Heterogeneity: Not applicable				
Test for overall effect: Not applicable				
1.10.2 ≤ 1 cm				
JGOG-3016	-0.2692	0.2265	100.0%	0.76 [0.49 , 1.19]
Subtotal (95% CI)			**100.0%**	**0.76 [0.49 , 1.19]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.19 (P = 0.23)				
1.10.3 > 1 cm				
JGOG-3016	-0.2944	0.1325	100.0%	0.74 [0.57 , 0.97]
Subtotal (95% CI)			**100.0%**	**0.74 [0.57 , 0.97]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.22 (P = 0.03)				
1.10.4 No surgery				
Subtotal (95% CI)				**Not estimable**
Heterogeneity: Not applicable				
Test for overall effect: Not applicable				

Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%

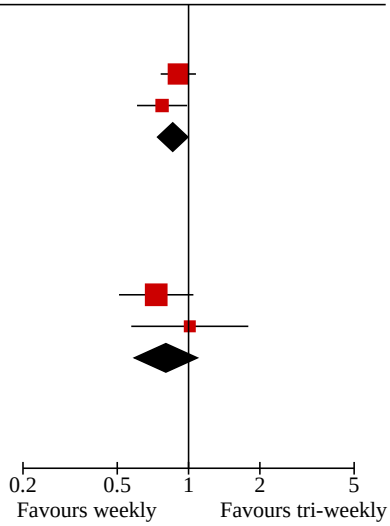


Analysis 1.11. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 11: Overall survival, subgroup analysis by FIGO stage



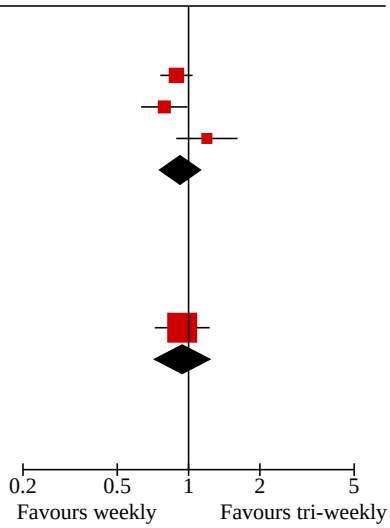
Analysis 1.12. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 12: Overall survival, subgroup analysis by ECOG status

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.12.1 ECOG 0 or 1				
ICON-8	-0.0996	0.0874	65.6%	0.91 [0.76 , 1.07]
JGOG-3016	-0.2575	0.1242	34.4%	0.77 [0.61 , 0.99]
Subtotal (95% CI)			**100.0%**	**0.86 [0.74 , 0.99]**
Heterogeneity: Tau² = 0.00; Chi² = 1.08, df = 1 (P = 0.30); I² = 7%				
Test for overall effect: Z = 2.05 (P = 0.04)				
1.12.2 ECOG 2, 3 or 4				
ICON-8	-0.3145	0.1844	71.2%	0.73 [0.51 , 1.05]
JGOG-3016	0.0119	0.2902	28.8%	1.01 [0.57 , 1.79]
Subtotal (95% CI)			**100.0%**	**0.80 [0.59 , 1.09]**
Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 1 (P = 0.34); I² = 0%				
Test for overall effect: Z = 1.42 (P = 0.16)				
Test for subgroup differences: Chi² = 0.15, df = 1 (P = 0.70), I² = 0%				



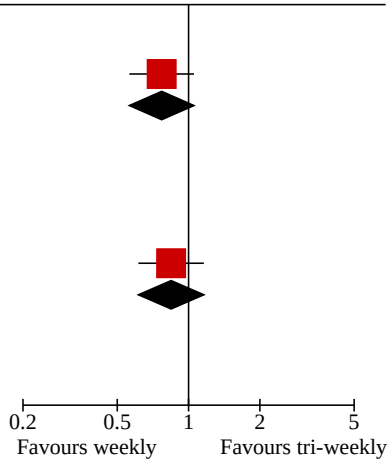
Analysis 1.13. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 13: Overall survival, subgroup analysis by bevacizumab receipt

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.13.1 No bevacizumab				
ICON-8	-0.1178	0.0801	42.3%	0.89 [0.76 , 1.04]
JGOG-3016	-0.2357	0.1151	32.9%	0.79 [0.63 , 0.99]
MITO-7	0.1781	0.1521	24.9%	1.19 [0.89 , 1.61]
Subtotal (95% CI)			**100.0%**	**0.92 [0.76 , 1.12]**
Heterogeneity: Tau² = 0.02; Chi² = 4.78, df = 2 (P = 0.09); I² = 58%				
Test for overall effect: Z = 0.82 (P = 0.41)				
1.13.2 Mixed population of participants who did/did not receive bevacizumab				
GOG-0262	-0.0619	0.136	100.0%	0.94 [0.72 , 1.23]
Subtotal (95% CI)			**100.0%**	**0.94 [0.72 , 1.23]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.46 (P = 0.65)				
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.90), I² = 0%				



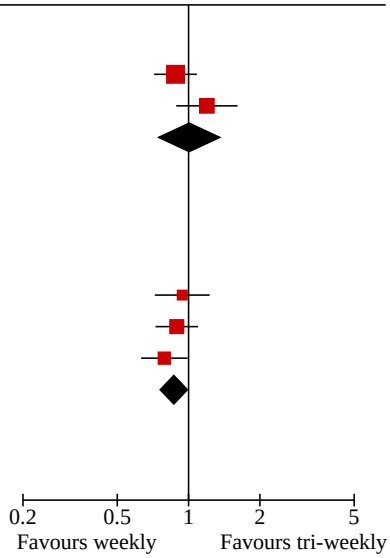
Analysis 1.14. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 14: Overall survival, subgroup analysis by age distribution

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.14.1 < 60 years				
JGOG-3016	-0.2614	0.1602	100.0%	0.77 [0.56 , 1.05]
Subtotal (95% CI)			**100.0%**	**0.77 [0.56 , 1.05]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.63 (P = 0.10)				
1.14.2 >/= 60 years				
JGOG-3016	-0.1696	0.1623	100.0%	0.84 [0.61 , 1.16]
Subtotal (95% CI)			**100.0%**	**0.84 [0.61 , 1.16]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.04 (P = 0.30)				
Test for subgroup differences: Chi² = 0.16, df = 1 (P = 0.69), I² = 0%				



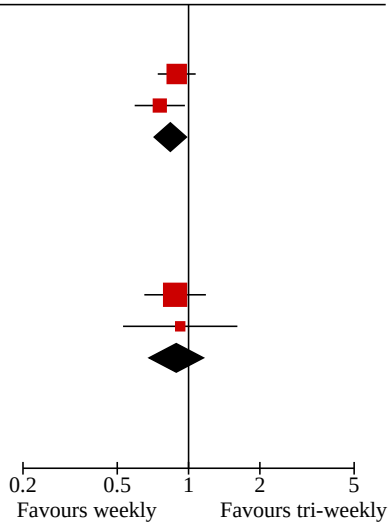
Analysis 1.15. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 15: Overall survival, subgroup analysis by carboplatin schedule in dose-dense arm

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.15.1 Weekly carboplatin				
ICON-8	-0.1268	0.106	56.4%	0.88 [0.72 , 1.08]
MITO-7	0.1781	0.1521	43.6%	1.19 [0.89 , 1.61]
Subtotal (95% CI)			**100.0%**	**1.01 [0.75 , 1.35]**
Heterogeneity: Tau² = 0.03; Chi² = 2.70, df = 1 (P = 0.10); I² = 63%				
Test for overall effect: Z = 0.04 (P = 0.97)				
1.15.2 Tri-weekly carboplatin				
GOG-0262	-0.0619	0.136	24.6%	0.94 [0.72 , 1.23]
ICON-8	-0.1148	0.1051	41.1%	0.89 [0.73 , 1.10]
JGOG-3016	-0.2357	0.1151	34.3%	0.79 [0.63 , 0.99]
Subtotal (95% CI)			**100.0%**	**0.87 [0.76 , 0.99]**
Heterogeneity: Tau² = 0.00; Chi² = 1.08, df = 2 (P = 0.58); I² = 0%				
Test for overall effect: Z = 2.13 (P = 0.03)				
Test for subgroup differences: Chi² = 0.81, df = 1 (P = 0.37), I² = 0%				



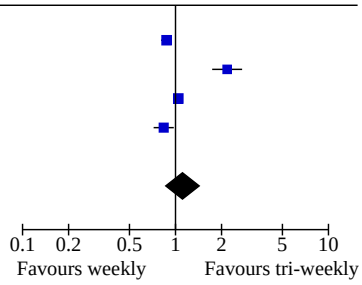
Analysis 1.16. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 16: Overall survival, subgroup analysis by histotype

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.16.1 Serous				
ICON-8	-0.1152	0.094	62.3%	0.89 [0.74 , 1.07]
JGOG-3016	-0.2797	0.1245	37.7%	0.76 [0.59 , 0.96]
Subtotal (95% CI)			**100.0%**	**0.84 [0.72 , 0.98]**
Heterogeneity: Tau² = 0.00; Chi² = 1.11, df = 1 (P = 0.29); I² = 10%				
Test for overall effect: Z = 2.22 (P = 0.03)				
1.16.2 Non-serous				
ICON-8	-0.1308	0.1526	77.5%	0.88 [0.65 , 1.18]
JGOG-3016	-0.0812	0.2835	22.5%	0.92 [0.53 , 1.61]
Subtotal (95% CI)			**100.0%**	**0.89 [0.68 , 1.15]**
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.88); I² = 0%				
Test for overall effect: Z = 0.89 (P = 0.37)				
Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.71), I² = 0%				



Analysis 1.17. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 17: Grade 3 or 4 neutropenia

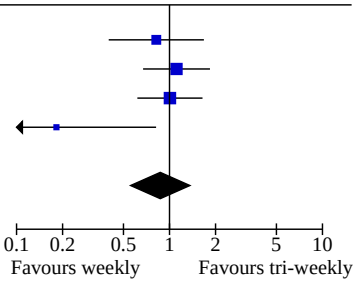
Study or Subgroup	Weekly Events	Weekly Total	Tri-weekly Events	Tri-weekly Total	Weight	Risk Ratio M-H, Random, 95% CI
GOG-0262	246	340	284	343	26.3%	0.87 [0.81 , 0.95]
ICON-8	333	1023	76	508	22.2%	2.18 [1.74 , 2.73]
JGOG-3016	286	312	276	314	26.8%	1.04 [0.99 , 1.10]
MITO-7	167	399	200	400	24.7%	0.84 [0.72 , 0.97]
Total (95% CI)		**2074**		**1565**	**100.0%**	**1.11 [0.86 , 1.43]**
Total events:	1032		836			
Heterogeneity: Tau² = 0.06; Chi² = 73.70, df = 3 (P < 0.00001); I² = 96%						
Test for overall effect: Z = 0.82 (P = 0.41)						
Test for subgroup differences: Not applicable						



Analysis 1.18. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 18: Febrile neutropenia

Study or Subgroup	Weekly Events	Weekly Total	Tri-weekly Events	Tri-weekly Total	Weight	Risk Ratio M-H, Random, 95% CI
GOG-0262	13	340	16	343	23.5%	0.82 [0.40 , 1.68]
ICON-8	47	1023	21	508	34.0%	1.11 [0.67 , 1.84]
JGOG-3016	29	312	29	314	34.8%	1.01 [0.62 , 1.64]
MITO-7	2	399	11	400	7.7%	0.18 [0.04 , 0.82]
Total (95% CI)		**2074**		**1565**	**100.0%**	**0.87 [0.56 , 1.36]**
Total events:	91		77			

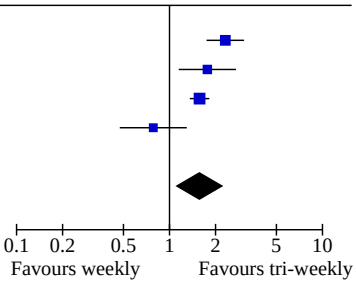
Heterogeneity: Tau² = 0.09; Chi² = 5.30, df = 3 (P = 0.15); I² = 43%
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Not applicable



Analysis 1.19. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 19: Grade 3 or 4 anaemia

Study or Subgroup	Weekly Events	Weekly Total	Tri-weekly Events	Tri-weekly Total	Weight	Risk Ratio M-H, Random, 95% CI
GOG-0262	124	340	54	343	27.3%	2.32 [1.75 , 3.07]
ICON-8	89	1023	25	508	21.8%	1.77 [1.15 , 2.72]
JGOG-3016	214	312	137	314	31.7%	1.57 [1.36 , 1.82]
MITO-7	25	399	32	400	19.2%	0.78 [0.47 , 1.30]
Total (95% CI)		**2074**		**1565**	**100.0%**	**1.57 [1.12 , 2.20]**
Total events:	452		248			

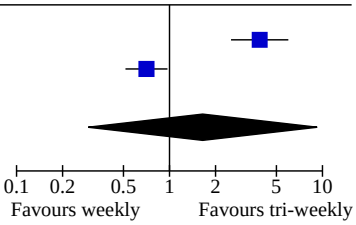
Heterogeneity: Tau² = 0.09; Chi² = 14.47, df = 3 (P = 0.002); I² = 79%
Test for overall effect: Z = 2.61 (P = 0.009)
Test for subgroup differences: Not applicable



Analysis 1.20. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 20: Grade 3 or 4 leucopenia

Study or Subgroup	Weekly Events	Weekly Total	Tri-weekly Events	Tri-weekly Total	Weight	Risk Ratio M-H, Random, 95% CI
ICON-8	171	1044	22	522	49.6%	3.89 [2.52 , 5.98]
MITO-7	55	399	78	400	50.4%	0.71 [0.52 , 0.97]
Total (95% CI)		**1443**		**922**	**100.0%**	**1.65 [0.29 , 9.23]**
Total events:	226		100			

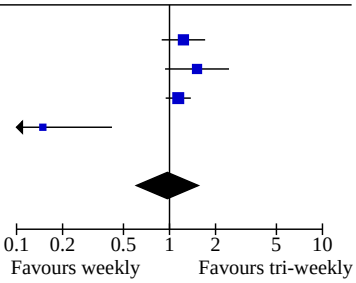
Heterogeneity: Tau² = 1.51; Chi² = 41.56, df = 1 (P < 0.00001); I² = 98%
Test for overall effect: Z = 0.57 (P = 0.57)
Test for subgroup differences: Not applicable



Analysis 1.21. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 21: Grade 3 or 4 thrombocytopenia

Study or Subgroup	Weekly Events	Weekly Total	Tri-weekly Events	Tri-weekly Total	Weight	Risk Ratio M-H, Random, 95% CI
GOG-0262	66	340	54	343	29.5%	1.23 [0.89 , 1.71]
ICON-8	64	1023	21	508	25.2%	1.51 [0.94 , 2.45]
JGOG-3016	136	312	120	314	32.6%	1.14 [0.94 , 1.38]
MITO-7	4	399	27	400	12.7%	0.15 [0.05 , 0.42]
Total (95% CI)		**2074**		**1565**	**100.0%**	**0.97 [0.61 , 1.54]**
Total events:	270		222			

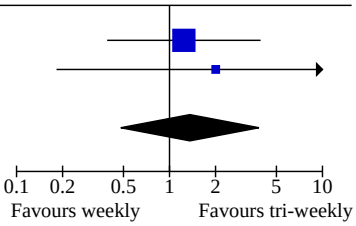
Heterogeneity: Tau² = 0.16; Chi² = 16.63, df = 3 (P = 0.0008); I² = 82%
Test for overall effect: Z = 0.14 (P = 0.89)
Test for subgroup differences: Not applicable



Analysis 1.22. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 22: Grade 3 or 4 transaminitis

Study or Subgroup	Weekly Events	Weekly Total	Tri-weekly Events	Tri-weekly Total	Weight	Risk Ratio M-H, Random, 95% CI
ICON-8	10	1023	4	508	81.2%	1.24 [0.39 , 3.94]
MITO-7	2	399	1	400	18.8%	2.01 [0.18 , 22.02]
Total (95% CI)		**1422**		**908**	**100.0%**	**1.36 [0.48 , 3.85]**
Total events:	12		5			

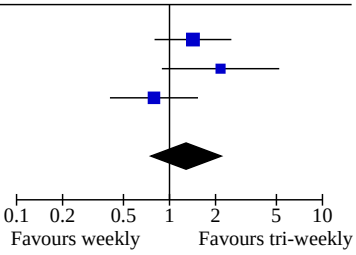
Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.58 (P = 0.56)
Test for subgroup differences: Not applicable



Analysis 1.23. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 23: Grade 3 or 4 fatigue

Study or Subgroup	Weekly Events	Weekly Total	Tri-weekly Events	Tri-weekly Total	Weight	Risk Ratio M-H, Random, 95% CI
ICON-8	43	1023	15	508	40.4%	1.42 [0.80 , 2.54]
JGOG-3016	15	312	7	314	24.6%	2.16 [0.89 , 5.22]
MITO-7	15	399	19	400	35.1%	0.79 [0.41 , 1.54]
Total (95% CI)		**1734**		**1222**	**100.0%**	**1.28 [0.76 , 2.18]**
Total events:	73		41			

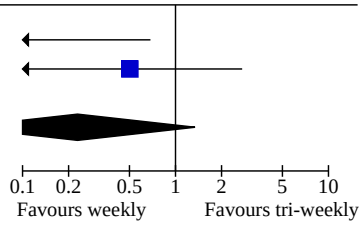
Heterogeneity: Tau² = 0.09; Chi² = 3.49, df = 2 (P = 0.17); I² = 43%
Test for overall effect: Z = 0.92 (P = 0.36)
Test for subgroup differences: Not applicable



Analysis 1.24. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 24: Grade 3 or 4 myalgia

Study or Subgroup	Weekly Events	Weekly Total	Tri-weekly Events	Tri-weekly Total	Weight	Risk Ratio M-H, Random, 95% CI
ICON-8	1	1023	6	508	43.7%	0.08 [0.01 , 0.69]
JGOG-3016	2	312	4	314	56.3%	0.50 [0.09 , 2.73]
Total (95% CI)		**1335**		**822**	**100.0%**	**0.23 [0.04 , 1.34]**
Total events:	3		10			

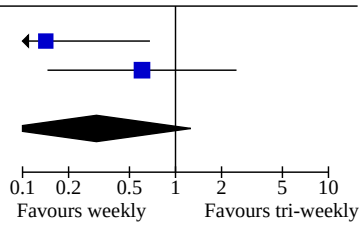
Heterogeneity: Tau² = 0.70; Chi² = 1.74, df = 1 (P = 0.19); I² = 42%
Test for overall effect: Z = 1.63 (P = 0.10)
Test for subgroup differences: Not applicable



Analysis 1.25. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 25: Grade 3 or 4 arthralgia

Study or Subgroup	Weekly Events	Weekly Total	Tri-weekly Events	Tri-weekly Total	Weight	Risk Ratio M-H, Random, 95% CI
ICON-8	2	1023	7	508	47.3%	0.14 [0.03 , 0.68]
JGOG-3016	3	312	5	314	52.7%	0.60 [0.15 , 2.51]
Total (95% CI)		**1335**		**822**	**100.0%**	**0.30 [0.07 , 1.26]**
Total events:	5		12			

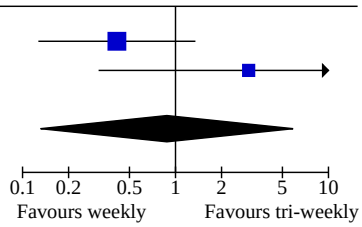
Heterogeneity: Tau² = 0.47; Chi² = 1.80, df = 1 (P = 0.18); I² = 45%
Test for overall effect: Z = 1.64 (P = 0.10)
Test for subgroup differences: Not applicable



Analysis 1.26. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 26: Grade 3 or 4 anorexia

Study or Subgroup	Weekly Events	Weekly Total	Tri-weekly Events	Tri-weekly Total	Weight	Risk Ratio M-H, Random, 95% CI
ICON-8	5	1023	6	508	62.1%	0.41 [0.13 , 1.35]
MITO-7	3	399	1	400	37.9%	3.01 [0.31 , 28.79]
Total (95% CI)		**1422**		**908**	**100.0%**	**0.88 [0.13 , 5.87]**
Total events:	8		7			

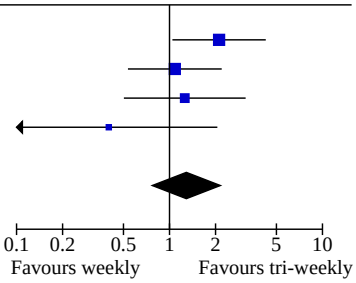
Heterogeneity: Tau² = 1.15; Chi² = 2.36, df = 1 (P = 0.12); I² = 58%
Test for overall effect: Z = 0.13 (P = 0.89)
Test for subgroup differences: Not applicable



Analysis 1.27. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 27: Grade 3 or 4 diarrhoea

Study or Subgroup	Weekly Events	Weekly Total	Tri-weekly Events	Tri-weekly Total	Weight	Risk Ratio M-H, Random, 95% CI
GOG-0262	23	340	11	343	34.0%	2.11 [1.04 , 4.26]
ICON-8	24	1023	11	508	33.8%	1.08 [0.53 , 2.19]
JGOG-3016	10	312	8	314	23.4%	1.26 [0.50 , 3.15]
MITO-7	2	399	5	400	8.9%	0.40 [0.08 , 2.05]
Total (95% CI)		**2074**		**1565**	**100.0%**	**1.29 [0.77 , 2.15]**
Total events:	59		35			

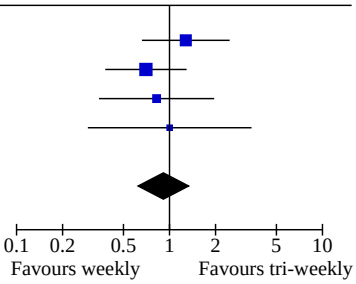
Heterogeneity: Tau² = 0.07; Chi² = 4.06, df = 3 (P = 0.25); I² = 26%
Test for overall effect: Z = 0.97 (P = 0.33)
Test for subgroup differences: Not applicable



Analysis 1.28. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 28: Grade 3 or 4 vomiting

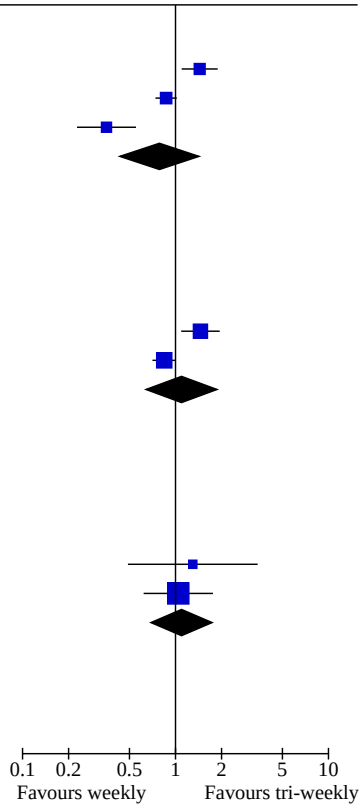
Study or Subgroup	Weekly Events	Weekly Total	Tri-weekly Events	Tri-weekly Total	Weight	Risk Ratio M-H, Random, 95% CI
GOG-0262	19	340	15	343	33.0%	1.28 [0.66 , 2.47]
ICON-8	24	1023	17	508	38.4%	0.70 [0.38 , 1.29]
JGOG-3016	9	312	11	314	19.1%	0.82 [0.35 , 1.96]
MITO-7	5	399	5	400	9.5%	1.00 [0.29 , 3.44]
Total (95% CI)		**2074**		**1565**	**100.0%**	**0.91 [0.62 , 1.33]**
Total events:	57		48			

Heterogeneity: Tau² = 0.00; Chi² = 1.79, df = 3 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable



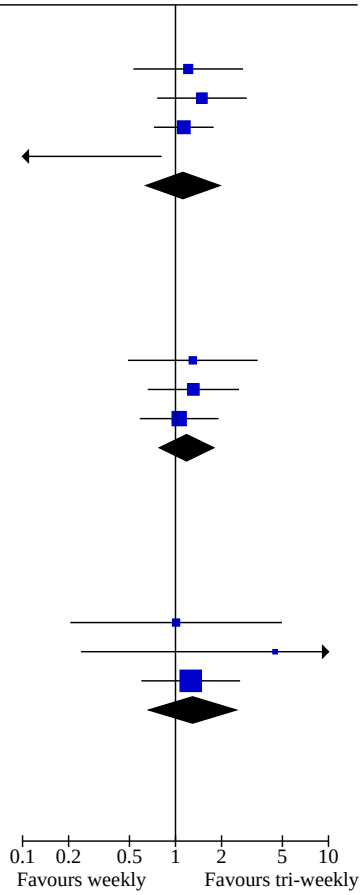
Analysis 1.29. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 29: Grade ≥ 2 neuropathy

Study or Subgroup	Weekly Events	Weekly Total	Tri-weekly Events	Tri-weekly Total	Weight	Risk Ratio M-H, Random, 95% CI
1.29.1 Not otherwise specified						
GOG-0262	97	340	68	343	34.0%	1.44 [1.10 , 1.89]
ICON-8	285	1023	163	508	35.6%	0.87 [0.74 , 1.02]
MITO-7	24	399	68	400	30.4%	0.35 [0.23 , 0.55]
Subtotal (95% CI)		**1762**		**1251**	**100.0%**	**0.78 [0.43 , 1.42]**
Total events:	406		299			
Heterogeneity: Tau² = 0.25; Chi² = 28.83, df = 2 (P < 0.00001); I² = 93%						
Test for overall effect: Z = 0.80 (P = 0.43)						
1.29.2 Sensory neuropathy						
GOG-0262	88	340	61	343	47.7%	1.46 [1.09 , 1.95]
ICON-8	243	1023	143	508	52.3%	0.84 [0.71 , 1.01]
Subtotal (95% CI)		**1363**		**851**	**100.0%**	**1.09 [0.64 , 1.87]**
Total events:	331		204			
Heterogeneity: Tau² = 0.13; Chi² = 9.91, df = 1 (P = 0.002); I² = 90%						
Test for overall effect: Z = 0.33 (P = 0.74)						
1.29.3 Motor neuropathy						
GOG-0262	9	340	7	343	22.2%	1.30 [0.49 , 3.44]
ICON-8	42	1023	20	508	77.8%	1.04 [0.62 , 1.76]
Subtotal (95% CI)		**1363**		**851**	**100.0%**	**1.09 [0.69 , 1.73]**
Total events:	51		27			
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%						
Test for overall effect: Z = 0.39 (P = 0.70)						
Test for subgroup differences: Chi² = 0.89, df = 2 (P = 0.64), I² = 0%						



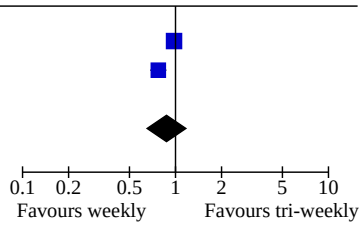
Analysis 1.30. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 30: Grade 3 or 4 neuropathy

Study or Subgroup	Weekly Events	Weekly Total	Tri-weekly Events	Tri-weekly Total	Weight	Risk Ratio M-H, Random, 95% CI
1.30.1 Not otherwise specified						
GOG-0262	12	340	10	343	24.9%	1.21 [0.53 , 2.76]
ICON-8	33	1023	11	508	30.6%	1.49 [0.76 , 2.92]
JGOG-3016	36	312	32	314	40.9%	1.13 [0.72 , 1.78]
MITO-7	0	399	10	400	3.6%	0.05 [0.00 , 0.81]
Subtotal (95% CI)		**2074**		**1565**	**100.0%**	**1.12 [0.64 , 1.94]**
Total events:	81		63			
Heterogeneity: Tau² = 0.14; Chi² = 5.81, df = 3 (P = 0.12); I² = 48%						
Test for overall effect: Z = 0.40 (P = 0.69)						
1.30.2 Sensory neuropathy						
GOG-0262	9	340	7	343	17.4%	1.30 [0.49 , 3.44]
ICON-8	29	1023	11	508	35.3%	1.31 [0.66 , 2.60]
JGOG-3016	21	312	20	314	47.3%	1.06 [0.58 , 1.91]
Subtotal (95% CI)		**1675**		**1165**	**100.0%**	**1.18 [0.79 , 1.77]**
Total events:	59		38			
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 2 (P = 0.88); I² = 0%						
Test for overall effect: Z = 0.80 (P = 0.42)						
1.30.3 Motor neuropathy						
GOG-0262	3	340	3	343	17.0%	1.01 [0.21 , 4.96]
ICON-8	4	1023	0	508	5.0%	4.47 [0.24 , 82.93]
JGOG-3016	15	312	12	314	78.0%	1.26 [0.60 , 2.64]
Subtotal (95% CI)		**1675**		**1165**	**100.0%**	**1.29 [0.67 , 2.49]**
Total events:	22		15			
Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 2 (P = 0.67); I² = 0%						
Test for overall effect: Z = 0.77 (P = 0.44)						
Test for subgroup differences: Chi² = 0.11, df = 2 (P = 0.95), I² = 0%						



Analysis 1.31. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 31: Any-grade alopecia

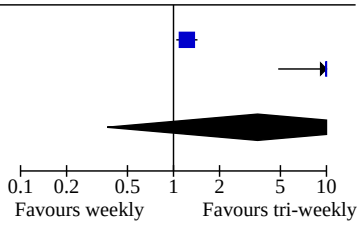
Study or Subgroup	Weekly Events	Weekly Total	Tri-weekly Events	Tri-weekly Total	Weight	Risk Ratio M-H, Random, 95% CI
ICON-8	914	1023	464	508	52.0%	0.98 [0.95 , 1.01]
MITO-7	201	399	261	400	48.0%	0.77 [0.68 , 0.87]
Total (95% CI)		**1422**		**908**	**100.0%**	**0.87 [0.65 , 1.17]**
Total events:	1115		725			
Heterogeneity: Tau² = 0.04; Chi² = 21.48, df = 1 (P < 0.00001); I² = 95%						
Test for overall effect: Z = 0.91 (P = 0.36)						
Test for subgroup differences: Not applicable						



Analysis 1.32. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 32: Any-grade mucositis

Study or Subgroup	Weekly Events	Weekly Total	Tri-weekly Events	Tri-weekly Total	Weight	Risk Ratio M-H, Random, 95% CI
ICON-8	362	1023	147	508	51.6%	1.22 [1.04 , 1.43]
MITO-7	66	399	6	400	48.4%	11.03 [4.84 , 25.14]
Total (95% CI)		**1422**		**908**	**100.0%**	**3.55 [0.37 , 34.17]**
Total events:	428		153			

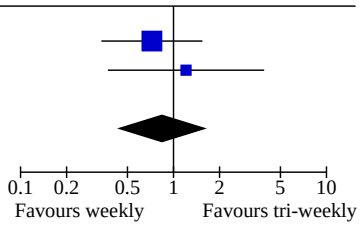
Heterogeneity: Tau² = 2.58; Chi² = 29.16, df = 1 (P < 0.00001); I² = 97%
Test for overall effect: Z = 1.10 (P = 0.27)
Test for subgroup differences: Not applicable



Analysis 1.33. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 33: Grade 3 or 4 hypersensitivity

Study or Subgroup	Weekly Events	Weekly Total	Tri-weekly Events	Tri-weekly Total	Weight	Risk Ratio M-H, Random, 95% CI
ICON-8	16	1023	11	508	70.5%	0.72 [0.34 , 1.54]
JGOG-3016	6	312	5	314	29.5%	1.21 [0.37 , 3.92]
Total (95% CI)		**1335**		**822**	**100.0%**	**0.84 [0.44 , 1.59]**
Total events:	22		16			

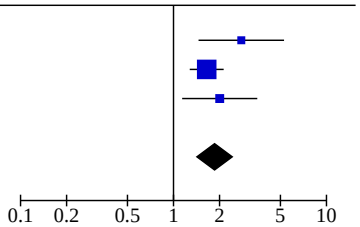
Heterogeneity: Tau² = 0.00; Chi² = 0.52, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 0.53 (P = 0.59)
Test for subgroup differences: Not applicable



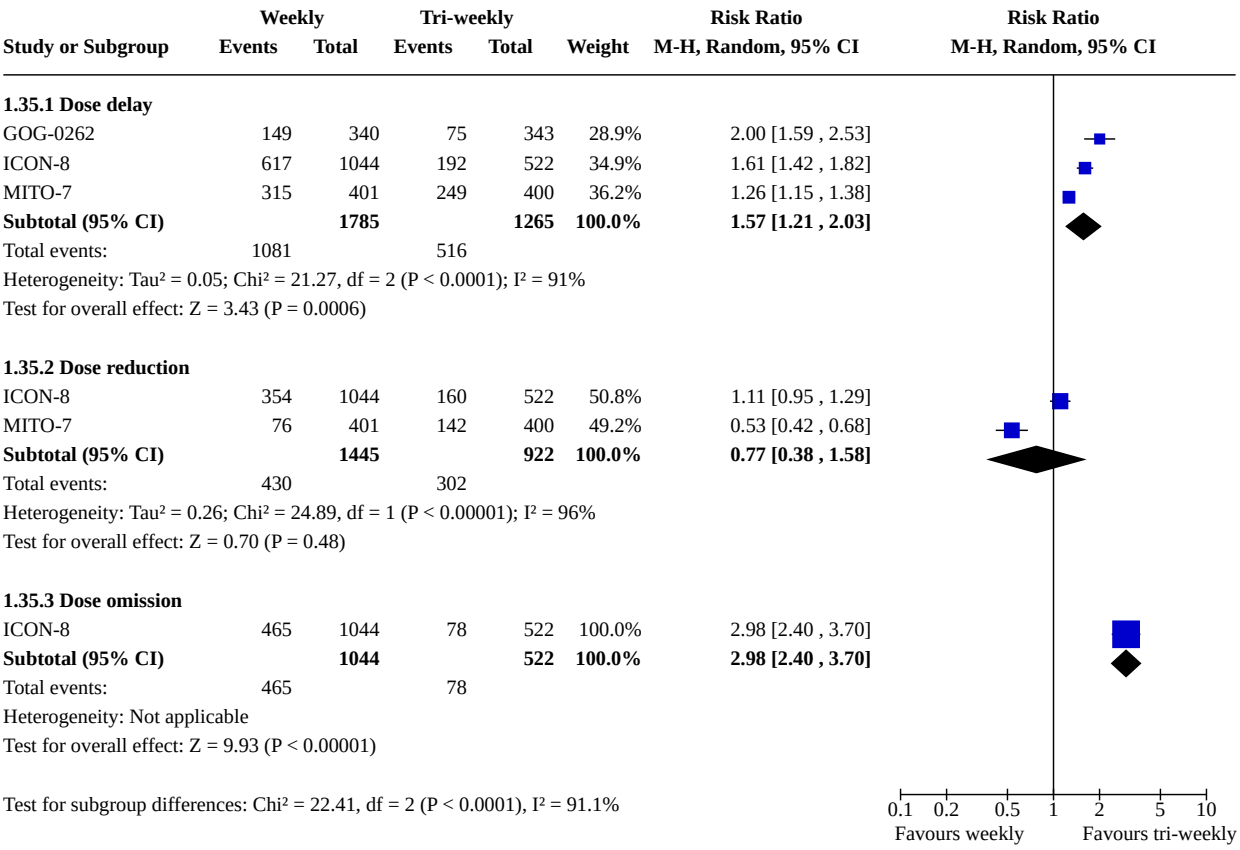
Analysis 1.34. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 34: Treatment discontinuation

Study or Subgroup	Weekly Events	Weekly Total	Tri-weekly Events	Tri-weekly Total	Weight	Risk Ratio M-H, Random, 95% CI
GOG-0262	33	340	12	343	15.4%	2.77 [1.46 , 5.28]
JGOG-3016	113	312	69	314	65.1%	1.65 [1.28 , 2.13]
MITO-7	34	399	17	400	19.4%	2.01 [1.14 , 3.53]
Total (95% CI)		**1051**		**1057**	**100.0%**	**1.86 [1.42 , 2.42]**
Total events:	180		98			

Heterogeneity: Tau² = 0.01; Chi² = 2.38, df = 2 (P = 0.30); I² = 16%
Test for overall effect: Z = 4.56 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.35. Comparison 1: Weekly paclitaxel plus carboplatin compared to tri-weekly paclitaxel plus carboplatin for first-line treatment, Outcome 35: Dose modification



APPENDICES

Appendix 1. Search strategy - CENTRAL

#1 mesh explode Ovarian Neoplasms/
#2 (ovar* near/5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*))
#3 #1 or #2
#4 mesh explode Paclitaxel/
#5 (paclitaxel or taxol or praxel or anzatax or nsc125973 or nsc 125973 or paxene or onxol or abraxane).mp.
#6 #4 or #5
#7 mesh explode Drug Administration Schedule/
#8 mesh descriptor AD
#9 (dose or dosage or dosing or dose-dense or PcW or Pc3W or week or weekly or schedule*).mp.
#10 #7 or #8 or #9
#11 #3 and #6 and #10

Appendix 2. Search strategy - MEDLINE OVID

1 exp Ovarian Neoplasms/
2 (ovar* adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*)).mp.
3 1 or 2
4 Paclitaxel/
5 (paclitaxel or taxol or praxel or anzatax or nsc125973 or nsc 125973 or paxene or onxol or abraxane).mp.
6 4 or 5
7 exp Drug Administration Schedule/
8 ad.fs.
9 (dose or dosage or dosing or dose-dense or PcW or Pc3W or week or weekly or schedule*).mp.

10 7 or 8 or 9
11 randomized controlled trial.pt.
12 controlled clinical trial.pt.
13 randomized.ab.
14 placebo.ab.
15 Clinical trials as topic.sh.
16 randomly.ab.
17 Trial.ti.
18 11 or 12 or 13 or 14 or 15 or 16 or 17
19 Animals.sh. not (humans.sh. and animals.sh.)
20 18 not 19
21 3 and 6 and 10 and 20

Key:
mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier
ab=abstract
fs=floating subheading

Appendix 3. Search strategy - Embase OVID

1. exp ovary tumor/
2. (ovar* adj5 (cancer* or tumor* or tumour* or neoplas* or carcinoma* or adenocarcinoma* or malignan*)).mp.
3. 1 or 2
4. exp paclitaxel/
5. (paclitaxel or taxol or praxel or anzatax or nsc125973 or nsc 125973 or paxene or onxol or abraxane).mp.
6. 4 or 5
7. exp drug administration/
8. ad.fs.
9. (dose or dosage or dosing or dose-dense or PcW or Pc3W or week or weekly or schedule*).mp.
10. 7 or 8 or 9
11. crossover procedure/
12. double-blind procedure/
13. randomised controlled trial/
14. single-blind procedure/
15. random*.mp.
16. factorial*.mp.
17. (crossover* or cross over* or cross-over*).mp.
18. placebo*.mp.
19. (double* adj blind*).mp.
20. (singl* adj blind*).mp.
21. assign*.mp.
22. allocat*.mp.
23. volunteer*.mp.
24. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 3 and 6 and 10 and 24

Appendix 4. Risk of bias criteria

We used the following criteria to assess risk of bias.

- Random sequence generation
  - Low risk of bias, e.g. participants assigned to treatments on basis of a computer-generated random sequence or a table of random numbers.
  - High risk of bias, e.g. participants assigned to treatments on basis of date of birth, clinic id-number or surname, or no attempt to randomise participants.
  - Unclear risk of bias, e.g. not reported, information not available.
- Allocation concealment
  - Low risk of bias, e.g. where the allocation sequence could not be foretold.
  - High risk of bias, e.g. allocation sequence could be foretold by women, investigators or treatment providers.
  - Unclear risk of bias, e.g. not reported.

- Blinding of participants and personnel (NB blinding of women and treatment providers is usually only possible for pharmacological interventions)
  - Low risk of bias if participants and personnel were adequately blinded.
  - High risk of bias if participants were not blinded to the intervention that the participant received.
  - Unclear risk of bias if this was not reported or unclear.
- Blinding of outcome assessors
  - Low risk of bias if outcome assessors were adequately blinded.
  - High risk of bias if outcome assessors were not blinded to the intervention that the participant received.
  - Unclear risk of bias if this was not reported or unclear.
- Incomplete outcome data: recorded the proportion of participants whose outcomes were not reported at the end of the study. We coded a satisfactory level of loss to follow-up for each outcome as follows.
  - Low risk of bias if fewer than 20% of women were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms.
  - High risk of bias if more than 20% of women were lost to follow-up or reasons for loss to follow-up differed between treatment arms.
  - Unclear risk of bias if loss to follow-up was not reported.
- Selective reporting of outcomes
  - Low risk of bias, e.g. review reports all outcomes specified in the protocol.
  - High risk of bias, e.g. It is suspected that outcomes have been selectively reported.
  - Unclear risk of bias, e.g. It is unclear whether outcomes had been selectively reported.
- Other bias
  - Low risk of bias if review authors do not suspect any other source of bias and the trial appears to be methodologically sound.
  - High risk of bias if review authors suspect that the trial was prone to an additional bias.
  - Unclear risk of bias if review authors are uncertain whether an additional bias may have been present.

HISTORY

Protocol first published: Issue 12, 2015

CONTRIBUTIONS OF AUTHORS

Obtained copies of trials: Nicholas Syn, Natalie Ngoi, Elizabeth James, Adrian Cook, Andrew Clamp
Selected which trials to include: Natalie Ngoi, Nicholas Syn, David Tan, Robby Goh
Extracted data from trials: Nicholas Syn, Natalie Ngoi, Robby Goh
Entered data into RevMan: Nicholas Syn, Natalie Ngoi
Carried out the analysis: Nicholas Syn, Natalie Ngoi
Interpreted the analysis: Natalie Ngoi, Nicholas Syn, David Tan, Yu Yang Soon, Robby Goh, Boon Cher Goh, Ruby Huang, Elizabeth James, Adrian Cook, Andrew Clamp
Drafted the final review: Natalie Ngoi, Nicholas Syn, David Tan, Yu Yang Soon, Robby Goh, Boon Cher Goh, Ruby Huang, Elizabeth James, Adrian Cook, Andrew Clamp
Update the review: Natalie Ngoi, Nicholas Syn, David Tan, Yu Yang Soon, Robby Goh, Boon Cher Goh, Ruby Huang, Elizabeth James, Adrian Cook, Andrew Clamp

DECLARATIONS OF INTEREST

Natalie Ngoi: has declared that they have no conflict of interest.
Nicholas Li-Xun Syn: has declared that they have no conflict of interest.
Robby M Goh: has declared that they have no conflict of interest.
Boon Cher Goh: has declared that they have no conflict of interest.
Ruby Yun-Ju Huang: has declared that they have no conflict of interest.
Yu Yang Soon: has declared that they have no conflict of interest.
Elizabeth James: was a study investigator of a study eligible for inclusion - ICON-8 trial. This trial is funded by the charity Cancer Research UK, and supported by the UK Medical Research Council.
Adrian Cook: was a study investigator of a study eligible for inclusion - ICON-8 trial. This trial is funded by the charity Cancer Research UK, and supported by the UK Medical Research Council.
Andrew Clamp: was the chief investigator of a study eligible for inclusion - ICON-8 trial. This trial is funded by the charity Cancer Research UK, and supported by the UK Medical Research Council.
David Shao Peng Tan: reports having received grants from the Singapore Ministry of Health's National Medical Research Council Clinician Scientist award and Pangestu Family Foundation Gynaecological Cancer Research Fund. He also reports fees for advisory board and

consultancy roles from AstraZeneca, Roche, MSD, Merck Serono, GSK and Eisai for a presentation; paid to himself. In additional he reports research funding AstraZeneca, Roche, Bayer, BMS, MSD, Eisai, and Karyopharm.; paid to institution. He also reports have stock ownership in the Asian Microbiome Library (AMiLi); personal payment. He declares that none of the companies listed have an interest in the interventions related to this review.

SOURCES OF SUPPORT

Internal sources

- None, Other

External sources

- None, Other

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- In our protocol, we stated that we would only include randomised controlled trials. In the review, we further elaborated that we considered both full text and abstract publications.
- In our protocol, we stated that interventions considered would be weekly paclitaxel, including metronomic (similar cumulative dosage) or dose-dense (increased cumulative dosage) in combination with carboplatin. The control considered would be tri-weekly paclitaxel in combination with carboplatin. Other chemotherapeutic agents, including platinum agents, molecular therapies such as those which target the epidermal growth factor receptor (i.e. anti-EGFR), and immunotherapy are allowed, but must be given in both groups which are being compared. In the review, we have specified the dose range for carboplatin in intervention and control as carboplatin AUC (area under curve) to a total dose of 5 mg/mL to 6 mg/mL per cycle. We have also specified the dose range for paclitaxel in control as paclitaxel 175 mg/m^2 to 180 mg/m^2, dosed every three weeks.
- In our protocol, we stated the primary toxicity outcome to be severe (grade 3 to 4) neutropenia. In our review we further elaborated that this refers to grading classified according to Common Terminology Criteria for Adverse Events (CTCAE) version 2.0, 3.0 and 4.0.
- In our review we also reached out to trial study teams for individualised participant data; this was not stated in the protocol.
- In our review, for time-to-event data, we additionally performed individual participant data analysis. We used individual participant data if available from the trial study team. If individual participant data were not available, we extracted information about time-to-event outcomes using the methods described by Guyot 2012. This was not stated in the protocol.
- We provided detailed methods on reconstruction and synthesis of individual participant data in the review; this was not stated in the protocol.
- We intended to perform subgroup analyses related to participant ethnicity and intraperitoneal chemotherapy. However, we could not carry this out due to limited information available.
- We performed additional subgroup analyses to what was initially planned. Additional subgroup analyses that were not stated in the protocol include analyses by: FIGO disease stage, ECOG performance status, participant age distribution, epithelial ovarian cancer histotype and frequency of carboplatin dosing.