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Angiogenesis inhibitors for the treatment of epithelial ovarian cancer (Review)

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[Intervention Review]

Angiogenesis inhibitors for the treatment of epithelial ovarian cancer

Kezia Gaitskell[1], Ewelina Rogozińska[2], Sarah Platt[3,4], Yifan Chen[5], Mohamed Abd El Aziz[6], Abigail Tattersall[7], Jo Morrison[8]

[1]Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK. [2]The Evidence-Based Medicine Consultancy Ltd, Bath, UK. [3]Obstetrics and Gynaecology, St Mary's Hospital, University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK. [4]Department of Gynaecological Oncology, St. Michael's Hospital, Bristol, UK. [5]Oxford Medical School, University of Oxford, Oxford, UK. [6]Internal Medicine Department, Mercyone North Iowa, Mason City, Iowa, USA. [7]Kingston Hospital NHS Foundation Trust, Kingston upon Thames, UK. [8]Department of Gynaecological Oncology, Musgrove Park Hospital, Somerset NHS Foundation Trust, Taunton, UK

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

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ABSTRACT

Background

Many women, and other females, with epithelial ovarian cancer (EOC) develop resistance to conventional chemotherapy drugs. Drugs that inhibit angiogenesis (development of new blood vessels), essential for tumour growth, control cancer growth by denying blood supply to tumour nodules.

Objectives

To compare the effectiveness and toxicities of angiogenesis inhibitors for treatment of epithelial ovarian cancer (EOC).

Search methods

We identified randomised controlled trials (RCTs) by searching CENTRAL, MEDLINE and Embase (from 1990 to 30 September 2022). We searched clinical trials registers and contacted investigators of completed and ongoing trials for further information.

Selection criteria

RCTs comparing angiogenesis inhibitors with standard chemotherapy, other types of anti-cancer treatment, other angiogenesis inhibitors with or without other treatments, or placebo/no treatment in a maintenance setting, in women with EOC.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. Our outcomes were overall survival (OS), progression-free survival (PFS), quality of life (QoL), adverse events (grade 3 and above) and hypertension (grade 2 and above).

Main results

We identified 50 studies (14,836 participants) for inclusion (including five studies from the previous version of this review): 13 solely in females with newly-diagnosed EOC and 37 in females with recurrent EOC (nine studies in platinum-sensitive EOC; 19 in platinum-resistant EOC; nine with studies with mixed or unclear platinum sensitivity). The main results are presented below.

Newly-diagnosed EOC
Bevacizumab, a monoclonal antibody that binds vascular endothelial growth factor (VEGF), given with chemotherapy and continued as maintenance, likely results in little to no difference in OS compared to chemotherapy alone (hazard ratio (HR) 0.97, 95% confidence interval

(CI) 0.88 to 1.07; 2 studies, 2776 participants; moderate-certainty evidence). Evidence is very uncertain for PFS (HR 0.82, 95% CI 0.64 to 1.05; 2 studies, 2746 participants; very low-certainty evidence), although the combination results in a slight reduction in global QoL (mean difference (MD) -6.4, 95% CI -8.86 to -3.94; 1 study, 890 participants; high-certainty evidence). The combination likely increases any adverse event (grade ≥ 3) (risk ratio (RR) 1.16, 95% CI 1.07 to 1.26; 1 study, 1485 participants; moderate-certainty evidence) and may result in a large increase in hypertension (grade ≥ 2) (RR 4.27, 95% CI 3.25 to 5.60; 2 studies, 2707 participants; low-certainty evidence).

Tyrosine kinase inhibitors (TKIs) to block VEGF receptors (VEGF-R), given with chemotherapy and continued as maintenance, likely result in little to no difference in OS (HR 0.99, 95% CI 0.84 to 1.17; 2 studies, 1451 participants; moderate-certainty evidence) and likely increase PFS slightly (HR 0.88, 95% CI 0.77 to 1.00; 2 studies, 2466 participants; moderate-certainty evidence). The combination likely reduces QoL slightly (MD -1.86, 95% CI -3.46 to -0.26; 1 study, 1340 participants; moderate-certainty evidence), but it increases any adverse event (grade ≥ 3) slightly (RR 1.31, 95% CI 1.11 to 1.55; 1 study, 188 participants; moderate-certainty evidence) and may result in a large increase in hypertension (grade ≥ 3) (RR 6.49, 95% CI 2.02 to 20.87; 1 study, 1352 participants; low-certainty evidence).

Recurrent EOC (platinum-sensitive)
Moderate-certainty evidence from three studies (with 1564 participants) indicates that bevacizumab with chemotherapy, and continued as maintenance, likely results in little to no difference in OS (HR 0.90, 95% CI 0.79 to 1.02), but likely improves PFS (HR 0.56, 95% CI 0.50 to 0.63) compared to chemotherapy alone. The combination may result in little to no difference in QoL (MD 0.8, 95% CI -2.11 to 3.71; 1 study, 486 participants; low-certainty evidence), but it increases the rate of any adverse event (grade ≥ 3) slightly (RR 1.11, 1.07 to 1.16; 3 studies, 1538 participants; high-certainty evidence). Hypertension (grade ≥ 3) was more common in arms with bevacizumab (RR 5.82, 95% CI 3.84 to 8.83; 3 studies, 1538 participants).

TKIs with chemotherapy may result in little to no difference in OS (HR 0.86, 95% CI 0.67 to 1.11; 1 study, 282 participants; low-certainty evidence), likely increase PFS (HR 0.56, 95% CI 0.44 to 0.72; 1 study, 282 participants; moderate-certainty evidence), and may have little to no effect on QoL (MD 6.1, 95% CI -0.96 to 13.16; 1 study, 146 participants; low-certainty evidence). Hypertension (grade ≥ 3) was more common with TKIs (RR 3.32, 95% CI 1.21 to 9.10).

Recurrent EOC (platinum-resistant)
Bevacizumab with chemotherapy and continued as maintenance increases OS (HR 0.73, 95% CI 0.61 to 0.88; 5 studies, 778 participants; high-certainty evidence) and likely results in a large increase in PFS (HR 0.49, 95% CI 0.42 to 0.58; 5 studies, 778 participants; moderate-certainty evidence). The combination may result in a large increase in hypertension (grade ≥ 2) (RR 3.11, 95% CI 1.83 to 5.27; 2 studies, 436 participants; low-certainty evidence). The rate of bowel fistula/perforation (grade ≥ 2) may be slightly higher with bevacizumab (RR 6.89, 95% CI 0.86 to 55.09; 2 studies, 436 participants).

Evidence from eight studies suggest TKIs with chemotherapy likely result in little to no difference in OS (HR 0.85, 95% CI 0.68 to 1.08; 940 participants; moderate-certainty evidence), with low-certainty evidence that it may increase PFS (HR 0.70, 95% CI 0.55 to 0.89; 940 participants), and may result in little to no meaningful difference in QoL (MD ranged from -0.19 at 6 weeks to -3.40 at 4 months). The combination increases any adverse event (grade ≥ 3) slightly (RR 1.23, 95% CI 1.02 to 1.49; 3 studies, 402 participants; high-certainty evidence). The effect on bowel fistula/perforation rates is uncertain (RR 2.74, 95% CI 0.77 to 9.75; 5 studies, 557 participants; very low-certainty evidence).

Authors' conclusions

Bevacizumab likely improves both OS and PFS in platinum-resistant relapsed EOC. In platinum-sensitive relapsed disease, bevacizumab and TKIs probably improve PFS, but may or may not improve OS. The results for TKIs in platinum-resistant relapsed EOC are similar. The effects on OS or PFS in newly-diagnosed EOC are less certain, with a decrease in QoL and increase in adverse events. Overall adverse events and QoL data were more variably reported than were PFS data.

There appears to be a role for anti-angiogenesis treatment, but given the additional treatment burden and economic costs of maintenance treatments, benefits and risks of anti-angiogenesis treatments should be carefully considered.

PLAIN LANGUAGE SUMMARY

Do medicines that restrict new blood vessel growth (angiogenesis inhibitors) help women with epithelial ovarian cancer?

What did we want to find out?

We wanted to find out if treatments that prevent new blood vessel formation (angiogenesis) improve outcomes for women with epithelial ovarian cancer (EOC).

Ovarian cancer is the eighth most common cancer in women (and other females) worldwide, with an annual mortality rate of 4.2 per 100,000 women. EOC originates from the surface layers of ovaries or fallopian tubes and represents 90% of all ovarian cancers.

Treatment of EOC involves surgery to remove cancer deposits and platinum-based chemotherapy (medicines that kill fast-growing cells). However, despite good initial response, many with advanced disease eventually require further treatment.

Cancers need new blood vessels to supply oxygen and nutrients for growth; inhibiting angiogenesis may slow or stop cancer growth. Angiogenesis can be blocked either by smothering the angiogenesis hormone (called VEGF) with a monoclonal antibody (an antibody that recognises a single target) or by interfering with cell responses to VEGF binding with its receptor (VEGF-R), by inhibiting enzymes (tyrosine kinases (TK)) associated with VEGF-R (tyrosine kinase inhibitor (TKI)).

What did we do?

We collected and analysed all relevant studies in women with EOC. Studies compared angiogenesis inhibitors with or without conventional chemotherapy, or different biological agents against treatment with placebo (a dummy medicine), no treatment or different biological agents. We investigated whether these medicines improved how long women with EOC lived after treatment (overall survival (OS)), if medicines delayed disease re-growth (progression-free survival (PFS)), what were the harms (adverse events), and whether they impacted on quality of life. How well EOC responds to subsequent chemotherapy depends on previous chemotherapy treatment and time from last platinum-based chemotherapy, so we analysed the results by whether people had newly-diagnosed or recurrent EOC, and by platinum-sensitivity.

What did we find?

We found 50 studies with 14,836 women.

Main results

Newly-diagnosed EOC

Monoclonal antibody treatment (called bevacizumab or Avastin) given with chemotherapy, and continued as maintenance, probably has little effect on survival following an initial diagnosis of EOC. The evidence for delaying progression is very uncertain. Treatment increases serious side effects and slightly reduces quality of life.

TKIs given with chemotherapy and continued as maintenance, probably have little effect on survival following an initial diagnosis of EOC, but may delay disease progression. Treatment causes a slight reduction in quality of life, and a slight increase in the risk of serious side effects, with a big increase in the risk of needing treatment for high blood pressure (hypertension).

Recurrent EOC (platinum-sensitive; relapse over a year after last platinum chemotherapy)

For women with platinum-sensitive recurrent EOC, bevacizumab given with chemotherapy and continued as maintenance may have little effect on survival, but may delay progression. There may be little impact on quality of life, but treatment slightly increases the risk of serious side effects. All studies found that treatment increased rates of hypertension.

In this same group of women, TKIs given with chemotherapy and continued as maintenance probably have little effect on survival after relapse, likely delays progression, and may have little to no effect on quality of life. We were not able to estimate the effect on overall serious side effects, although serious hypertension was more common with treatment.

Recurrent EOC (platinum-resistant; relapse within six months of last platinum chemotherapy)

For women with platinum-resistant recurrent EOC, bevacizumab increased survival and probably results in a large delay in progression. However, treatment causes significant risk of hypertension and may increase the risk of bowel perforation. Other serious side effects were inconsistently reported, as were quality of life outcomes.

The addition of TKIs to chemotherapy in this group probably doesn't affect survival, but may delay progression, with little meaningful difference in quality of life. However, TKIs increase the risk of serious side effects slightly. The effect of treatment on bowel perforation rates and hypertension is very uncertain, largely due to small studies and different TKI drugs used in different studies.

What are the limitations of the evidence?

This is a rapidly moving field and evidence may change with further studies and longer follow-up of studies.

How up to date is this evidence?

This review updates our previous review of 2011 and is up to date to September 2022.

Key messages

Newly-diagnosed epithelial ovarian cancer (EOC)

The effects of bevacizumab and TKI anti-angiogenesis treatment in women with newly diagnosed EOC are uncertain.

These treatments may have a minimal effect on how long women survive or disease re-growth (progression), with a decrease in quality of life and an increase in serious side effects.

Platinum-sensitive EOC

Bevacizumab and TKIs probably delay progression, but may or may not improve how long women live.

Platinum-resistant EOC

Bevacizumab probably improves how long women live and probably results in a large delay in progression.

TKIs probably delay disease progression, but may or may not improve how long women live.

There appears to be a role for anti-angiogenesis treatment, but additional treatment burden and financial costs of maintenance treatment of anti-angiogenesis treatments should be carefully considered.

SUMMARY OF FINDINGS

Summary of findings 1. Chemotherapy with bevacizumab followed by maintenance bevacizumab compared to chemotherapy alone in newly-diagnosed EOC

Patient or population: newly-diagnosed EOC
Setting: specialist hospital
Intervention: chemotherapy with bevacizumab followed by maintenance bevacizumab
Comparison: chemotherapy alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with chemotherapy alone	Risk with chemotherapy with bevacizumab and as maintenance				
Overall survival (OS) **Assessed with:** survival rate **Follow-up:** range 48.9 to 102.9 months	**Average**[a]		**HR 0.97** (0.88 to 1.07) (alive)	2776 (2 RCTs)	⊕⊕⊕◯ **Moderate**[b,c]	Chemotherapy with bevacizumab likely results in little to no difference in overall survival.
	590 per 1000	**599 per 1000** (569 to 629)				
Progression-free survival (PFS) **Assessed with:** progression-free rate according to RECIST criteria **Follow-up:** range 17.4 to 48.9 months	**Average**[d]		**HR 0.82** (0.64 to 1.05) (progression-free)	2746 (2 RCTs)	⊕◯◯◯ **Very low**[b,c,e]	The evidence is very uncertain about the effect of chemotherapy with bevacizumab on progression-free survival.
	550 per 1000	**612 per 1000** (534 to 682)				
Quality of life (QoL) **Assessed with:** EORTC core QoL questionnaire (QLQ-C30) **Scale from:** 0 to 100 **Follow-up:** 54 weeks	The mean global quality of life score was **76.1**	**MD 6.4 score lower** (8.86 lower to 3.94 lower)	-	890 (1 RCT)	⊕⊕⊕⊕ **High**	Chemotherapy with bevacizumab results in a slight reduction in global quality of life.
Any adverse event grade ≥ 3 **Assessed with:** CTCAE version 3.0-5.0 where reported	566 per 1000	**657 per 1000** (606 to 713)	**RR 1.16** (1.07 to 1.26)	1485 (1 RCT)	⊕⊕⊕◯ **Moderate**[b]	Chemotherapy with bevacizumab likely increases any adverse event (grade ≥ 3) slightly.
Hypertension (grade ≥ 2) **Assessed with:** CTCAE version 3.0-5.0 where reported	44 per 1000	**224 per 1000** (86 to 587)	**RR 4.27** (3.25 to 5.60)	2707 (2 RCTs)	⊕⊕◯◯ **Low**[f]	Chemotherapy with bevacizumab may result in a large increase in hypertension (grade ≥ 2).

Bowel fistula / perforation (grade ≥ 3)	-	-	-	-	-	Outcome not reported

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **CTCAE**: Common Terminology Criteria for Adverse Events; **EOC:** epithelial ovarian cancer; **EORTC:** European Organization for Research and Treatment of Cancer; **HR:** hazard ratio; **MD:** mean difference;**QoL**: quality of life; **RECIST**: Response Evaluation Criteria in Solid Tumors; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]The control risk is an average number of participants reported alive at 36 months in ICON7 2015, GOG-0218 2019 and AGO-OVAR 12 2020 trials (chemotherapy alone arms)
[b]Downgraded by one level due to imprecision (wide confidence interval around the effect estimate crossing a line of no difference)
[c]Evidence of non-proportionality of hazards
[d]The control risk is an average number of participants reported progression-free at 12 months in ICON7 2015, GOG-0218 2019, AGO-OVAR 12 2020, and TRINOVA-3 2019 trials (chemotherapy alone arms)
[e]Downgraded by two levels due to inconsistency (an indicator of statistical heterogeneity, $I^2 > 80\%$)
[f]Downgraded by two levels due to inconsistency (an indicator of statistical heterogeneity, $I^2 = 90\%$)

Summary of findings 2. Chemotherapy with TKI followed by TKI maintenance compared to chemotherapy alone in newly-diagnosed EOC

Patient or population: newly-diagnosed EOC
Setting: specialist hospital
Intervention: chemotherapy with TKI followed by maintenance with TKI
Comparison: chemotherapy alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with chemotherapy alone	Risk with chemotherapy with TKI and as maintenance				
Overall survival (OS) **Assessed with:** survival rate **Follow-up:** 60.9 months	**Average**[a]		**HR 0.99** (0.84 to 1.17) [alive]	1451 (2 RCTs)	⊕⊕⊕○ **Moderate**[b]	Chemotherapy with TKI likely results in little to no difference in OS.
	590 per 1000	**593 per 1000**				

		(539 to 642)				
Progression-free survival (PSF) **Assessed with:** progression-free rate according to RECIST criteria **Follow-up:** 60.9 months	**Average**[c] 550 per 1000	**591 per 1000** (550 to 631)	**HR 0.88** (0.77 to 1.00) [progression-free]	1451 (2 RCTs)	⊕⊕⊕◯ **Moderate**[b]	Chemotherapy with TKI likely increases PFS slightly.
Quality of life (QoL) **Assessed with:** EORTC core QoL questionnaire (QLQ-C30) **Scale from:** 0 to 100 **Follow-up:** not specified	The mean quality of life score was **70.68**	**MD 1.86 score lower** (3.46 lower to 0.26 lower)	-	1340 (1 RCT)	⊕⊕⊕◯ **Moderate**[d]	Chemotherapy with TKI likely reduces QoL slightly, although this may not be clinically significant.
Any adverse event grade ≥ 3 **Assessed with:** CTCAE version 3.0	703 per 1000	**921 per 1000** (780 to 1000)	**RR 1.31** (1.11 to 1.55)	188 (1 RCTs)	⊕⊕⊕◯ **Moderate**[b]	Chemotherapy with TKI likely increases any adverse event (grade ≥ 3) slightly.
Hypertension grade ≥ 3 **Assessed with:** CTCAE version 3.0	7 per 1000	**43 per 1000** (13 to 139)	**RR 6.49** (2.02 to 20.87)	1352 (1 RCT)	⊕⊕◯◯ **Low**[e]	Chemotherapy with TKI may result in a large increase in hypertension grade ≥3.
Bowel fistula / perforation (grade ≥ 3)	-	-	-	-	-	Outcome not reported

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **CTCAE**: Common Terminology Criteria for Adverse Events; **EOC:** epithelial ovarian cancer; **EORTC:** European Organization for Research and Treatment of Cancer; **HR:** hazard ratio; **MD:** mean difference; **QoL**: quality of life; **RECIST**: Response Evaluation Criteria in Solid Tumors; **RR:** risk ratio; **TKI**: tyrosine kinase inhibitor

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.

[a]The control risk is an average number of participants reported alive at 36 months in ICON7 2015, GOG-0218 2019 and AGO-OVAR 12 2020 (chemotherapy alone arms)
[b]Downgraded by one level due to imprecision (wide confidence interval around the effect estimate)
[c]The control risk is an average number of progression-free participants at 12 months in ICON7 2015, GOG-0218 2019, AGO-OVAR 12 2020, and TRINOVA-3 2019 trials (chemotherapy alone arms)
[d]Downgraded by one level due to imprecision (wide confidence interval around the effect estimate)

[e]Downgraded by two levels due to imprecision (very wide confidence interval around the effect estimate)

Summary of findings 3. Chemotherapy with TKI (peptide-Fc fusion protein) followed by TKI maintenance compared to chemotherapy alone in newly-diagnosed EOC

Patient or population: newly-diagnosed EOC
Setting: specialist hospital
Intervention: chemotherapy with TKI (peptide-Fc fusion protein) followed by maintenance TKI
Comparison: chemotherapy alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with chemotherapy alone	Risk with chemotherapy with TKI [peptide-Fc fusion protein] and as maintenance				
Overall survival (OS) **Assessed with:** survival rate **Follow-up:** 27.4 months	Average[a]		**HR 0.99** (0.79 to 1.25) [alive]	1015 (1 RCTs)	⊕⊕⊕○ **Moderate**[b,c]	Chemotherapy with TKI [peptide-Fc fusion protein] likely results in little to no difference in overall survival.
	590 per 1000	593 per 1000 (517 to 659)				
Progression-free survival (PSF) **Assessed with:** progression-free rate according to RECIST criteria **Follow-up:** 27.4 months	Average[d]		**HR 0.93** (0.79 to 1.09) [progression-free]	1015 (1 RCTs)	⊕⊕⊕○ **Moderate**[b]	Chemotherapy with TKI [peptide-Fc fusion protein] likely results in little to no difference in progression-free survival.
	550 per 1000	574 per 1000 (521 to 624)				
Quality of life (QoL)	-	-	-	-	-	Outcome not reported
Any adverse event grade ≥ 3 **Assessed with:** CTCAE version 3.0-5.0 where reported	661 per 1000	Ranged from 727 to 1000	RR ranged from 1.10 (grade 3) to 9.96 (grade 5)	1011 (1 RCTs)	⊕⊕⊕○ **Moderate**[b]	Chemotherapy with TKI [peptide-Fc fusion protein] likely increases any adverse event grade ≥ 3 slightly.
Hypertension grade ≥ 3	-	-	-	-	-	Outcome not reported
Bowel fistula / perforation (grade ≥ 3)	-	-	-	-	-	Outcome not reported

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **CTCAE**: Common Terminology Criteria for Adverse Events; **EOC:** epithelial ovarian cancer; **EORTC:** European Organization for Research and Treatment of Cancer; **HR:** hazard ratio; **MD:** mean difference; **QoL**: quality of life; **RECIST**: Response Evaluation Criteria in Solid Tumors; **RR:** risk ratio; **TKI:** tyrosine kinase inhibitor

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.

[a]The control risk is an average number of participants reported alive at 36 months in ICON7 2015, GOG-0218 2019 and AGO-OVAR 12 2020 (chemotherapy alone arms).
[b]Downgraded by one level due to imprecision (wide confidence interval around the effect estimate)
[c]Immature OS data
[d]The control risk is an average number of progression-free participants at 12 months in ICON7 2015, GOG-0218 2019, AGO-OVAR 12 2020 and TRINOVA-3 2019 trials (chemotherapy alone arms).

Summary of findings 4. Chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone in recurrent platinum-sensitive EOC

Patient or population: recurrent platinum-sensitive EOC
Setting: specialist hospital
Intervention: chemotherapy with bevacizumab followed by maintenance bevacizumab
Comparison: chemotherapy alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with chemotherapy alone	Risk with chemotherapy with bevacizumab and as maintenance				
Overall survival (OS) **Assessed with:** survival rate **Follow-up:** range 20.1 to 49.6 months	**Average**[a]		**HR 0.90** (0.79 to 1.02) [alive]	1564 (3 RCTs)	⊕⊕⊕○ **Moderate**[b]	Chemotherapy with bevacizumab followed by maintenance bevacizumab likely results in little to no difference in overall survival.
	490 per 1000	**526 per 1000** (483 to 569)				

Progression-free survival (PFS) **Assessed with:** progression-free rate according to RECIST versions 1.0-1.1 **Follow-up:** range 20.1 to 49.6 months	**Average**[c] 230 per 1000	**439 per 1000** (396 to 480)	**HR 0.56** (0.50 to 0.63) [progression-free]	1564 (3 RCTs)	⊕⊕⊕○ **Moderate**[d]	Chemotherapy with bevacizumab followed by maintenance bevacizumab likely increases progression free-survival.
Quality of life (QoL) **Assessed with:** TOI-FACT-OC questionnaire **Scale from:** 0 to 152 **Follow-up**: 12 months after cycle 1	The mean quality of life was **77**	**MD 0.8 higher** (2.11 lower to 3.71 higher)	-	486 (1 RCT)	⊕⊕○○ **Low**[e]	Chemotherapy with bevacizumab followed by maintenance bevacizumab likely results in little to no difference in quality of life.
Any adverse event (grade ≥3) **Assessed with:** CTCAE versions 3.0-4.0 where reported	804 per 1000	**892 per 1000** (860 to 933)	**RR 1.11** (1.07 to 1.16)	1538 (3 RCTs)	⊕⊕⊕⊕ **High**	Chemotherapy with bevacizumab followed by maintenance bevacizumab increases any adverse event (grade ≥ 3) slightly.
Hypertension (grade ≥ 2) **Assessed with:** CTCAE versions 3.0-4.0 where reported	-	-	-	-	-	All three trials included in this comparison reported only hypertension grade ≥ 3.
Bowel fistula / perforation (grade ≥ 3) **Assessed with:** CTCAE versions 3.0-4.0 where reported	-	-	-	-	-	Two trials included in this comparison (MITO-16b 2021 and GOG-0213 2017) reported only gastrointestinal perforations of any grade.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **CTCAE**: Common Terminology Criteria for Adverse Events; **EOC:** epithelial ovarian cancer; **EORTC:** European Organization for Research and Treatment of Cancer; **HR:** hazard ratio; **MD:** mean difference; **QoL**: quality of life; **RECIST**: Response Evaluation Criteria in Solid Tumors; **RR:** risk ratio; **TOI-FACT- OC**: Trial Outcome Index score of Functional Assessment of Cancer Therapy—Ovarian Cancer

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.

[a]The control risk is an average number of participants reported alive at 36 months in ICON6 2021, GOG-0213 2017 and OCEANS 2015 trials (chemotherapy arms only).
[b]Downgraded by one level due to imprecision (wide confidence interval around the effect estimate crossing a line of no difference)
[c]The control risk is an average number of participants reported progression-free at 12 months in ICON6 2021, GOG-0213 2017, OCEANS 2015 and MITO-16b 2021 trials (chemotherapy alone arms).
[d]Despite the I^2 statistic equalling 50%, we decided not to downgrade the evidence due to inconsistency as the direction of the effect in all studies favours combination of chemotherapy with bevacizumab over chemotherapy alone.
[e]Downgraded by two levels due to imprecision (very wide confidence interval around the effect estimate crossing line of no difference)

Summary of findings 5. Chemotherapy with TKI followed by TKI maintenance compared to chemotherapy alone in recurrent platinum-sensitive EOC

Patient or population: recurrent platinum-sensitive EOC
Setting: specialist hospital
Intervention: chemotherapy with TKI followed by maintenance TKI
Comparison: chemotherapy alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with chemotherapy alone	Risk with chemotherapy with TKI and as maintenance				
Overall survival (OS) **Assessed with**: survival rate **Follow-up**: median 83.7 months	**Average**		**HR 0.86** (0.67 to 1.11) [alive]	282 (1 RCT)	⊕⊕◯◯ **Low**[c,d]	Chemotherapy with TKI followed by maintenance with TKI likely results in little to no difference in overall survival.
	490 per 1000[a,b]	**541 per 1000** (453 to 620)				
Progression-free survival (PFS) **Assessed with**: progression-free rate according to RECIST 1.0 criteria **Follow-up**: median 19.5 months	**Average**		**HR 0.56** (0.44 to 0.72) [progression-free]	282 (1 RCT)	⊕⊕⊕◯ **Moderate**[d]	Chemotherapy with TKI followed by maintenance with TKI likely increases progression-free survival.
	230 per 1000	**439 per 1000** (347 to 524)				
Quality of life (QoL) **Assessed with:** Global Quality of Life and EORTC core QoL questionnaire (QLQ-C30) **Follow-up:** 12 months	The mean quality of lIfe was **62.6**	**MD 6.1 higher** (0.96 lower to 13.16 higher)	-	146 (1 RCT)	⊕⊕◯◯ **Low**[e]	Chemotherapy with TKI followed by maintenance with TKI may result in little to no difference in quality of life.
Any adverse events (grade ≥ 3)	-	-	-	-	-	Outcome not reported

Hypertension (grade ≥ 2)	-	-	-	-	-	A single trial included in this comparison reported only events of grade ≥ 3 (ICON6 2021).
Bowel fistula/perforation (grade ≥ 3)	-	-	-	-	-	Outcome not reported

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **CTCAE**: Common Terminology Criteria for Adverse Events; **EOC:** epithelial ovarian cancer; **EORTC:** European Organization for Research and Treatment of Cancer; **HR:** hazard ratio; **MD:** mean difference; **QoL:** quality of life; **RECIST**: Response Evaluation Criteria in Solid Tumors; **RR:** risk ratio; **TKI**: tyrosine kinase inhibitor

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.

[a]The control risk is an average number of participants reported alive at 36 months in ICON6 2021, OCEANS 2015 and GOG-0213 2017 trials (chemotherapy alone arms).
[b]The control risk is an average number of participants reported progression-free at 12 months in MITO-16b 2021, ICON6 2021, OCEANS 2015 and GOG-0213 2017 trials (chemotherapy alone arms).
[c]Downgraded by one level due to imprecision (wide confidence interval around the effect estimate crossing line of no difference)
[d]Evidence of non-proportionality of hazards
[e]Downgraded by two levels due to imprecision (very wide confidence interval around the effect estimate crossing line of no difference)

Summary of findings 6. Chemotherapy with bevacizumab compared to chemotherapy alone in recurrent platinum-resistant EOC

Patient or population: recurrent platinum-resistant EOC
Setting: specialist hospital
Intervention: chemotherapy with bevacizumab
Comparison: chemotherapy alone

Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with chemotherapy alone	**Risk with chemotherapy with bevacizumab**				

Overall survival (OS) **Assessed with:** survival rate **Follow-up:** range 8.7 to 13.9 months where reported	**Average**[a] 10 per 1000	**35 per 1000** (19 to 60)	**HR 0.73** (0.61 to 0.86) [alive]	778 (5 RCTs)	⊕⊕⊕⊕ **High**	Chemotherapy with bevacizumab increases overall survival.
Progression-free survival (PFS) **Assessed with:** progression-free rate according to RECIST 1.0-1.1 where reported **Follow-up:** range 8.7 to 13.9 months where reported	**Average**[b] 40 per 1000	**207 per 1000** (155 to 259)	**HR 0.49** (0.42 to 0.58) [progression-free]	778 (5 RCTs)	⊕⊕⊕◯ **Moderate**[c,d]	Chemotherapy with bevacizumab likely results in a large increase in progression-free survival.
Quality of life	-	-	-	-	-	Outcome not reported
Any adverse event grade ≥ 3 **Assessed with:** CTCAE version 3.0	460 per 1000	**773 per 1000** (350 to 1000)	**RR 1.68** (0.76 to 3.69)	101 (1 RCT)	⊕⊕◯◯ **Low** [e,f]	Chemotherapy with bevacizumab may increase any adverse events (grade > 3) slightly.
Hypertension (grade ≥ 2) **Assessed with:** CTCAE version 3.0	73 per 1000	**228 per 1000** (134 to 387)	**RR 3.11** (1.83 to 5.27)	436 (2 RCT)	⊕⊕◯◯ **Low**[e,f]	Chemotherapy with bevacizumab may result in a large increase in hypertension (grade ≥ 2).
Bowel fistula / perforation (grade ≥ 2) **Assessed with:** CTCAE version 3.0	4 per 1000[g]	**28 per 1000** (3 to 220)	**RR 6.89** (0.86 to 55.09)	436 (2 RCTs)	⊕⊕◯◯ **Low**[e,f]	Chemotherapy with bevacizumab may increase rates of bowel fistula / perforation (grade ≥ 2) slightly. Two studies included in this comparison although one reported only gastrointestinal perforations (grade ≥ 2) (AURELIA 2014).

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **CTCAE**: Common Terminology Criteria for Adverse Events; **EOC:** epithelial ovarian cancer; **EORTC:** European Organization for Research and Treatment of Cancer; **HR:** hazard ratio; **MD:** mean difference; **RECIST**: Response Evaluation Criteria in Solid Tumors; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]The control risk is an average number of participants reported alive at 36 months in AURELIA 2014, MITO-11 2015 and TRIAS 2018 trials (chemotherapy alone arms).
[b]The control risk is an average number of participants reported progression-free at 12 months in APPROVE 2022, AURELIA 2014, METRO-BIBF 2020, MITO-11 2015, Nishikawa 2020, OCTOVA 2021 and TRIAS 2018 trials (chemotherapy alone arms).
[c]Downgraded by one level due to risk of bias (five out of six trials contributing to synthesis have open-label design)
[d]Despite the I^2 statistic being over 50%, we decided not to downgrade the evidence due to inconsistency as the direction of the effect in all studies favours the combination of chemotherapy with bevacizumab over chemotherapy alone.
[e]Downgraded by one level due to risk of bias (trial with an open-label design)
[f]Downgraded by one level due to imprecision (wide confidence interval around the effect estimate)
[g]No episodes of ≥ Grade 2 GI perforation in control groups (n = 218), baseline risk therefore estimated at 4 per 1000

Summary of findings 7. Chemotherapy with TKI compared to chemotherapy alone in recurrent platinum-resistant EOC

Patient or population: recurrent platinum-resistant EOC
Setting: specialist hospital
Intervention: chemotherapy with TKI
Comparison: chemotherapy alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with chemotherapy alone	Risk with chemotherapy with TKI				
Overall survival (OS) **Assessed with:** survival rate **Follow-up:** range 10 to 22.2 months	**Average[a]**		**HR 0.85** (0.68 to 1.08) [alive]	940 (8 RCTs)	⨁⨁⨁◯ **Moderate[b]**	Chemotherapy with TKI likely results in little to no difference in overall survival.
	10 per 1000	**16 per 1000** (8 to 29)				
Progression-free survival (PFS) **Assessed with:** progression-free rate according to RECIST 1.1 criteria where specified **Follow-up:** range 10 to 22.2 months	**Average[c]**		**HR 0.70** (0.55 to 0.89) [progression-free]	940 (8 RCTs)	⨁⨁◯◯ **Low[d,e]**	Chemotherapy with TKI may increase progression-free survival.
	40 per 1000	**87 per 1000** (61 to 119)				
Quality of life (QoL) **assessed with:** Global Quality of Life and EORTC core QoL questionnaire (QLQ-C30) **Scale from:** 0 to 100 **Follow-up:** range 6 to 12 weeks	MD in Quality of Life score ranged from -0.19 (95%CI -9.77 to 9.39) at 6 weeks (METRO-BIBF 2020) to -3.40 (95%CI -13.22 to 6.42) at 4 months (TAPAZ 2022)			164 (3 RCTs)	⨁⨁◯◯ **Low[b,d]**	Chemotherapy with TKI may result in little to no difference in quality of life.

Any adverse events (grade ≥3) **Assessed with:** CTCAE versions 3.0-4.1	581 per 1000	**657 per 1000** (604 to 720)	**RR 1.23** (1.02 to 1.49)	548 (4 RCTs)	⊕⊕◯◯ **Low**[d, f, g]	Chemotherapy with TKI may increase any adverse events (grade ≥ 3) slightly.
Hypertension (grade ≥ 2)	-	-				Trials included in this comparison reported only on events of grade ≥ 3.
Bowel fistula / perforation (grade ≥ 3) **Assessed with:** CTCAE versions 4.0-4.1	4 per 1000	**11 per 1000** (3 to 39)	**RR 2.74** (0.77 to 9.75)	557 (5 RCTs)	⊕◯◯◯ **Very low**[d,g,h]	The evidence is very uncertain about the effect of chemotherapy with TKI on bowel fistula/perforation (grade ≥ 3).

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **CTCAE**: Common Terminology Criteria for Adverse Events; **EOC:** epithelial ovarian cancer; **EORTC:** European Organization for Research and Treatment of Cancer; **HR:** hazard ratio; **MD:** mean difference; **RECIST**: Response Evaluation Criteria in Solid Tumors; **RR:** risk ratio; **TKI:** tyrosine kinase inhibitor

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.

[a]The control risk is an average number of participants reported alive at 36 months in AURELIA 2014, MITO-11 2015 and TRIAS 2018 (chemotherapy alone arms).
[b]Downgraded by one level due to imprecision (wide confidence interval around the effect estimate crossing line of no difference)
[c]The control risk is an average number of participants reported progression-free at 12 months in APPROVE 2022, AURELIA 2014, METRO-BIBF 2020, MITO-11 2015, Nishikawa 2020, OCTOVA 2021 and TRIAS 2018 trials (chemotherapy alone arms).
[d]Downgraded by one level due to risk of bias (open-label design)
[e]Downgraded by one level due to inconsistency (I^2 statistic = 65%, subgroup difference P = 0.009)
[f]Downgraded by one level due to inconsistency (I^2 statistic = 60%)
[g]Pooled estimate includes data from APPROVE 2022 trial which reported treatment-related adverse events.
[h]Downgraded by two levels due to imprecision (very wide confidence interval around the effect estimate crossing line of no difference)

Summary of findings 8. Chemotherapy with TKI (peptide-Fc fusion protein) compared to chemotherapy alone in recurrent EOC

Patient or population: recurrent EOC
Setting: specialist hospital
Intervention: chemotherapy with TKI [peptide-Fc fusion protein]
Comparison: chemotherapy alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with chemotherapy alone	Risk with chemotherapy with TKI [peptide-Fc fusion protein]				
Overall survival (OS) **Assessed with:** survival rate **Follow-up:** range 12.4 to 18 months	**Average**[a] 60 per 1000	75 per 1000 (51 to 105)	**HR 0.92** (0.80 to 1.06) [alive]	1250 (3 RCTs)	⨁⨁⨁◯ **Moderate**[b,c]	Chemotherapy with TKI [peptide-Fc fusion protein] likely results in little to no difference in overall survival.
Progression-free survival (PFS) **Assessed with:** progression-free rate according to RECIST version 1.1 criteria **Follow-up:** range range 10.1 to 16 months	**Average**[d] 110 per 1000	200 per 1000 (164 to 238)	**HR 0.73** (0.65 to 0.82) [progression-free]	1250 (3 RCTs)	⨁⨁⨁⨁ **High**[c]	Chemotherapy with TKI [peptide-Fc fusion protein] increases progression-free survival.
Quality of life (QoL) **Assessed with:** TOI-FACT-OC questionnaire **Scale from:** 0 to 152 **Follow-up**: 25 weeks	The mean change from baseline QoL was **-1.6**	**MD 0.8 lower** (4.31 lower to 2.71 higher)	-	315 (1 RCT)	⨁⨁◯◯ **Low**[e]	Chemotherapy with TKI [peptide-Fc fusion protein] may result in little to no difference in quality of life.
Any adverse events (grade ≥3)	-	-	-	-	-	Outcome not reported
Hypertension (grade ≥ 2)	-	-	-	-	-	All three trials included in this comparison reported events of grade ≥ 3.
Bowel fistula / perforation (grade ≥ 3) **Assessed with:** CTCAE versions 3.0	18 per 1000	**6 per 1000** (0 to 151)	**RR 0.35** (0.01 to 8.30)	108 (1 RCT)	⨁⨁◯◯ **Low**[e]	Chemotherapy with TKI [peptide-Fc fusion protein] may result in little to no difference in bowel perforation/fistula G3+.

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

CI: confidence interval; **CTCAE**: Common Terminology Criteria for Adverse Events; **EOC:** epithelial ovarian cancer; **EORTC:** European Organization for Research and Treatment of Cancer; **HR:** hazard ratio; **MD:** mean difference; **QoL:** quality of life; **RECIST**: Response Evaluation Criteria in Solid Tumors; **RR:** risk ratio; **TKI**: tyrosine kinase inhibitor; **TOI-FACT-OC:** Trial Outcome Index score Functional Assessment of Cancer Therapy—Ovarian Cancer questionnaire

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.

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[a]The control risk is an average number of participants reported alive at 36 months in TAPAZ 2022, TRINOVA-1 2016 and TRINOVA-2 2017 trials (chemotherapy alone arms).
[b]Downgraded by one level due to imprecision (wide confidence interval around the effect estimate crossing line of no difference)
[c]Evidence of non-proportionality of hazards
[d]The control risk is an average number of participants reported progression-free at 12 months in Duska 2020, Richardson 2018, SWOG-S0904 2014, TAPAZ 2022, TRINOVA-1 2016 and TRINOVA-2 2017 trials (chemotherapy alone arms).
[e]Downgraded by two levels due to imprecision (very wide confidence interval around the effect estimate crossing line of no difference)

BACKGROUND

Description of the condition

This is an update of the review, originally published in 2011 (Gaitskell 2011).

Each year, worldwide, over 300,000 women and people with ovaries are diagnosed with epithelial ovarian cancer (EOC) and over 200,000 die, corresponding to an annual age-standardised incidence of 6.6 cases per 100,000 females, an annual mortality rate of 4.2 deaths per 100,000, and a cumulative lifetime risk of 0.73% for incidence and 0.49% for mortality (GLOBOCAN 2020). In terms of both incidence and mortality, it is the eighth most common cancer in females. The onset is often insidious, as abnormal cells developing on the surface of the ovaries or lining of the fallopian tubes have ready access to spread throughout the abdominal cavity, with no effective screening tests. Approximately 60% of women with EOC in the USA are diagnosed when the disease has spread (stage III or IV) and the five-year survival rate is 20% to 30% (Berek 2018; Cancer Research UK 2022; Siegel 2021). EOC accounts for 90% of all ovarian cancers and typically presents in post-menopausal women, with a peak incidence when women are in their early sixties, although it does occur in younger women, often associated with genetic predispositions (Quinn 2001).

EOC may be divided into several different histological types, on the basis of different microscopic appearances and characteristic molecular features. There is growing evidence that these different histological types may have different origins (Kurman 2011; Prat 2012; Prat 2018; WHO 2020). In particular, many cases of high-grade serous ovarian carcinoma (the most common type, accounting for about 70% of EOC (Prat 2018)) are thought to arise from precursor lesions within the fallopian tubes (serous tubal intraepithelial carcinomas) which share the same *p53* mutations characteristics of high-grade serous carcinoma (Ahmed 2010; Kurman 2013; Labidi-Galy 2017; Shih 2021). Some cases of endometrioid and clear cell ovarian cancer are thought to arise from endometriosis (Kurman 2011).

Description of the intervention

Management of advanced ovarian cancer consists of a combination of debulking surgery, either before or during chemotherapy, and platinum-based chemotherapy, with or without the addition of a taxane (Coleridge 2021; Stewart 1999). However, in women presenting with advanced disease, the five-year survival rate for stage III to IV of the disease remains poor (Engel 2002; Cancer Research UK 2022; Siegel 2021). Despite good initial response to platinum-based chemotherapy, the majority of women with advanced disease at presentation will relapse, require further treatment with chemotherapy, and eventually develop resistance to conventional chemotherapeutic agents.

Conventional chemotherapeutic agents have activity on all rapidly dividing cells; hence, the common side effects, such as hair loss, bone marrow suppression, and mucositis (inflammation and ulceration of the mucous membranes lining the digestive tract). Increasing knowledge of the genetic basis for cancer has led to the development of novel reagents, which target cancer-specific pathways. It is hoped that these reagents will spare normal cells and reduce the toxic side effects of chemotherapy, in addition to having an enhanced therapeutic effect.

Since the 2011 version of this review, bevacizumab is now approved for use in both first-line and second-line settings in clinical practice in several regions, including the USA (NCCN 2022), Europe (Colombo 2019; Ledermann 2013) and the UK (BGCS 2017). Bevacizumab is sometimes used as part of first-line therapy in advanced disease, where it may be given both concurrently with conventional first-line cytotoxic chemotherapy, and then continued alone as a maintenance treatment. Bevacizumab is also sometimes given alongside chemotherapy in the second-line (relapsed/resistant) setting. In some cases, bevacizumab may also be given alongside another type of novel therapy known as poly(ADP-ribose) polymerase (PARP) inhibitors (NCCN 2022).

How the intervention might work

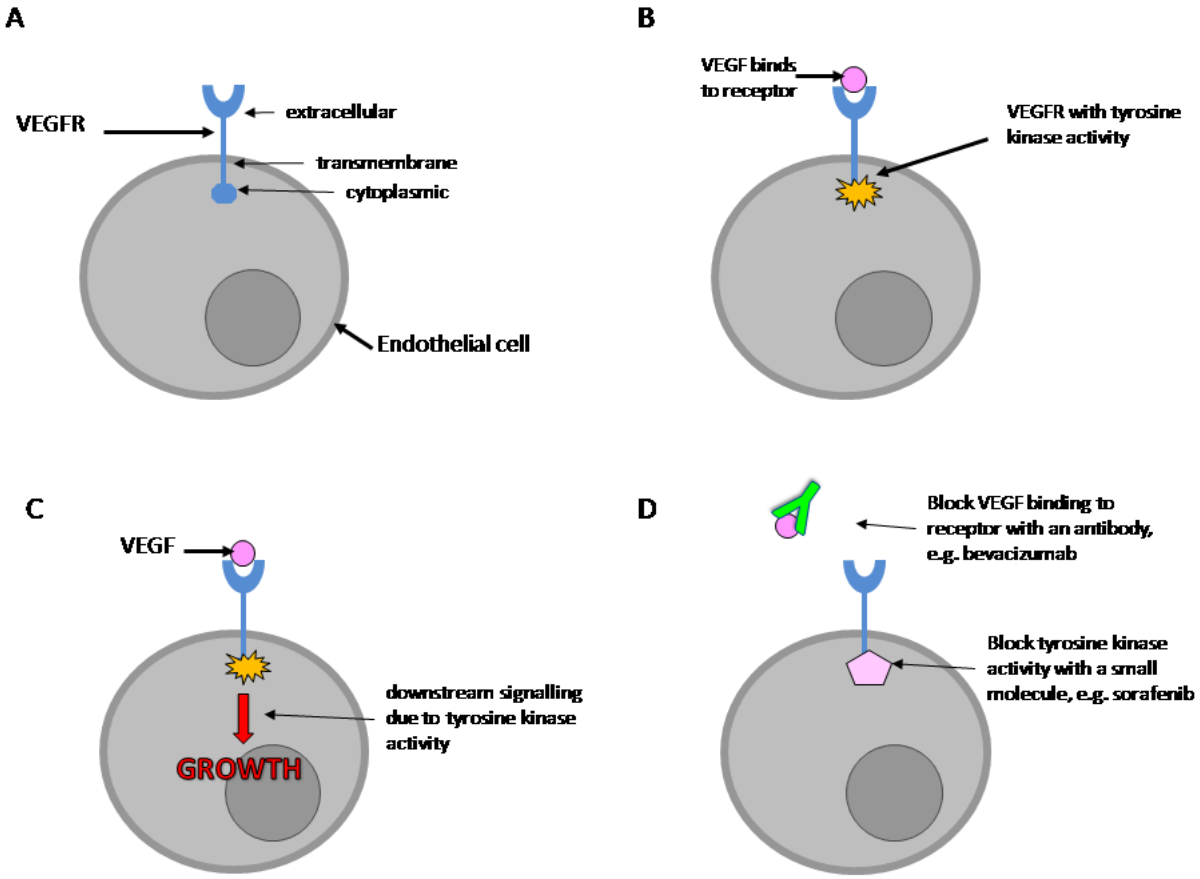
Angiogenesis and ovarian cancer

Angiogenesis is the development of new blood vessels. Once a tumour deposit is larger than 1 mm in diameter, it cannot receive adequate nutrients or oxygen from surrounding tissues by diffusion alone, and it must then stimulate new blood vessel formation to support further growth. Angiogenesis is a vital part of embryo development, but is tightly controlled in adults and normally occurs during wound healing and as part of ovulation. Abnormal angiogenesis can occur in a variety of illnesses, either stimulated by low oxygen levels in tissues (e.g. diabetes and metastatic cancer), or in inflammatory conditions, such as rheumatoid arthritis (Fidler 1994; Folkman 1990). In contrast to the ordered formation of new blood vessels during embryonic angiogenesis, tumour angiogenesis is disordered and results in abnormal and leaky blood vessels (McDonald 2002). Blocking this process may prevent growth of small tumour deposits and improve survival of people with cancer.

Angiogenesis requires signalling between tumour cells and nearby endothelial (lining)cells of normal blood vessels, stimulating them to sprout, multiply and invade the growing tumour. The process involves release of agents by cancer cells, stimulated by low oxygen levels or low pH. These agents bind to receptors on endothelial cells, which then trigger downstream intracellular signalling, leading to growth and migration of endothelial cells. This process can be inhibited at each of these stages. Because angiogenesis is normally inactive in adults, its inhibition is an attractive candidate for selective anti-tumour therapies. Another advantage is that tumour endothelial cells are not themselves malignant and so, unlike cancer cells themselves, do not have pre-existing mutations that favour the development of further mutations, which could lead to drug resistance. In addition, anti-angiogenic agents may work synergistically with conventional chemotherapeutic agents or other novel systemic agents, due to their different mechanisms of action.

Vascular endothelial growth factor (VEGF) is one of the key elements in the stimulation of angiogenesis. VEGF is released by cancer cells and binds to a receptor on endothelial cells (VEGF-R) (Figure 1 A-B). VEGF binding stimulates tyrosine kinase activity in the VEGF-R (Figure 1 B), which in turn stimulates downstream signalling and activation of endothelial cells (Figure 1 C). VEGF over-expression is associated with ascites formation (build up of fluid within the abdominal cavity) and poorer prognosis (Oehler 2000). There are different forms of VEGF: VEGF-A has an important role in the formation of new blood vessels; VEGF-B is involved with the maintenance of newly formed blood vessels (Zhang 2009).

Figure 1. (A) The VEGF-R is a transmembrane protein, found on cells, which line blood vessels (endothelial cells). (B) Following binding to its ligand, VEGF, the VEGF-R is stimulated and develops tyrosine kinase activity. (C) Tyrosine kinase activity sets off a sequence of downstream events that lead to stimulation of cell growth and new vessels grow in, to supply the growing tumour. (D) VEGF-R activity can be blocked by antibodies, which bind to VEGF, and so stop it binding to the receptor, or using chemicals, which inhibit the tyrosine kinase enzyme activity of the VEGF-R.



VEGF signalling can be blocked at several levels (Figure 1 D). First, anti-VEGF antibodies or soluble VEGF-R molecules mop up excess VEGF and prevent binding to, and stimulation of, cellular VEGF-R. Second, antibodies have been developed that bind to VEGF-R and block binding and activation by VEGF. Third, VEGF-R signalling may also be inhibited by small molecules which specifically inhibit the intracellular tyrosine kinase activity of VEGF-R following stimulation by angiogenic factors.

VEGF-R inhibitors

Small molecule inhibitors of VEGF-R tyrosine kinase (tyrosine kinase inhibitors (TKIs)) have been developed and investigated in clinical trials. One advantage of these compounds is that many are orally active. For details of the mechanism of action, see Table 1.

- Cediranib (AZD2171 or Recentin AstraZeneca) is a small molecule inhibitor of VEGF-R and also inhibits the c-kit proto-oncogene receptor tyrosine kinase, and has some weak activity against platelet-derived growth factor receptor (PDGF-R) (Wedge 2005; Brave 2011; NCI-DCTD-Cediranib 2022; ICON6 2021).
- Pazopanib is a potent selective receptor tyrosine kinase inhibitor of VEGF-R, PDGF-R and c-kit that blocks tumour growth and inhibits angiogenesis (Sonpavde 2007; Richardson 2018).
- Nintedanib (BIBF 1120) is an oral, small molecule, triple angiokinase inhibitor, targeting VEGF-R, fibroblast growth factor receptor (FGF-R) and PDGF-R (Erber 2004; Hilberg 2008; Ledermann 2011).
- Brivanib is a small molecule inhibitor targeting the VEGF-R and FGF-R tyrosine kinase receptor families (Bhide 2010; Cai 2008).
- Cabozantinib is a small molecule inhibitor targeting multiple tyrosine kinase receptors, primarily c-MET (mesenchymal epithelial transition) and VEGF-R2, but also c-kit, Tie-2 (an angiopoietin receptor), FLT-3 (Fms-like receptor tyrosine kinase-3) and RET (REarranged during Transfection - a proto-oncogene) (Yakes 2011; Matulonis 2019).

- Vandetanib (ZD6474) is a small molecule inhibitor of VEGF-R, EGF-R and RET(Carlomagno 2002; Wedge 2002; SWOG-S0904 2014).
- Sorafenib (BAY 43-9006/Nexavar) is a small molecule tyrosine kinase inhibitor that directly inhibits VEGF-R in addition to other angiogenic and growth stimulatory pathways, including via PDGF-R and Raf kinase inhibition (Mross 2007; Siu 2006).
- Sunitinib (SU11248) is a small molecule inhibitor of the VEGF-R, c-kit and FLT3 tyrosine kinase receptors (Abrams 2003; Mendel 2003).
- Apatinib is a small molecule inhibitor targeting several tyrosine kinase receptors, including VEGF-R2 (Ding 2019; Tian 2011).

VEGF blockade

Monoclonal antibodies are antibodies that have a specific target pattern to which they bind. Bevacizumab (Avastin) is a humanised monoclonal antibody that binds VEGF, prevents it binding to VEGF-R, and so inhibits VEGF-R activation and angiogenesis (Ferrara 2004). Bevacizumab has been shown to have activity in phase II trials in women who had platinum-resistant relapsed ovarian cancer (13% to 16% partial response rates and 25% to 55% stable disease), although complete responses, in this group of pre-treated patients, were low (0% to 5%) (Burger 2007; Cannistra 2007). Side effects encountered were different to those seen with conventional chemotherapy, in line with its alternative mode of action. They included hypertension, bleeding episodes, thromboembolism and bowel perforation.

On the basis of success from these studies, phase III trials have been performed combining bevacizumab with carboplatin and taxol chemotherapy in postoperative patients with ovarian cancer in the GOG 218 (GOG-0218 2019) and the ICON 7 (ICON7 2015) studies. These trials are also assessing the role of bevacizumab in the maintenance treatment of these patients.

Aflibercept is a recombinant fusion protein that binds to VEGF-A and VEGF-B, acting as a soluble decoy receptor (Ciombor 2014; NICE 2022).

VEGF inhibitors combined with PARP inhibitors

PARP inhibitors are a novel type of cancer treatment that targets the DNA damage repair pathways in cancer cells. They work particularly well in people who have already inherited genetic mutations affecting other DNA damage pathways (e.g. the *BRCA* breast and ovarian cancer susceptibility gene variants). There have been several studies investigating PARP inhibitors as a possible treatment for ovarian cancer; in some cases, alongside bevacizumab (Tattersall 2022). Part of the rationale for trying the combination of PARP inhibitors and angiogenesis inhibitors is that there is some early evidence that some angiogenesis agents may also affect DNA damage repair pathways, while PARP inhibitors may also affect angiogenesis, and thus the combination of these two types of treatment might be even more effective at targeting both DNA damage repair and angiogenesis (Alvarez Secord 2021).

Agents targeting other aspects of angiogenesis

Trebananib (AMG 386) inhibits angiogenesis via a different mechanism. Trebananib is a peptide-Fc fusion protein (composed of the Fc portion of human immunoglobulin IgG1 fused to a peptide of interest) which inhibits angiogenesis by binding to the angiopoietins Ang1 and Ang2, and so preventing them binding to the receptor Tie2 (Neal 2010; Oliner 2004; TRINOVA-1 2016).

Celecoxib is an inhibitor of the enzyme cyclo-oxygenase-2 (COX-2) and is a non-steroidal anti-inflammatory drug. There is also some evidence that it can act to inhibit angiogenesis (Gupta 2019; Masferrer 1999; Masferrer 2000).

Olaratumab (IMC-3G3) is a monoclonal antibody targeting platelet-derived growth factor alpha (PDGFRα), a transmembrane receptor tyrosine kinase which is involved in the maturation of new blood vessels. Olaratumab inhibits angiogenesis by binding to PDGFRα and so inhibiting these pro-angiogenic downstream signalling pathways (Choi 2015; McGuire 2018).

Why it is important to do this review

Novel treatment strategies working in different ways to conventional chemotherapy have been developed. It is important to establish whether the addition of these new drugs to conventional chemotherapy regimens has additional benefit, in terms of survival, and if so, at what cost, in terms of additional harmful effects. Furthermore, since these compounds may be less toxic compared to conventional chemotherapeutic agents, these newer treatments are used increasingly in people who are not currently taking chemotherapy (so-called maintenance treatment), to reduce the chance of, or delay, the recurrence of their ovarian cancer. Ensuring that maintenance treatment gives additional benefit, with improvement in overall survival without significant degradation of quality of life, is extremely important in what, for many, will be a life-limiting illness. Since the previous version of the review was published (Gaitskell 2011), there have been significant developments in this area and this represents a significant update in the field.

OBJECTIVES

To compare the effectiveness and toxicities of angiogenesis inhibitors for treatment of epithelial ovarian cancer.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) of angiogenesis inhibitors plus conventional chemotherapy versus conventional chemotherapy alone, and angiogenesis inhibitors versus no treatment. We only included results from trials with a minimum of 10 participants.

Types of participants

We included adult women (and other females), aged 18 and over, with histologically-proven epithelial ovarian cancer (EOC) (including high grade serous tubal and primary peritoneal malignancies). We excluded women with other concurrent malignancies.

In this review update, we planned to stratify by clinically relevant treatment setting; that is, to analyse separately those with newly-diagnosed EOC and relapsed EOC. We further subdivided recurrent EOC by platinum-sensitivity (platinum-sensitive, platinum-resistant/refractory and studies with a mixed or

unclear platinum sensitivity) since these have different biology and response rates to chemotherapy treatment.

We had not previously explicitly specified that the review was limited to EOC, although all previously included studies were limited to those with EOC.

Types of interventions

There have been a number of developments in this field since the publication of the original protocol and previous version of the review (Gaitskell 2011). Angiogenesis inhibitors are used as standard of care for some people in some settings. We therefore planned to include studies that contained the following comparisons in this update of the review:

- angiogenesis inhibitors plus conventional chemotherapy versus conventional chemotherapy (including studies where the angiogenesis inhibitor is continued as maintenance after chemotherapy);
- angiogenesis inhibitors versus no treatment (e.g. in a maintenance setting);
- angiogenesis inhibitor 1 versus angiogenesis inhibitor 2, with either chemotherapy in each arm or no other treatment;
- chemotherapy plus angiogenesis inhibitor 1 versus chemotherapy plus angiogenesis inhibitor 1 plus angiogenesis inhibitor 2;
- angiogenesis inhibitor versus an alternative chemotherapy treatment.

Types of outcome measures

Primary outcomes

Overall survival (OS): survival until death from any cause

Secondary outcomes

- Progression-free survival (PFS)
- Quality of life (QoL), measured by a validated scale
- Toxicity. Based on the outcomes reported by studies included in the 2011 version of this review, we identified the following adverse event outcomes by Common Terminology Criteria for Adverse Events (CTCAE) criteria:
  - any severe adverse event (grade 3 or higher (≥ G3));
  - hypertension (≥ G2);
  - proteinuria (≥ G2);
  - pain (≥ G2);
  - abdominal pain (≥ G2);
  - neutropenia (≥ G3);
- febrile neutropenia (any grade);
- venous thromboembolic event (any grade);
- arterial thromboembolic event (any grade);
- non-central nervous system bleeding (≥ G3);
- gastrointestinal adverse events (≥ G2);
- bowel fistula or perforation (≥ G3).

Please see academy.myeloma.org.uk/wp-content/uploads/2015/04/CTCAE_v5.pdf for details regarding CTCAE criteria.

Search methods for identification of studies

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

Electronic searches

See Cochrane Gynaecological Cancer Group methods used in reviews.
We searched the following electronic databases from 1990 to 30 September 2022:

- Cochrane Gynaecological Cancer Review Group's trials register;
- Cochrane Central Register of Controlled Trials (CENTRAL; 2022, Issue 9) in the Cochrane Library;
- MEDLINE Ovid;
- Embase Ovid.

We present the CENTRAL, MEDLINE and Embase search strategies in Appendix 1, Appendix 2 and Appendix 3, respectively.

We searched databases from 1990 to October 2010 for the 2011 version of this review, and from October 2010 to 30 September 2022 for this update. The novel agents we focus on in this review have been developed relatively recently: trials published before 1990 would not have been relevant.

We also used the 'related articles' feature on PubMed, and searched the reference lists of included studies in this review and systematic reviews on this topic published between 2020 and September 2022. We limited our search to systematic reviews published in the last two years, as many of the primary studies included in this review were only published in the last few years, and thus older systematic reviews would not be comparable.

Searching other resources

We searched the Physician Data Query (the US National Cancer Institute's comprehensive cancer database), three clinical trials registers (the ISRCTN registry: www.isrctn.com; ClinicalTrials.gov: www.clinicaltrials.gov; and the National Cancer Institute clinical trials portal, www.cancer.gov/about-cancer/treatment/clinical-trials) and the National Research Register (NRR) for ongoing trials on 29 September 2022. We also sought details of ongoing or unpublished trials from the FDA (Food and Drug Administration, the regulatory body for medicines within the USA, www.fda.gov), the EMEA (European Medicines Agency, the drug regulatory body within Europe, www.emea.europa.eu) and from pharmaceutical company sources. We contacted the main investigators of the relevant completed and ongoing trials for further information.

Correspondence

We contacted authors of relevant trials to ask if they knew of further data which may or may not have been published.

Data collection and analysis

Selection of studies

For this update of the review, we downloaded all titles and abstracts retrieved by electronic searching to Covidence (Covidence), and removed duplicates. Two review authors (a combination of KG, SP, YC, MAEA and JM) independently examined the remaining references. We excluded those references which clearly did not

meet the inclusion criteria and obtained copies of the full texts of potentially relevant references. Two review authors (a combination of KG, SP, YC, MAEA and JM) independently assessed the eligibility of retrieved papers. We resolved disagreements by discussion between the two review authors and, when necessary, by involving a third review author (ER and/or JM). We listed studies that initially appeared to meet the inclusion criteria but that we later excluded in the Characteristics of excluded studies table, with the reasons for exclusion.

Data extraction and management

For included studies, we extracted the following data.

- Author, year of publication and journal citation (including language)
- Country
- Setting
- Inclusion and exclusion criteria
- Study design, methodology
- Study population
  - Total number enrolled
  - Participant characteristics
  - Age
  - Comorbidities
  - Previous treatment
- Total study duration
- Total number of intervention groups
- Ovarian cancer details at diagnosis
  - FIGO stage (FIGO = Fédération Internationale de Gynécologie et d'Obstétrique or International Federation of Gynaecology and Obstetrics), derived from FIGO's five-stage typology of cancer (stages 0 to 4)
  - Histological cell type
  - Tumour grade
  - Extent of disease
- Intervention details
  - Type of angiogenesis inhibitor
  - Dose
  - Duration of treatment
  - Consolidation treatment or treatment of active disease
- Comparison details
  - Type of control: conventional chemotherapy or no treatment
  - Dose (if appropriate)
  - Duration (if appropriate)
- Deviations from protocol
- Risk of bias in study (see Assessment of risk of bias in included studies below)
- Duration of follow-up
- Outcomes: OS, PFS, QoL, toxicity.
  - For each outcome: outcome definition (with diagnostic criteria if relevant).
  - Unit of measurement (if relevant).
  - For scales: upper and lower limits, and whether high or low score is good.
  - Results: number of participants allocated to each intervention group.
  - For each outcome of interest: sample size; missing participants.

We extracted data on outcomes as follows.

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

When reported, we extracted both unadjusted and adjusted statistics. Where we extracted adjusted results, we recorded the variables that were adjusted for. Where possible, all data that we extracted were those relevant to an intention-to-treat (ITT) analysis, in which participants were analysed in the groups to which they were assigned. We noted the time points at which outcomes were collected and reported. In the case of repeated reporting of outcome measurement, we used the data with the longest follow-up. Where time-to-event outcomes were assessed by more than one method (e.g. independent radiology review, investigator assessment or independent oncology review), we used the independent radiology review data. For toxicity, we recorded whether the outcomes were reported as any adverse event or drug-related adverse event. If both were given, we used any adverse events. Where a trial evaluated the same drug in two or more different doses, we extracted all the combined data, but in the data synthesis we used only the estimated individual data for the most efficacious dose/regimen versus the comparator.

For this update of the review, two review authors (a combination of KG, SP, YC, MAEA, AT, ER and JM) extracted data onto a data extraction form specially designed for the review. The review authors resolved differences by discussion or by appeal to a third review author (JM and/or ER) when necessary.

Assessment of risk of bias in included studies

We assessed the risk of bias in included RCTs using Cochrane's risk of bias tool (Higgins 2011). This included assessment of the following domains:

- random sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessment (detection bias);
- incomplete outcome data (attrition bias). We recorded the proportion of participants whose outcomes were not reported at the end of the study; we noted whether loss to follow-up was not reported. We coded a satisfactory level of loss to follow-up for each outcome as:

- 'low risk', if fewer than 20% of participants were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms;
- 'high risk', if more than 20% of participants were lost to follow-up or reasons for loss to follow-up differed between treatment arms; and
- 'unclear risk' if loss to follow-up was not reported.

- selective reporting of outcomes (reporting bias);
- other possible sources of bias.

Two review authors (a combination of KG, SP, YC, MAEA, AT, ER and JM) independently applied the risk of bias tool and resolved differences by discussion or by appeal to a third review author (JM or ER). We have presented results in both a risk of bias graph and a risk of bias summary. We interpreted the results of meta-analyses in light of the findings with respect to risk of bias.

Measures of treatment effect

We used hazard ratios (HR) with 95% confidence intervals (CIs) for time-to-event data, risk ratios (RR) with 95% CIs for dichotomous outcomes, and mean differences (MD) with 95% CIs for continuous outcomes.

Unit of analysis issues

The unit of analysis was the individual participant. As some of the eligible trials included women with recurrent EOC regardless of their platinum sensitivity status (sensitive and resistant), we decided to incorporate these trials into the analyses along with trials including solely women with recurrent platinum-resistant EOC.

Dealing with missing data

We did not impute missing outcome data for any of the outcomes.

Assessment of heterogeneity

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

Assessment of reporting biases

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

Data synthesis

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

Dealing with multi-arm trials

The GOG-0218 2019 trial had multiple treatment groups (three-arm trial). We divided the control group between the treatment groups and treated comparisons between each treatment group and a split control group as independent comparisons for all adverse event outcomes. This was not necessary for overall survival, as we obtained HR estimates from a Cox regression model.

Dealing with non-proportional hazards

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

Subgroup analysis and investigation of heterogeneity

For populations with newly diagnosed EOC, we added a subgroup analysis by risk of disease progression. Although this was a post hoc subgroup analysis, it is in line with the current use of bevacizumab in clinical practice.

We stratified all tyrosine kinase inhibitors (TKI) analyses by the inhibitor type, with data pooled only for the TKIs with a similar mechanism of action.

Sensitivity analysis

We performed sensitivity analysis for survival outcomes (overall survival, progression-free survival) for one comparison (the combination of TKI with chemotherapy in recurrent platinum-resistant EOC) to explore the influence of our decision to incorporate in the analysis data from studies in recurrent EOC that recruited mixed populations (i.e. participants with platinum-sensitive EOC, platinum-resistant EOC, or unclear platinum sensitivity).

Summary of findings and assessment of the certainty of the evidence

We generated summary of findings tables for the most clinically relevant comparisons (chemotherapy with bevacizumab versus chemotherapy alone, and chemotherapy with TKI versus chemotherapy alone) (Schünemann 2017a), for the following outcomes:

- overall survival (OS);
- progression-free survival (PFS);
- quality of life (QoL);
- adverse events: overall severe adverse events (Grade 3+);
- adverse events: hypertension (Grade 2+);
- adverse events: bowel fistula/perforation (Grade 3+).

For each assumed risk cited in the tables, we provided a rationale and used the GRADE system to rank the certainty of the evidence (Schünemann 2017b). If the following limitations were present, we downgraded the evidence certainty by one or

two levels, according to the seriousness of the limitation: study design limitations, inconsistency, imprecision, indirectness and publication bias. Where the evidence was based on single studies, or where there was no evidence for a specific outcome, we included the outcome in the summary of findings tables and graded or explained accordingly. We reported and interpreted results based on the interactive GRADEpro summary of findings table guidance (Schünemann 2019).

RESULTS

Description of studies

For details of included, excluded, 'awaiting classification' and ongoing studies, see: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies, respectively.

Results of the search

This review was first published in 2011 (Gaitskell 2011), when we identified five relevant randomised controlled trials (with 20 references) from an initial de-duplicated yield of 4248 references. These studies had at least published preliminary results in the form of conference abstracts.

Updated searches (starting in November 2010, with the most recent conducted on 30 September 2022) yielded the following:

- CENTRAL: 631 references;
- MEDLINE: 2617 references;
- Embase: 2638 references.

Following preliminary de-duplication across the databases, the combined total yield was 5339 references. We found an additional five published articles from five included studies by handsearching after 30 September 2022. We retrieved trial protocols (e.g. from the MetaRegister of Controlled Trials, or the ClinicalTrials.gov website) for 60 studies (across all four categories: Included, Excluded, Ongoing, or Awaiting classification studies). See Figure 2 for details of the results of this search update. In total, we sifted 5406 references following de-duplication for this update of the review, and we excluded 5124 by screening titles and abstracts.

Figure 2. PRISMA flow diagram of studies considered for this review update. Please see previous version of review for further details of previous search (Gaitskell 2011).

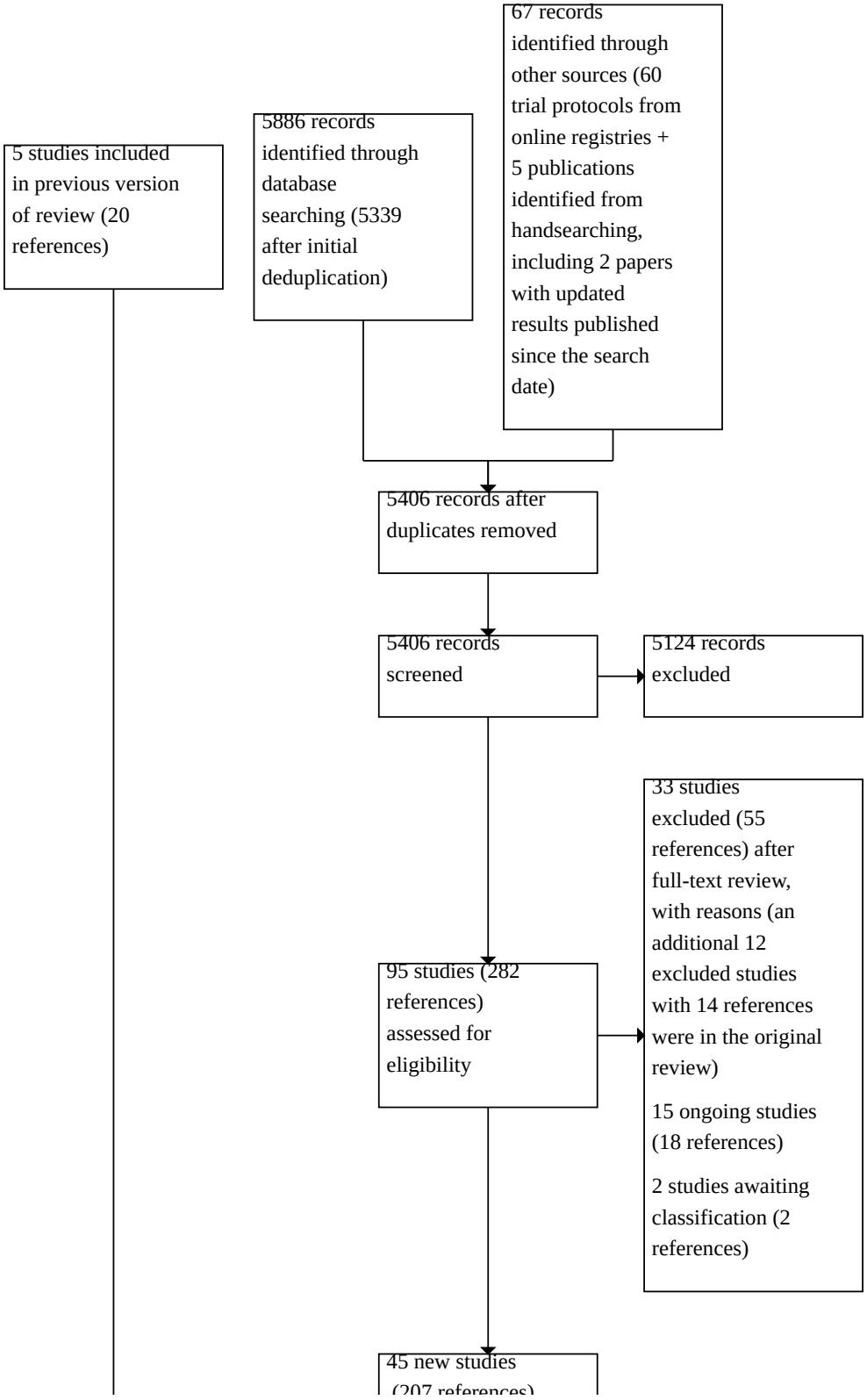
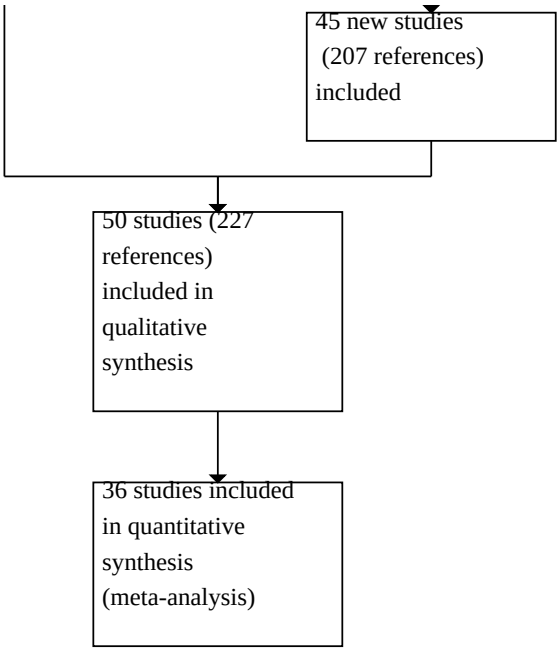


Figure 2. (Continued)



We identified 95 studies (282 references) as potentially eligible for this review through title and abstract screening by two independent review authors (two of KG, SP, YC, MAEA and JM). We excluded 33 studies (55 references) after obtaining the full texts, for the reasons described in the Excluded studies section. We identified 50 studies (227 references) with at least preliminary results data published, which were suitable for inclusion, including the five studies (20 references) already included in the previous version of this review. Of these, 36 contributed data to the meta-analysis. We summarise the characteristics of these studies in Table 1.

From searching online registers of clinical trials, we identified 15 ongoing studies (18 references) which are likely to be relevant for this review when completed (see Characteristics of ongoing studies). We identified two further studies which may or may not be relevant to this review when they are completed or we are able to obtain full texts (see Studies awaiting classification).

Included studies

We included 50 RCTs with a total of 14,836 participants (AGO-OVAR 12 2020; AGO-OVAR 16 2019; AMBITION 2022; ANTHALYA 2017; APPROVE 2022; AURELIA 2014; AVANOVA2 2019; BAROCCO 2022; CHIVA 2019; Cong 2019; Duska 2020; EORTC-1508 2021; GEICO-1205 2019; GOG-0213 2017; GOG-0218 2019; GOG-0241 2019; Gotlieb 2012; Gupta 2019; Hainsworth 2015; Herzog 2013; ICON6 2021; ICON7 2015; Karlan 2012; Ledermann 2011; Li 2019; Li 2021; Liu 2019a; Liu 2019b; Liu 2021a; Liu 2022; Matulonis 2019; McGuire 2018; METRO-BIBF 2020; MITO-11 2015; MITO-16b 2021; NICCC 2020; Nishikawa 2020; OCEANS 2015; OCTOVA 2021; Reyners 2012; Richardson 2018; Roque 2022; Sharma 2021; SWOG-S0904 2014; TAPAZ 2022; TRIAS 2018; TRINOVA-1 2016; TRINOVA-2 2017; TRINOVA-3 2019; Zhao 2015).

Five of these studies were included in the previous version of the review, using information from conference abstracts and presentations (GOG-0218 2019; Gotlieb 2012; ICON7 2015; Karlan 2012; Ledermann 2011).

Eleven studies - now included in the review - were identified in the previous version of this review as ongoing studies (AGO-OVAR 12 2020; AGO-OVAR 16 2019; AURELIA 2014; GOG-0213 2017; Hainsworth 2015; Herzog 2013; ICON6 2021; McGuire 2018; OCEANS 2015; TRIAS 2018; TRINOVA-1 2016). In some cases, they were listed under their ClinicalTrials.gov reference IDs.

We grouped the included studies by the main clinically relevant settings that we used for analyses, looking separately at newly-diagnosed EOC and recurrent EOC, which we further divided into platinum-sensitive EOC, platinum-resistant EOC, and those with mixed populations (i.e. participants with platinum-sensitive EOC, platinum-resistant EOC, or unclear platinum-sensitivity). Details of included studies are summarised by category in Table 1.

Newly-diagnosed epithelial ovarian cancer (EOC)

We included 13 studies evaluating the effect of angiogenesis inhibitors in 7708 participants with newly-diagnosed EOC (AGO-OVAR 12 2020; AGO-OVAR 16 2019; ANTHALYA 2017; CHIVA 2019; GEICO-1205 2019; GOG-0218 2019; GOG-0241 2019; Hainsworth 2015; Herzog 2013; ICON7 2015; Reyners 2012; TRINOVA-3 2019; Zhao 2015).

GOG-0241 2019 was a study in mucinous epithelial ovarian cancer and contained participants with both newly-diagnosed and recurrent disease. Since the original review protocol, it has become clear that this disease differs from other types of EOC. Thus, we did not include this study in meta-analysis.

Bevacizumab

Six trials evaluated use of bevacizumab in newly-diagnosed EOC (ANTHALYA 2017; GEICO-1205 2019; GOG-0218 2019; GOG-0241 2019; ICON7 2015; Zhao 2015).

ANTHALYA 2017 was a multi-centre, open-label, phase II trial, evaluating the effect of adding bevacizumab (three cycles) to neoadjuvant chemotherapy (four cycles of carboplatin and paclitaxel) in 95 women with initially unresectable FIGO stage IIIC/IV ovarian cancer. After interval debulking surgery, all women received adjuvant chemotherapy (four cycles of carboplatin-paclitaxel), with bevacizumab added in the sixth cycle and continued as maintenance therapy (up to 26 cycles). The primary outcome was the complete resection rate; the secondary outcome was safety/adverse events.

GEICO-1205 2019 was an open-label, phase II trial evaluating the effect of adding bevacizumab (three cycles) to neoadjuvant chemotherapy (four cycles of carboplatin and paclitaxel) in 68 women with newly-diagnosed stage III/IV high-grade serous or endometrioid EOC. After interval debulking surgery, all women received adjuvant chemotherapy (three cycles), with bevacizumab alongside and continued as maintenance therapy for up to 15 months. The primary outcome was the complete macroscopic response rate at interval debulking surgery; secondary outcomes included safety, surgical operability, optimal cytoreduction, response rate, and progression-free survival.

GOG-0218 2019 was a double-blind, phase III trial in 1873 women with newly-diagnosed, incompletely resected, stage III/IV EOC. The study compared three regimens of treatment: chemotherapy alone (six cycles of carboplatin and paclitaxel) versus chemotherapy plus concurrent bevacizumab (in cycles 2 to 6) versus chemotherapy plus concurrent and maintenance bevacizumab (cycles 2 to 22). The primary outcome was progression-free survival (changed from overall survival during the trial); secondary outcomes included overall survival, safety, and quality of life (as measured by the Functional Assessment of Cancer Therapy-Ovary Trial Outcome Index (FACT-O TOI)).

GOG-0241 2019 was an open-label, multi-centre, phase III factorial trial in 50 women with mucinous EOC of FIGO stage II-IV or recurrent stage I. The study randomised participants to four different treatment arms, evaluating the effect of adding bevacizumab to either chemotherapy with carboplatin and paclitaxel, or chemotherapy with oxaliplatin and capecitabine. The primary outcome was intended to be overall survival; secondary outcomes were progression-free survival, response rate, toxicity, and quality of life. The trial was stopped early by the data monitoring committee due to difficulty recruiting in this rare histological type of EOC.

ICON7 2015 was a multi-centre, open-label, phase III trial in 1528 women with newly-diagnosed EOC that was either high-risk early-stage disease (high-grade stage I-IIa) or more advanced disease (FIGO IIb-IV). The study compared chemotherapy (six cycles of carboplatin and paclitaxel) to chemotherapy plus bevacizumab (given concurrently with chemotherapy and then as maintenance therapy for up to 12 further cycles). The primary outcome was progression-free survival; secondary outcomes were overall survival and safety; exploratory outcomes included quality of life, health economics, and translational research.

Zhao 2015 was a phase III trial evaluating the effect of adding bevacizumab to cisplatin (both delivered intraperitoneally) in 58 women with EOC and malignant ascites (i.e. an accumulation of fluid in the abdomen due to the ovarian cancer). The primary outcome was the objective response rate of partial or complete remission of the ascites; secondary outcomes included safety, the number of required peritoneal drainages during the trial, the speed of peritoneal drainage, and quality of life (measured by Karnofsky Performance Status). The trial population was somewhat unclear, but appeared to be mainly women with newly-diagnosed EOC (as prior anti-tumour treatment was an exclusion criterion).

Tyrosine kinase inhibitors (TKIs)

Six trials evaluated the use of tyrosine kinase inhibitors (AGO-OVAR 12 2020; AGO-OVAR 16 2019; CHIVA 2019; Hainsworth 2015; Herzog 2013; TRINOVA-3 2019).

AGO-OVAR 12 2020 was a double-blind, placebo-controlled, phase III trial evaluating the effect of adding nintedanib to chemotherapy (carboplatin and paclitaxel), in 1366 women with newly-diagnosed FIGO stage IIB-IV EOC. The primary outcome was progression-free survival; secondary endpoints included overall survival, time to tumour marker progression, safety and quality of life (as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire ovarian cancer module (EORTC QLQ-OV 28) and EORTC core quality of life (QLQ-C30) questionnaires).

AGO-OVAR 16 2019 was a multi-centre, double-blind, placebo-controlled, phase III trial evaluating the effect of adding pazopanib maintenance therapy for up to 24 months after first-line chemotherapy (with platinum and a taxane) in 940 women with newly diagnosed FIGO stage II-IV EOC. The primary outcome was progression-free survival; secondary outcomes included overall survival, safety and quality of life.

CHIVA 2019 was a multi-centre, placebo-controlled, phase II trial evaluating the effect of adding nintedanib to neoadjuvant chemotherapy (three to four cycles of carboplatin and paclitaxel) prior to interval debulking surgery, and continuing nintedanib as maintenance therapy for up to two years, in 188 women with FIGO stage IIIC-IV EOC. The primary outcome was progression-free survival; the secondary outcome was response rate.

Hainsworth 2015 was a multi-centre, open-label, phase II trial evaluating the effect of adding sorafenib to chemotherapy (up to six cycles of carboplatin and paclitaxel), and continuing sorafenib as maintenance therapy for up to a total of 12 months, in 85 women with FIGO stage III/IV EOC and residual measurable disease or elevated serum cancer antigen 125 (CA125 - an ovarian tumour marker) levels after maximal surgical cytoreduction. The primary outcome was progression-free survival; secondary outcomes included overall survival and safety.

Herzog 2013 was a multi-centre, double-blind, placebo-controlled, phase II trial evaluating the effect of adding sorafenib as maintenance therapy in 246 women with FIGO stage III/IV EOC with clinical complete response following tumour debulking surgery and chemotherapy (platinum and a taxane). The primary outcome was progression-free survival; secondary outcomes included overall survival, safety and quality of life.

TRINOVA-3 2019 was a multi-centre, double-blind, phase III trial evaluating the effect of adding trebananib to chemotherapy (carboplatin and paclitaxel), and continuing trebananib as maintenance therapy for up to 18 months afterwards, in 1015 women with FIGO stage III/IV EOC. The primary outcome was progression-free survival; secondary outcomes included overall survival, safety, pharmacokinetics and patient-reported outcomes.

Other anti-angiogenic agents

Reyners 2012 was an open-label, phase II trial evaluating the effect of adding the selective cyclo-oxygenase-2 (COX-2) inhibitor, celecoxib, to first-line chemotherapy (docetaxel and carboplatin) in 196 women with newly-diagnosed ovarian cancer. The primary outcomes were response rate and progression-free survival; secondary outcomes included safety/toxicity and overall survival.

Recurrent epithelial ovarian cancer

We included 37 studies evaluating the effect of angiogenesis inhibitors in 7128 participants with solely recurrent EOC: nine studies in 3034 women with recurrent platinum-sensitive disease (AVANOVA2 2019; Cong 2019; GOG-0213 2017; ICON6 2021; Li 2019; Liu 2019b; Liu 2022; MITO-16b 2021; OCEANS 2015), 19 in 2174 women with recurrent platinum-resistant disease (AMBITION 2022; APPROVE 2022; AURELIA 2014; BAROCCO 2022; EORTC-1508 2021; Gotlieb 2012; Li 2021; Liu 2019a; Liu 2021a; McGuire 2018; METRO-BIBF 2020; MITO-11 2015; NICCC 2020; Nishikawa 2020; OCTOVA 2021; Roque 2022; Sharma 2021; SWOG-S0904 2014; TRIAS 2018), and nine studies in 1920 participants recruited regardless of their platinum sensitivity status (Duska 2020; Gupta 2019; Karlan 2012; Ledermann 2011; Matulonis 2019; Richardson 2018; TAPAZ 2022; TRINOVA-1 2016; TRINOVA-2 2017).

Platinum-sensitive recurrent EOC

Bevacizumab

Five studies evaluated the effect of adding bevacizumab to chemotherapy in women with platinum-sensitive recurrent ovarian cancer (Cong 2019; GOG-0213 2017; Li 2019; MITO-16b 2021; OCEANS 2015). Cong 2019 evaluated the effect of adding bevacizumab to chemotherapy (carboplatin and paclitaxel) in 164 women with platinum-sensitive recurrent ovarian cancer. The primary outcome was the objective response rate; secondary outcomes included progression-free survival, overall survival, safety and quality of life. GOG-0213 2017 was a multi-centre, open-label, phase III trial evaluating the effect of adding bevacizumab to chemotherapy (carboplatin and paclitaxel) in 674 women with platinum-sensitive recurrent ovarian cancer. The primary outcome was overall survival; secondary outcomes included progression-free survival, safety and quality of life. Li 2019 evaluated the effect of adding bevacizumab to chemotherapy (carboplatin and paclitaxel) in 68 women with platinum-sensitive recurrent ovarian cancer. Outcomes included safety and "clinical efficacy". MITO-16b 2021 was a multi-centre, open-label, phase III trial evaluating the effect of adding bevacizumab to chemotherapy (carboplatin plus one of paclitaxel, gemcitabine, or pegylated liposomal doxorubicin) in 406 women with platinum-sensitive recurrent ovarian cancer. The primary outcome was progression-free survival; secondary outcomes included overall survival, objective response rate, safety and biomarkers. OCEANS 2015 was a multi-centre, blinded, placebo-controlled, phase III trial evaluating the effect of adding bevacizumab to chemotherapy (carboplatin and gemcitabine) in 484 women with platinum-sensitive recurrent ovarian cancer. The primary outcome was progression-free survival; secondary outcomes included objective response rate, duration of response, overall survival and safety. AVANOVA2 2019 was an open-label, phase II trial evaluating the effect of adding bevacizumab to the PARP inhibitor niraparib in 97 women with platinum-sensitive and partially platinum-sensitive recurrent ovarian cancer. The primary outcome was progression-free survival; secondary outcomes included the objective response rate, patient-reported outcomes and safety/tolerability; exploratory outcomes included overall survival.

Tyrosine kinase inhibitors

One study evaluated the effect of adding a tyrosine kinase inhibitor to chemotherapy in women with platinum-sensitive ovarian cancer (ICON6 2021). ICON6 2021 was a multi-centre, double-blind, placebo-controlled, phase III trial evaluating the effect of adding cediranib alongside chemotherapy (carboplatin with either paclitaxel or gemcitabine), or cediranib alongside chemotherapy followed by cediranib maintenance therapy, compared to chemotherapy alone (three arms), in 486 women with platinum-sensitive recurrent ovarian cancer. The primary outcome was progression-free survival (changed during the trial); secondary outcomes included overall survival, safety and quality of life.

Two studies evaluated a tyrosine kinase inhibitor in combination with a PARP inhibitor in women with platinum-sensitive recurrent ovarian cancer (Liu 2019b; Liu 2022). Liu 2022 was an open-label, three-arm, phase III trial evaluating the effect of adding cediranib to the PARP inhibitor olaparib, compared to olaparib alone, or to chemotherapy (carboplatin with either paclitaxel, gemcitabine or liposomal doxorubicin), in 565 women with recurrent platinum-sensitive ovarian cancer. The primary outcome was progression-free survival; secondary outcomes included overall survival, safety and patient-reported outcomes. Liu 2019b was a multi-centre, open-label, phase II trial evaluating the effect of adding cediranib to olaparib in 90 women with recurrent platinum-sensitive ovarian cancer. The primary outcome was progression-free survival; secondary outcomes included the objective response rate, safety/toxicity and overall survival.

Platinum-resistant recurrent EOC

Nineteen studies evaluated the use of angiogenesis inhibitors in platinum-resistant recurrent ovarian cancer (AMBITION 2022; APPROVE 2022; AURELIA 2014; BAROCCO 2022; EORTC-1508 2021; Gotlieb 2012; Li 2021; Liu 2019a; Liu 2021a; McGuire 2018; METRO-BIBF 2020; MITO-11 2015; NICCC 2020; Nishikawa 2020; OCTOVA 2021; Roque 2022; Sharma 2021; SWOG-S0904 2014; TRIAS 2018).

Bevacizumab

Six studies evaluated the effect of adding bevacizumab to chemotherapy in women with platinum-resistant recurrent EOC (AURELIA 2014; Li 2021; Liu 2019a; Liu 2021a; Nishikawa 2020; Roque 2022). AURELIA 2014 was an open-label, phase III trial evaluating the effect of adding bevacizumab to single-agent chemotherapy (investigator choice of pegylated liposomal doxorubicin, weekly paclitaxel or topotecan) in 361 women with platinum-resistant EOC. The primary outcome was progression-free survival; secondary outcomes included objective response rate, overall survival, safety, tolerability and quality of life. Li 2021 was a study with 70 participants, which appears to have compared albumin-binding paclitaxel monotherapy (days 1, 8

and 15) with or without bevacizumab. Treatment was for six cycles and there does not appear to have been a maintenance phase following chemotherapy. The details available are limited to an English-language abstract and we have not been able to access a copy of the full-text (Chinese) paper to date. Details are therefore unclear, including risk of bias in all categories and whether the study was blinded or open label. Outcomes included progression-free survival, overall survival, objective response rate, adverse reactions, quality of life and immune function. As this study is at such high risk of bias, we have not included its results in the meta-analyses, and will not do so until the full text paper can be interrogated. Liu 2019a evaluated the effect of adding bevacizumab to chemotherapy (albumin-bound paclitaxel) in 86 women with platinum-resistant EOC. The primary outcome was the objective response rate; secondary outcomes included progression-free survival, overall survival and safety/toxicity. Liu 2021a evaluated the effect of adding bevacizumab to chemotherapy (liposomal doxorubicin) in 76 women with platinum-resistant recurrent EOC. Primary outcomes included the objective response rate and disease control rate; secondary outcomes included progression-free survival, overall survival and safety. The study was open-label and follow-up ranged from 3.2 to 30.0 months. Insufficient data were provided to allow us to extract hazard ratio (HR) data for overall survival and progression-free survival. Adverse outcomes were presented as total number of adverse events, not by participant, and were not categorised by grade of adverse event. We were therefore not able to include these data in the meta-analyses. Nishikawa 2020 was an open-label, phase II trial evaluating the effect of adding bevacizumab to single-agent chemotherapy in 103 women with platinum-resistant EOC. All participants had previously been treated with at least three cycles of bevacizumab in previous lines of chemotherapy. The primary outcome was progression-free survival; secondary outcomes included objective response rate, safety and tolerability. Roque 2022 was a multi-centre, phase II trial evaluating the effect of adding bevacizumab to chemotherapy (ixabepilone, a microtubule-stabilising agent) in 76 women with platinum-resistant/refractory ovarian cancer. The primary outcome was progression-free survival; secondary outcomes included overall survival, safety and response rates.

One other study evaluated bevacizumab in platinum-resistant recurrent ovarian cancer (EORTC-1508 2021). EORTC-1508 2021 was a multi-centre, phase II trial that evaluated the effect of adding bevacizumab to atezolizumab (an immunotherapy drug), and also the effect of adding bevacizumab to atezolizumab and acetylsalicylic acid (aspirin, an inhibitor of the cyclo-oxygenase enzymes COX 1/2), in 122 women with platinum-resistant recurrent EOC. The primary outcome was progression-free survival at six months; secondary outcomes included safety, progression-free survival, response rate and time to first subsequent therapy.

A further study evaluated a different antibody targeting angiogenesis in platinum-resistant ovarian cancer (Gotlieb 2012). Gotlieb 2012 was a double-blind, placebo-controlled, phase II study evaluating the effect of giving aflibercept in 55 women with chemotherapy-resistant ovarian cancer and recurrent symptomatic malignant ascites (accumulated fluid in the abdomen due to the ovarian cancer). The primary outcome was the time to repeat paracentesis (draining of the abdominal fluid); secondary outcomes included the frequency of paracentesis, safety and patient-reported outcomes.

Olaratumab

Olaratumab (IMC-3G3) is a monoclonal antibody targeting platelet-derived growth factor alpha (PDGFRα). McGuire 2018 was a randomised, open-label, phase II study evaluating olaratumab plus liposomal doxorubicin compared with liposomal doxorubicin alone in 123 participants with platinum-resistant and platinum-refractory recurrent ovarian cancer. The primary outcome was progression-free survival; secondary outcomes included overall survival, objective response rate, duration of response and safety.

Tyrosine kinase inhibitors

Seven studies evaluated the effect of adding a tyrosine kinase inhibitor to chemotherapy in women with platinum-resistant recurrent EOC (APPROVE 2022; METRO-BIBF 2020; MITO-11 2015; NICCC 2020; Sharma 2021; SWOG-S0904 2014; TRIAS 2018). APPROVE 2022 was a multi-centre, open-label, phase II trial evaluating the effect of adding apatinib to chemotherapy (pegylated liposomal doxorubicin) in 150 women with platinum-resistant recurrent ovarian cancer. The primary outcome was progression-free survival; secondary outcomes included overall survival, objective response rate, disease control rate and safety. METRO-BIBF 2020 was a double-blind, placebo-controlled, phase II trial evaluating the effect of adding nintedanib to chemotherapy (low dose metronomic cyclophosphamide) in 117 women with platinum-resistant recurrent ovarian cancer. The primary outcome was overall survival; secondary outcomes included progression-free survival, response rate, toxicity and quality of life. MITO-11 2015 was an open-label, phase II trial evaluating the effect of adding pazopanib to chemotherapy (weekly paclitaxel) in 74 women with platinum-resistant or platinum-refractory ovarian cancer. The primary outcome was progression-free survival; secondary outcomes included overall survival, safety and objective response rate. NICCC 2020 was an open-label, phase II trial comparing nintedanib 200 mg or chemotherapy (paclitaxel, pegylated liposomal doxorubicin, or topotecan) in 91 participants with relapsed clear cell carcinoma. The primary outcome was progression-free survival in participants with clear cell EOC. Secondary outcomes included overall survival, response rate, disease control rate and patient reported outcomes. Sharma 2021 was an open-label, phase II trial evaluating the effect of adding pazopanib to chemotherapy (etoposide and cyclophosphamide) in 75 women with platinum resistant/refractory EOC. The primary outcome was progression-free survival; secondary outcomes included overall survival, safety and quality of life. SWOG-S0904 2014 was a phase II trial evaluating the effect of adding vandetanib to chemotherapy (docetaxel) in 129 women with platinum-resistant, refractory, persistent or recurrent ovarian cancer. The primary outcome was progression-free survival; secondary outcomes included response to treatment, overall survival and translational studies. TRIAS 2018 was a multi-centre, double-blind, placebo-controlled, phase II trial evaluating the effect of adding sorafenib to chemotherapy (topotecan) in 174 women with platinum-resistant/refractory recurrent ovarian cancer. The primary outcome was progression-free survival; secondary outcomes included overall survival, objective response rate, patient-reported outcomes and safety/tolerability.

Three other studies evaluated the use of tyrosine kinase inhibitors in platinum-resistant recurrent ovarian cancer. AMBITION 2022 was an umbrella study of biomarker-driven targeted therapy. One of the comparisons evaluated the effect of adding cediranib

to the PARP inhibitor olaparib, compared to adding the immunotherapy drug durvalumab to olaparib, in 30 women with homologous recombination-deficient platinum-resistant ovarian cancer. The primary outcome was the response rate; secondary outcomes included progression-free survival, overall survival, safety, immune-related response criteria and duration of response. BAROCCO 2022 was a phase II trial evaluating the effect of adding cediranib to the PARP inhibitor olaparib (in a continuous or intermittent schedule), compared to chemotherapy (paclitaxel) in 123 women with recurrent platinum-resistant high-grade EOC. The primary outcome was progression-free survival; secondary outcomes included treatment compliance, reasons for discontinuation and treatment modification, objective response rate, partial response, overall survival and quality of life. OCTOVA 2021 was an open-label, three-arm, phase II trial evaluating the effect of adding cediranib to the PARP inhibitor olaparib, compared to olaparib alone, or to chemotherapy (paclitaxel), in 139 participants. The primary outcome was progression-free survival; secondary outcomes included overall survival, safety/tolerability, objective response rate and quality of life.

Mixed recurrent EOC (platinum-sensitive, platinum-resistant and unclear)

Ten studies included mixed populations of women with platinum-sensitive and platinum-resistant recurrent ovarian cancer (Duska 2020; Gupta 2019; Karlan 2012; Ledermann 2011; Matulonis 2019; NICCC 2020; Richardson 2018; TAPAZ 2022; TRINOVA-1 2016; TRINOVA-2 2017).

Six studies evaluated the addition of a tyrosine kinase inhibitor to conventional therapy in women with recurrent ovarian cancer regardless of platinum-sensitivity status (Duska 2020; Karlan 2012; Richardson 2018; TAPAZ 2022; TRINOVA-1 2016; TRINOVA-2 2017). Duska 2020 was a multi-centre, open-label, phase II trial evaluating the effect of adding pazopanib to chemotherapy (weekly gemcitabine) in 148 women with persistent or recurrent EOC. The trial population included both platinum-resistant and platinum-sensitive participants. The primary outcome was progression-free survival; secondary outcomes included overall survival and safety/toxicity. Karlan 2012 was a double-blind, placebo-controlled, three-arm phase II trial evaluating the effect of adding trebananib (AMG 386) (at either a higher or a lower dose, in two separate trial arms) to chemotherapy (weekly paclitaxel) in 161 women with recurrent ovarian cancer. The trial population included platinum-refractory, platinum-resistant and platinum-sensitive participants. The primary outcome was progression-free survival; secondary outcomes included overall survival and safety. Richardson 2018 was a multi-centre, double-blind, placebo-controlled phase II trial evaluating the effect of adding pazopanib to chemotherapy (paclitaxel) in 106 women with persistent or recurrent ovarian cancer. The trial population included platinum-resistant and platinum-sensitive participants. The primary outcome was progression-free survival; secondary outcomes included safety, overall survival, proportion responding and duration of response. TAPAZ 2022 was a phase II trial evaluating the effect of adding pazopanib to weekly paclitaxel in 116 women with ovarian cancer who relapsed during bevacizumab maintenance therapy. The trial population included platinum-resistant and platinum-sensitive participants. The primary outcome was progression-free survival; secondary outcomes included overall survival, safety, pharmacokinetics and quality of life. TRINOVA-1 2016 was a multi-centre, double-blind, placebo-controlled, phase III trial evaluating the effect of adding trebananib to chemotherapy (weekly paclitaxel) in 919 women with recurrent EOC (the trial included a mixture of women with platinum-resistant and potentially platinum-sensitive disease). The primary outcome was progression-free survival; secondary outcomes included overall survival, objective response rate, safety and patient-reported outcomes. TRINOVA-2 2017 was a double-blind, placebo-controlled, phase III trial evaluating the effect of adding trebananib to chemotherapy (pegylated liposomal doxorubicin) in 223 women with recurrent partially platinum-sensitive or platinum-resistant ovarian cancer. The primary outcome was progression-free survival; secondary outcomes included overall survival, safety/toxicity, objective response rate and duration of response.

Four studies evaluated a tyrosine kinase inhibitor plus other agents or a tyrosine kinase inhibitor on its own, in a mixed population of women with platinum-sensitive and platinum-resistant recurrent EOC (Gupta 2019; Ledermann 2011; Matulonis 2019; NICCC 2020). Gupta 2019 was a phase II trial evaluating the effect of adding celecoxib to chemotherapy (oral cyclophosphamide) in 52 women with recurrent or persistent EOC. The trial population included platinum-refractory, platinum-resistant and platinum-sensitive participants. The primary outcome was response rate; secondary outcomes included safety/toxicity, time to treatment failure and overall survival. Ledermann 2011 was a double-blind, placebo-controlled, phase II trial evaluating the effect of giving nintedanib (BIBF 1120) maintenance therapy for up to 36 weeks in 84 women who had recently completed chemotherapy for recurrent ovarian cancer. Matulonis 2019 was an open-label, phase II trial evaluating cabozantinib versus chemotherapy (weekly paclitaxel) in 111 women with persistent or recurrent EOC. The trial population included platinum-resistant and platinum-sensitive participants. The primary outcome was progression-free survival; secondary outcomes included overall survival and safety/toxicity. NICCC 2020 was a multi-centre, open-label, phase II trial evaluating nintedanib versus chemotherapy (paclitaxel, pegylated liposomal doxorubicin or topotecan) in 91 women with recurrent clear cell ovarian cancer. The primary outcome was progression-free survival; secondary outcomes included overall survival, response rate, disease control rate and patient-reported outcomes. The investigators did not attempt to restrict the study population by platinum sensitivity, as clear cell ovarian cancer often shows poor response to platinum chemotherapy.

Excluded studies

In line with Cochrane guidelines, we describe here only those studies assessed and excluded at the full-text screening phase, which might plausibly have been included in the review (Lefebvre 2022, Section 4.6.5). In the previous version of the review, we excluded 12 studies (14 references); some of these do not now make the updated criteria for listing in the Excluded studies section. We have added additional references identified in this search update to some previously excluded studies. For this review update, we identified an additional 33 potentially relevant studies (55 references). Thus, there are now a total of 45 excluded studies (69 references). The reasons for study exclusion are as follows:

- ineligible study design: 18 studies (Azad 2008; Campos 2013; Colombo 2012; Hagemann 2013; Harter 2013; Ikeda 2013; Jones 2019; Krasner 2019; Ma 2022; Nasu 2022; NCT01972516; OCTAVIA

2014; Schilder 2013; Tillmans 2012; Tillmans 2013; Vergote 2017; Verschraegen 2012; Wenham 2013);

- ineligible comparator: 13 studies (Baumann 2012; NCT00017303; Ojeda 2011; PACOVAR-trial 2011; PAZOFOS 2020; Pfisterer 2021; Ray-Coquard 2019; Schwandt 2014; STAC 2011; Tew 2014; Tew 2018; Tredan 2022; Zhang 2020).
- ineligible intervention (e.g. alternative drug randomised and angiogenesis inhibitor in both arms): six studies (BOOST 2011; Chan 2016; DUO-O 2018; ENGOT-ov65 2021; GOG-3018 2020; Heiss 2010).
- ineligible population: two studies (ALIENOR/ENGOT-ov7 2020; Brown 2014).
- not clinical trials (e.g. review articles or systematic reviews): four studies (Burger 2010; Markman 2009; Osterweil 2010; Sennino 2010; Trillsch 2021).
- one study compared adding two cycles of intraperitoneal bevacizumab to carboplatin-paclitaxel chemotherapy prior to primary debulking surgery and looked at short-term outcomes (Tao 2022).

Risk of bias in included studies

For overall risk of bias and assessment of the risk of bias items for individual studies, see Figure 3 and Figure 4.

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

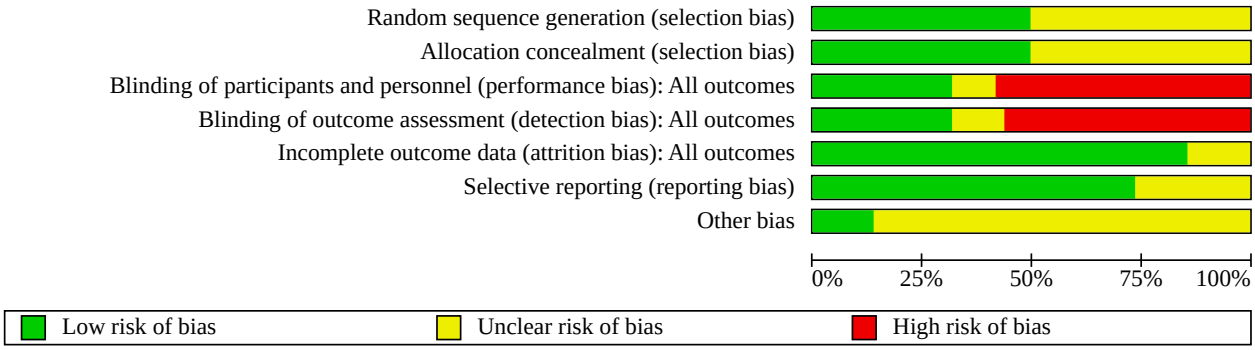


Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

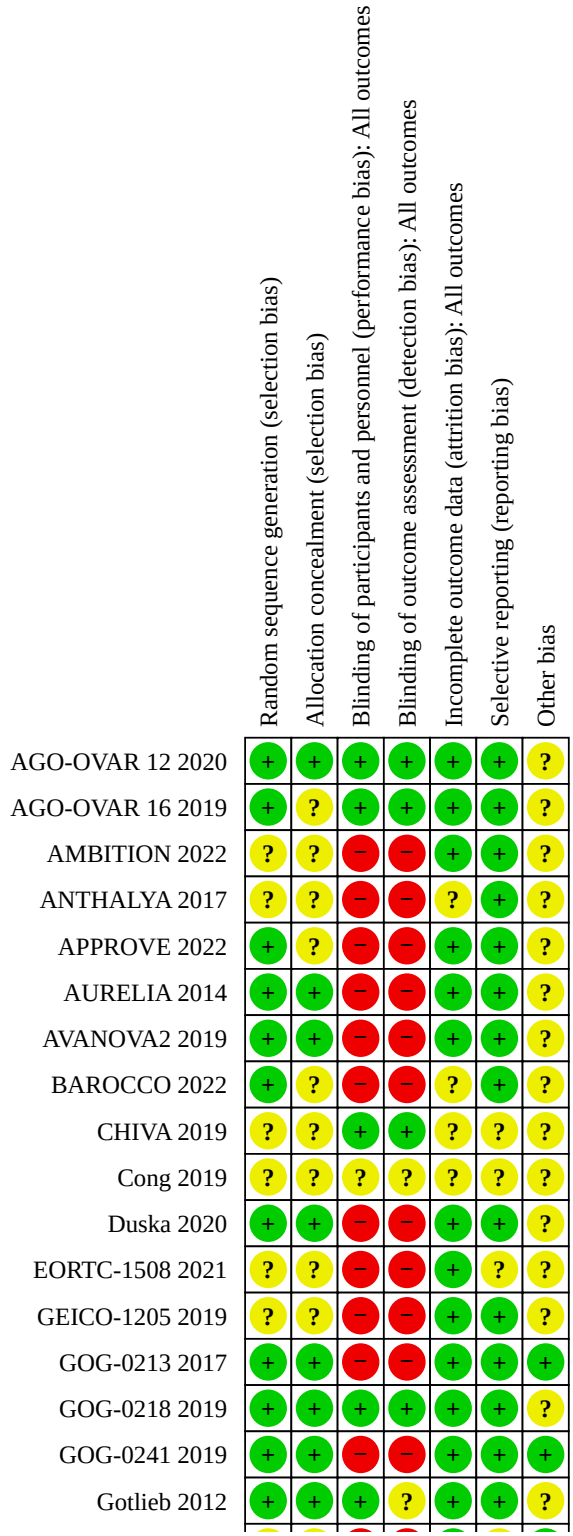
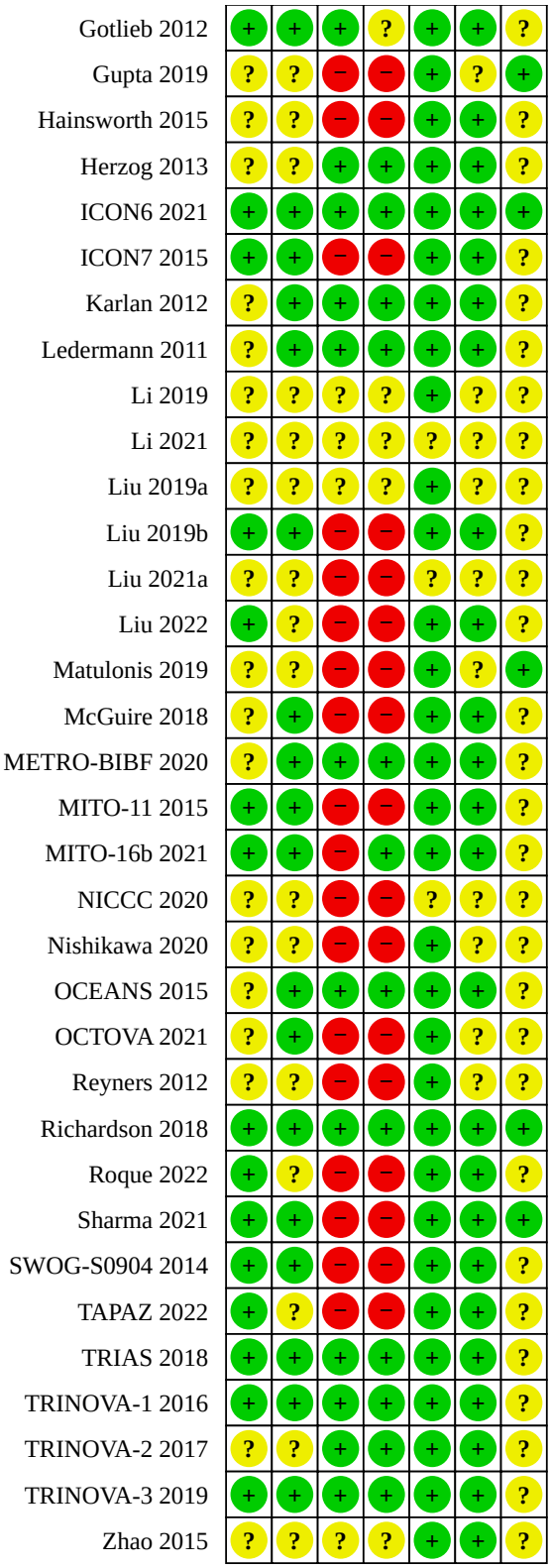


Figure 4. (Continued)



Allocation

Newly-diagnosed epithelial ovarian cancer (EOC)

Six of 13 studies in newly-diagnosed EOC specified the method of randomisation; we judged these to be at low risk of bias (AGO-OVAR 12 2020; AGO-OVAR 16 2019; GOG-0218 2019; GOG-0241 2019; ICON7 2015; TRINOVA-3 2019). In the remaining seven studies, we judged the method of randomisation to be at unclear risk of bias (ANTHALYA 2017; CHIVA 2019; GEICO-1205 2019; Hainsworth 2015; Herzog 2013; Reyners 2012; Zhao 2015).

Five of 13 studies in newly-diagnosed EOC specified the method of allocation concealment; we judged these to be at low risk of bias (AGO-OVAR 12 2020; GOG-0218 2019; GOG-0241 2019; ICON7 2015; TRINOVA-3 2019). In the remaining eight studies, we judged allocation concealment to be at unclear risk of bias, typically due to limited information (AGO-OVAR 16 2019; ANTHALYA 2017; CHIVA 2019; GEICO-1205 2019; Hainsworth 2015; Herzog 2013; Reyners 2012; Zhao 2015).

Recurrent EOC

Nineteen of 37 studies in recurrent EOC specified the method of randomisation; we judged these to be at low risk of bias. In 14 studies, we judged the method of randomisation to be at unclear risk of bias, typically due to limited information (AMBITION 2022; Cong 2019; EORTC-1508 2021; Gupta 2019; Karlan 2012; Ledermann 2011; McGuire 2018; Matulonis 2019; METRO-BIBF 2020; NICCC 2020; Nishikawa 2020; OCEANS 2015; OCTOVA 2021; TRINOVA-2 2017). We judged the remaining four studies to be at unclear risk of bias due to the methods used (e.g. random number table) (Li 2019; Li 2021; Liu 2019a; Liu 2021a).

Twenty of 37 studies in recurrent EOC specified the method of allocation concealment; we judged these to be at low risk of bias. In the remaining 17 studies, we judged the method of allocation concealment to be at unclear risk of bias, typically due to limited information (AMBITION 2022; APPROVE 2022; BAROCCO 2022; Cong 2019; EORTC-1508 2021; Gupta 2019; Li 2019; Li 2021; Liu 2019a; Liu 2022; Liu 2021a; NICCC 2020; Nishikawa 2020; Matulonis 2019; Roque 2022; TAPAZ 2022; TRINOVA-2 2017).

Blinding

Newly-diagnosed EOC

In six of 13 studies in newly diagnosed EOC (ANTHALYA 2017; GEICO-1205 2019; GOG-0241 2019; Hainsworth 2015; ICON7 2015; Reyners 2012), interventions were not concealed (open-label design), and hence participants and investigators were aware of the allocated treatment. As the key outcomes included progression-free survival and adverse events, which have an element of subjectivity in their assessment, the open-label design led to a potentially high risk of performance bias and detection bias. However, estimates for overall survival should be at low risk of bias. We judged the risk of performance and detection bias as low in six studies due to a 'double-blind' study design (in which both participants and investigators/assessors are masked as to intervention) (AGO-OVAR 12 2020; AGO-OVAR 16 2019; CHIVA 2019; GOG-0218 2019; Herzog 2013; TRINOVA-3 2019), and as unclear in one study (Zhao 2015), as the study did not specify whether it was open-label.

Recurrent EOC

In 22 of 37 studies in recurrent EOC, interventions were not concealed (open-label design) (AMBITION 2022; APPROVE 2022; AURELIA 2014; AVANOVA2 2019; BAROCCO 2022; Duska 2020; GOG-0213 2017; Gupta 2019; Liu 2019b; Liu 2021a; Liu 2022; McGuire 2018; Matulonis 2019; MITO-11 2015; MITO-16b 2021; NICCC 2020; Nishikawa 2020; OCTOVA 2021; Roque 2022; Sharma 2021; SWOG-S0904 2014; TAPAZ 2022). Thus, we judged assessment of outcomes such as PFS and adverse events to be at high risk of performance bias and detection bias, though estimates for overall survival should be at low risk of bias. One multi-arm study was described as 'double-blind' (EORTC-1508 2021), but appeared to be open-label for the comparison relevant to this review (i.e. with versus without bevacizumab). Thus, we considered it to be at high risk of bias for outcomes such as PFS and adverse events. We judged four studies to be at unclear risk of bias, typically because they were unclear about whether the trial was open-label (Cong 2019; Li 2019; Li 2021; Liu 2019a).

Incomplete outcome data

Newly-diagnosed EOC

We did not consider incomplete outcome data to be an issue in most studies, and judged them to at low risk of bias for this domain. The exceptions were ANTHALYA 2017, where it was difficult to judge this domain, as the analysis used a modified intention-to-treat approach, and CHIVA 2019, where there was insufficient information to judge this domain; we judged these to be at unclear risk of bias.

Recurrent EOC

We did not consider incomplete outcome data to be an issue in most studies, and judged them to be at low risk of bias for this domain. The exceptions were five studies in which we judged the risk of bias as unclear (BAROCCO 2022; Cong 2019; Li 2021; Liu 2021a; NICCC 2020), mostly because relevant published outcome information was only available from conference abstracts. We judged BAROCCO 2022 to be at unclear risk of attrition bias, as 12 of the 17 participants who did not complete four weeks of treatment were in the control arm of a three-arm study.

Selective reporting

Newly-diagnosed EOC

We did not consider selective reporting of outcomes to be an issue in most studies, and judged them to be at low risk of bias for this domain. The exceptions were CHIVA 2019 and Reyners 2012, where there was insufficient information to judge this domain.

Recurrent EOC

We did not consider selective reporting of outcomes to be an issue in the majority of studies, and judged them to be at low risk of bias for this domain. However, in 11 of 37 studies, there was insufficient information to judge this domain (Cong 2019; EORTC-1508 2021; Gupta 2019; Li 2019; Li 2021; Liu 2019a; Liu 2021a; Matulonis 2019; NICCC 2020; Nishikawa 2020; OCTOVA 2021), in some cases due to limited information from conference abstracts, and we assessed these as having an unclear risk of bias.

Other potential sources of bias

We judged 43 of 50 included studies (in both newly-diagnosed and recurrent settings) to have an unclear risk of bias in this domain because they were either fully or partly industry-sponsored, with at least some authors from each study disclosing a financial conflict of interest. The other studies appeared to have non-industry funding and no declared conflicts of interest.

Effects of interventions

See: **Summary of findings 1** Chemotherapy with bevacizumab followed by maintenance bevacizumab compared to chemotherapy alone in newly-diagnosed EOC; **Summary of findings 2** Chemotherapy with TKI followed by TKI maintenance compared to chemotherapy alone in newly-diagnosed EOC; **Summary of findings 3** Chemotherapy with TKI (peptide-Fc fusion protein) followed by TKI maintenance compared to chemotherapy alone in newly-diagnosed EOC; **Summary of findings 4** Chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone in recurrent platinum-sensitive EOC; **Summary of findings 5** Chemotherapy with TKI followed by TKI maintenance compared to chemotherapy alone in recurrent platinum-sensitive EOC ; **Summary of findings 6** Chemotherapy with bevacizumab compared to chemotherapy alone in recurrent platinum-resistant EOC; **Summary of findings 7** Chemotherapy with TKI compared to chemotherapy alone in recurrent platinum-resistant EOC; **Summary of findings 8** Chemotherapy with TKI (peptide-Fc fusion protein) compared to chemotherapy alone in recurrent EOC

This review assesses the treatment options at different time points in the treatment of EOC where it may be appropriate to use angiogenesis inhibitors, each of which is a separate clinical question. These time points are: newly-diagnosed EOC; and recurrent EOC, where disease may be further divided by platinum-sensitivity (platinum-sensitive recurrence; platinum-resistant recurrence; mixed/unclear platinum sensitivity). We divided studies between these different clinical scenarios; the studies are summarised in Table 1. We present summary of findings tables for the most clinically relevant comparisons.

Newly-diagnosed epithelial ovarian cancer (EOC)

Thirteen included studies evaluated the effect of angiogenesis inhibitors in newly-diagnosed EOC (AGO-OVAR 12 2020; AGO-OVAR 16 2019; ANTHALYA 2017; CHIVA 2019; GEICO-1205 2019; GOG-0218 2019; GOG-0241 2019; Hainsworth 2015; Herzog 2013; ICON7 2015; Reyners 2012; TRINOVA-3 2019; Zhao 2015). The GOG-0241 2019 and Zhao 2015 trials did not contribute data to quantitative synthesis due to their reporting of outcome data. Of the remaining trials, four evaluated the use of bevacizumab (ANTHALYA 2017; GEICO-1205 2019; GOG-0218 2019; ICON7 2015), and six evaluated the use of tyrosine kinase inhibitors (TKIs) (AGO-OVAR 12 2020; AGO-OVAR 16 2019; CHIVA 2019; Hainsworth 2015; Herzog 2013; TRINOVA-3 2019), in addition to or after standard chemotherapy. One study evaluated the use of celecoxib (Reyners 2012).

We graded the certainty of the evidence of the three most clinically relevant comparisons:

- chemotherapy with bevacizumab followed by maintenance bevacizumab compared to chemotherapy alone (Summary of findings 1);
- chemotherapy with TKI followed by TKI maintenance compared to chemotherapy alone (Summary of findings 2);
- chemotherapy with TKI (peptide-Fc fusion protein) followed by TKI maintenance compared to chemotherapy alone (Summary of findings 3).

1. Chemotherapy with bevacizumab compared to chemotherapy alone (placebo for all in the maintenance phase)

One included study compared chemotherapy with bevacizumab to chemotherapy alone for newly-diagnosed EOC (GOG-0218 2019). This three-armed study enrolled 1873 participants in total. For this comparison, 1250 women were randomised to one of two study arms (625 women to each arm).

Overall survival (OS)

Chemotherapy with bevacizumab likely results in little to no difference in OS compared to chemotherapy alone (hazard ratio (HR) 1.06, 95% confidence interval (CI) 0.94 to 1.20; 1250 participants; Analysis 1.1).

Progression-free survival (PFS)

Chemotherapy with bevacizumab likely results in little to no difference in PFS compared to chemotherapy alone (HR 0.91, 95% CI 0.79 to 1.04; 1250 participants; Analysis 1.2).

Quality of life (QoL)

Chemotherapy with bevacizumab likely results in little to no difference in QoL at six months of follow-up (measured using the Trial Outcome Index score of the Functional Assessment of Cancer Therapy - Ovarian Cancer questionnaire) compared to chemotherapy alone (mean difference (MD) 1.80, 95% CI -0.32 to 3.92; 709 participants; Analysis 1.3).

Adverse events

The GOG-0218 2019 trial did not report the effect of chemotherapy with bevacizumab on any severe adverse events (grade ≥ 3), proteinuria (grade ≥ 2), abdominal pain (grade ≥ 2), neutropenia (grade ≥3), or bowel fistula or perforation, which were the prespecified outcomes for this review. However, many studies detailed adverse events by different category groupings (e.g. grade 1-2 and grade ≥ 3). We judged it appropriate to present the data as reported, rather than discard the data. Chemotherapy with bevacizumab compared with chemotherapy alone likely results in a large increase in hypertension (grade ≥ 2) (RR 2.33, 95% CI 1.55 to 3.26; 1208 participants; Analysis 1.4); likely results in little to no difference in proteinuria (grade ≥ 3) (RR 0.99, 95% CI 0.25 to 3.94; 1 study, 1208 participants; Analysis 1.5) and pain (grade ≥ 2) (RR 1.00, 95% CI 0.88 to 1.14; 1208 participants; Analysis 1.6); slight increases in neutropenia (grade ≥ 4) (RR 1.16, 95% CI 1.06 to 1.26; 1208 participants; Analysis 1.7); likely results in little to no difference in febrile neutropenia (any grade) (RR 1.41, 95% CI 0.82 to 2.44; 1208 participants; Analysis 1.8), venous thromboembolic events (any grade) (RR 1.02, 95% CI 0.65 to 1.60; 1208 participants; Analysis 1.9), arterial thromboembolic event (any grade) (RR 0.79, 95% CI 0.21 to 2.94; 1208 participants; Analysis 1.10), non-central nervous system (non-CNS) bleeding (grade ≥ 3) (RR 1.58, 95% CI 0.52 to 4.81; 1208 participants; Analysis 1.11) and gastrointestinal adverse events (grade ≥2) (RR 1.88, 95% CI 0.88 to 4.01; 1208 participants; Analysis 1.12).

2. Chemotherapy with bevacizumab followed by maintenance bevacizumab compared to chemotherapy alone in newly-diagnosed EOC

Two included studies (2776 participants) compared chemotherapy with bevacizumab followed by maintenance bevacizumab versus chemotherapy alone (GOG-0218 2019; ICON7 2015). See Summary of findings 1.

Overall survival (OS)

Chemotherapy with bevacizumab followed by maintenance bevacizumab likely results in little to no difference in OS compared to chemotherapy alone (HR 0.97, 95% CI 0.88 to 1.07; 2776 participants; moderate-certainty evidence; Analysis 2.1). There was evidence of subgroup differences in the risk of disease (P = 0.007) (Analysis 2.2), which suggests that those at higher risk of disease progression may have more benefit (HR 0.86, 95% CI 0.76 to 0.98; 1316 participants) compared to those at lower risk (HR 1.13, 95% CI 0.97 to 1.31; 1460 participants). However, these data are based on retrospective subgroup analysis within the studies and should be interpreted with caution.

Progression-free survival (PFS)

The evidence is very uncertain about the effect of chemotherapy with bevacizumab followed by maintenance bevacizumab on PFS (HR 0.82, 95%CI 0.64 to 1.05; 2746 participants; very low-certainty evidence; Analysis 2.3).

Quality of life (QoL)

Studies differed in their reporting of quality of life measures. Chemotherapy with bevacizumab followed by maintenance bevacizumab compared to chemotherapy alone reduces QoL at 54 weeks, measured using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire (ICON7 2015) (MD -6.40, 95% CI -8.86 to -3.94; 1 study, 890 participants; high-certainty evidence; Analysis 2.4), and likely results in little to no difference in QoL at six months of follow-up, measured using Trial Outcome Index score of the Functional Assessment of Cancer Therapy—Ovarian Cancer questionnaire (GOG-0218 2019) (MD 2.00, 95% CI -0.12 to 4.12; 1 study; 709 participants; Analysis 2.4).

Adverse events

The two included studies for this comparison did not report the effect of chemotherapy with bevacizumab followed by maintenance bevacizumab by our prespecified outcomes of hypertension (grade ≥ 2), proteinuria (grade ≥ 2), abdominal pain (grade ≥ 2), venous thromboembolic events, arterial thromboembolic events, non-CNS bleeding, gastrointestinal adverse events or bowel fistula or perforation. For reasons described above, presented grades of hypertension, pain and abdominal pain are different from the prespecified outcomes and grade of pain data are limited to only grade 3 (not grade ≥ 3 as prespecified).

Chemotherapy with bevacizumab followed by maintenance bevacizumab compared to chemotherapy alone likely results in little to no difference in any adverse events (grade ≥ 3) (RR 1.16, 95% CI 1.07 to 1.26; 1 study, 1485 participants; moderate-certainty evidence; Analysis 2.5). Chemotherapy with bevacizumab followed by maintenance bevacizumab may result in a large increase in hypertension (grade ≥ 2) compared to chemotherapy alone (RR 4.27, 95% CI 3.25 to 5.60; 2 studies, 2707 participants; low-certainty evidence; Analysis 2.6).

Chemotherapy with bevacizumab followed by maintenance bevacizumab compared to chemotherapy alone likely increases proteinuria (grade ≥ 3) (RR 1.95, 95% CI 1.18 to 3.20; 2 studies, 2707 participants; Analysis 2.7); likely results in little to no difference in pain (grade ≥ 2) (RR 1.13, 95% CI 0.99 to 1.28; 1 study, 1209 participants; Analysis 2.8), neutropenia (grade ≥ 3: RR 1.09, 95% CI 0.86 to 1.38; 1 study, 2707 participants; grade ≥ 4: RR 1.10, 95% CI 1.00 to 1.20; 1 study, 1209 participants; Analysis 2.9), and febrile neutropenia (any grade) (RR 1.33, 95% CI 0.87 to 2.03; 2 studies, 2707 participants; Analysis 2.10). Chemotherapy with bevacizumab followed by maintenance bevacizumab compared to chemotherapy alone likely increases the rate of venous thromboembolic events (any grade) (RR 1.39, 95% CI 1.02 to 1.89; 2 studies, 2707 participants; Analysis 2.11) and arterial thromboembolic events (any grade) (RR 1.93, 95% CI 1.05 to 3.57; 2 studies, 2707 participants; Analysis 2.12); likely results in little to no difference in non-CNS bleeding (grade ≥ 3) (RR 2.10, 95% CI 0.85 to 5.21; 2 studies, 2707 participants; Analysis 2.13); likely results in a large increase in gastrointestinal adverse events (grade ≥ 2) (RR 2.17, 95% CI 1.04 to 4.55; 1 study, 1209 participants; Analysis 2.14); and may result in a large increase in gastrointestinal perforation (grade ≥ 3) (RR 3.71, 95% CI 1.04 to 13.23; 1 study, 1498 participants; Analysis 2.14).

3. Chemotherapy with tyrosine kinase inhibitors (TKIs) followed by TKI maintenance compared to chemotherapy alone in newly-diagnosed EOC

Three studies (1639 participants) compared chemotherapy with TKI followed by TKI maintenance compared to chemotherapy alone in newly-diagnosed EOC (AGO-OVAR 12 2020; CHIVA 2019; Hainsworth 2015). See Summary of findings 2. AGO-OVAR 12 2020 (1366 participants) evaluated the addition of pazopanib, CHIVA 2019 (188 participants) evaluated the addition of nintedanib, whereas Hainsworth 2015 (85 participants) evaluated the addition of sorafenib.

Overall survival (OS)

Chemotherapy with TKI followed by maintenance with TKI likely results in little to no difference in OS compared to chemotherapy alone (HR 0.99, 95% CI 0.84 to 1.17; 2 studies, 1451 participants; moderate-certainty evidence; Analysis 3.1).

Progression-free survival (PFS)

Chemotherapy with TKI followed by maintenance with TKI likely results in little to no difference in PFS compared to chemotherapy alone (HR 0.88, 95% CI 0.77 to 1.00; 1451 participants; moderate-certainty evidence; Analysis 3.2).

Quality of life (QoL)

Chemotherapy with TKI followed by maintenance with TKI (pazopanib) compared to chemotherapy alone reduces the mean global health status and QoL score over the treatment period, measured using the European Organisation for Research and Treatment of Cancer QLQ-C30 questionnaire in one study (AGO-OVAR 12 2020) (MD -1.86 95% CI -3.46 to -0.26; 1 study, 1340 participants; moderate-certainty evidence; Analysis 3.3).

Adverse events

The two included studies for this comparison did not report the effect of chemotherapy with TKI followed by maintenance with TKI on our prespecified outcomes of hypertension (grade ≥ 2), proteinuria (grade ≥ 2), pain (grade ≥ 2), abdominal pain (grade ≥ 2), venous thromboembolic events, arterial thromboembolic events, non-CNS bleeding, febrile neutropenia, gastrointestinal adverse events or bowel fistula or perforation. For reasons described above, presented grades of hypertension and abdominal pain are different from our prespecified outcomes.

Chemotherapy with TKI followed by maintenance with TKI compared to chemotherapy alone increases adverse events (grade ≥ 3) (RR 1.31, 95% CI 1.11 to 1.55; 1 study, 188 participants; moderate-certainty evidence; Analysis 3.4) and may result in a large increase in hypertension (grade ≥ 3) (RR 6.49, 95% CI 2.02 to 20.87; 1 study, 1352 participants; low-certainty evidence; Analysis 3.5). Chemotherapy with TKI followed by maintenance with TKI compared to chemotherapy alone likely results in little to no difference in abdominal pain (grade ≥ 3) (RR 1.54, 95% CI 0.81 to 2.92; 1 study, 1352 participants; Analysis 3.6). Chemotherapy with TKI followed by maintenance with TKI compared to chemotherapy alone likely results in little to no difference in neutropenia (grade ≥ 3) (RR 1.11, 95% CI 0.95 to 1.30; 1 study, 1352 participants; Analysis 3.7).

4. Chemotherapy with TKI (peptide-Fc fusion protein) followed by TKI maintenance compared to chemotherapy alone in newly-diagnosed EOC

One included study (1015 participants) evaluated the effect of the TKI agent trebananib, a peptide-Fc fusion protein (TRINOVA-3 2019) (see Summary of findings 3).

Overall survival (OS)

Chemotherapy with TKI (trebananib) followed by maintenance with TKI likely results in little to no difference in OS compared to chemotherapy alone (HR 0.99, 95% CI 0.79 to 1.25; moderate-certainty evidence; Analysis 4.1).

Progression-free survival (PFS)

Chemotherapy with TKI (trebananib) followed by maintenance with TKI likely results in little or no difference in PFS compared to chemotherapy alone (HR 0.93, 95% CI 0.79 to 1.09; moderate-certainty evidence; Analysis 4.2).

Quality of life (QoL)

TRINOVA-3 2019 did not report this outcome.

Adverse events

TRINOVA-3 2019 did not report the effect of chemotherapy with TKI (trebananib) followed by maintenance with TKI on hypertension (grade ≥ 2), proteinuria (grade ≥ 2), pain (grade ≥ 2), abdominal pain (grade ≥ 2), venous thromboembolic events, arterial thromboembolic events, non-CNS bleeding, gastrointestinal adverse events or bowel fistula or perforation. For reasons described above, presented grades of pain and abdominal pain are different from those we prespecified and grade of pain data are limited to only grade 3 (not grade ≥ 3 as prespecified).

Chemotherapy with TKI (trebananib) followed by maintenance with TKI compared to chemotherapy alone likely increases any adverse events (grade ≥ 3) (RR ranged from 1.10 (grade 3) to 9.96 (grade 5); moderate-certainty evidence; Analysis 4.3).

Chemotherapy with TKI (trebananib) followed by maintenance with TKI compared to chemotherapy alone may result in little to no difference in pain (grade 3) (RR 1.00, 95% CI 0.09 to 10.94; Analysis 4.4) and likely results in little to no difference in abdominal pain (grade ≥ 3) (RR 1.22, 95% CI 0.61 to 2.43; Analysis 4.5).

Chemotherapy with TKI (trebananib) followed by maintenance with TKI compared to chemotherapy alone likely results in little to no difference in neutropenia (grade ≥ 3) (RR 0.95, 95% CI 0.77 to 1.18; Analysis 4.6 (grade 3)). The evidence is very uncertain about the effect of TKI (trebananib) followed by maintenance with TKI on febrile neutropenia (RR ranged from 0.50 (grade 1 to 2) to 3.49 (grade 4); Analysis 4.7).

5. Maintenance with TKI versus placebo after first-line chemotherapy in newly-diagnosed EOC

Two studies (1186 participants) compared maintenance with TKI versus placebo after first-line chemotherapy in newly-diagnosed EOC (AGO-OVAR 16 2019; Herzog 2013). AGO-OVAR 16 2019 (940 participants) evaluated pazopanib versus placebo, whereas Herzog 2013 (246 participants) evaluated sorafenib versus placebo.

Overall survival (OS)

After standard chemotherapy, maintenance with TKI compared to placebo likely results in little to no difference in OS (HR 0.98, 95% CI 0.83 to 1.16; Analysis 5.1).

Progression-free survival (PFS)

After standard chemotherapy, maintenance with TKI compared to placebo likely results in little to no difference in PFS (HR 0.87, 95%CI 0.63 to 1.20; Analysis 5.2).

Quality of life (QoL)

After standard chemotherapy, maintenance with TKI compared to placebo likely results in little to no difference in QoL at the end of the maintenance phase, measured using the Functional Assessment of Cancer Therapy (FACT)/National Comprehensive Cancer Network (NCCN) Ovarian Symptom Index (FOSI) in one study (Herzog 2013) (MD 0.48 95% CI -0.70 to 1.66; 156 participants; Analysis 5.3).

Adverse events

The two included studies for this comparison did not report on any severe adverse events (grade ≥ 3), hypertension (grade ≥ 2), proteinuria (grade ≥ 2), pain (grade ≥ 2), abdominal pain (grade ≥ 2), neutropenia (grade ≥ 3), febrile neutropenia, venous thromboembolic events, arterial thromboembolic events, non-CNS bleeding, gastrointestinal adverse events, or bowel fistula or perforation. For reasons described above, presented grades of hypertension, proteinuria, abdominal pain and neutropenia are different from those we prespecified.

After standard chemotherapy, maintenance with TKI compared to placebo likely results in a large increase in hypertension (grade ≥ 3) (RR 5.59, 95% CI 3.78 to 8.25; 2 studies, 1184 participants; Analysis 5.4); and likely results in little to no difference in proteinuria (grade 3 or 4) (RR 2.90, 95%CI 0.59 to 14.29; 1 study, 938 participants; Analysis 5.5) and abdominal pain (grade ≥ 3) (RR 1.46, 95% CI 0.52 to 4.08; 1 study, 1184 participants; Analysis 5.6).

After standard chemotherapy, maintenance with TKI compared to placebo likely results in a large increase in neutropenia (grade 3 or 4) (RR 6.49, 95% CI 2.96 to 14.21; 1 study, 938 participants; Analysis 5.7).

6. Neoadjuvant chemotherapy with bevacizumab versus chemotherapy alone followed by adjuvant chemotherapy with bevacizumab and bevacizumab maintenance for all in newly-diagnosed EOC

Two studies (163 participants) assessed the effect of bevacizumab in participants who had neoadjuvant chemotherapy prior to interval debulking surgery and compared giving chemotherapy alone before surgery versus chemotherapy plus bevacizumab in combination, with all participants receiving chemotherapy and bevacizumab in combination following surgery (ANTHALYA 2017; GEICO-1205 2019).

Overall survival (OS)

Neither of the two included studies examining this comparison reported this outcome (ANTHALYA 2017; GEICO-1205 2019).

Progression-free survival (PFS)

Neoadjuvant chemotherapy with bevacizumab likely results in little or no difference in PFS compared to chemotherapy alone (HR 1.13, 95% CI 0.66 to 1.93; 1 study, 68 participants; Analysis 6.1).

Quality of life (QoL)

Neither of the two included studies examining this comparison reported this outcome (ANTHALYA 2017; GEICO-1205 2019).

Adverse events

The two included studies did not report the effect of neoadjuvant chemotherapy with bevacizumab on hypertension (grade ≥ 2), proteinuria (grade ≥ 2), pain (grade ≥ 2), abdominal pain (grade ≥ 2), febrile neutropenia, venous thromboembolic events, arterial thromboembolic events, non-CNS bleeding (grade ≥ 3), gastrointestinal adverse events (grade ≥ 2), and bowel fistula or perforation. For reasons described above, presented grades of hypertension, abdominal pain and gastrointestinal adverse events are different from those we prespecified.

The evidence is very uncertain about the effect of neoadjuvant chemotherapy with bevacizumab on any adverse events (grade ≥ 3) (RR 0.83, 95% CI 0.58 to 1.19; 2 studies, 163 participants; Analysis 6.2), hypertension (grade ≥ 3) (RR 0.94, 95% CI 0.06 to 14.47; 1 study, 68 participants; Analysis 6.3) and neutropenia (grade ≥ 3) (RR 1.89, 95% CI 0.37 to 9.62; 1 study, 68 participants; Analysis 6.5). Neoadjuvant chemotherapy with bevacizumab may result in little to no difference in abdominal pain (grade ≥ 3) (RR 0.19, 95% CI 0.01 to 3.79; 1 study, 68 participants; Analysis 6.4) and gastrointestinal adverse events (grade unclear) (RR 0.52, 95% CI 0.18 to 1.52; 1 study, 95 participants; Analysis 6.6), compared to chemotherapy alone.

7. Chemotherapy with celecoxib versus chemotherapy alone in newly-diagnosed EOC

One included study evaluated the addition of celecoxib to primary chemotherapy in women with newly-diagnosed ovarian cancer (Reyners 2012).

Overall survival (OS)

There may be little to no difference in OS (HR 1.16, 95% CI 0.86 to 1.57; 1 study, 196 participants; Analysis 7.1).

Progression-free survival (PFS)

There may be little to no difference in PFS (HR 1.07, 95% CI 0.85 to 1.34; 1 study, 196 participants; Analysis 7.2).

Quality of life (QoL)

Reyners 2012 did not report this outcome.

Adverse events

There may be little to no difference in febrile neutropenia (grade ≥ 3) (RR 0.94, 95% CI 0.45 to 1.96; 1 study, 196 participants; Analysis 7.3) or gastrointestinal adverse events (grade ≥ 3) (RR 1.15, 95% CI 0.46 to 2.85; 1 study, 196 participants; Analysis 7.4). There was evidence that participants in the group that received celecoxib may be more likely to have skin rash (11.2% versus 0%; P < 0.001) and changes in liver function tests (7.2% versus 1%; P = 0.034), but these were not outcomes included in our key outcomes. Overall, this was a small study, and our certainty in the survival results is lowered further by discontinuation of celecoxib for over six months in the study. This was due to wider safety concerns about another similar drug (rofecoxib) for which approval was withdrawn by the Food and Drug Administration (FDA) due to safety concerns regarding cardiovascular events. The study was re-started seven months later after participants were informed about the potential for increased cardiovascular toxicity. In the Reyners 2012 study, 24% (23/97) of participants in the chemotherapy plus celecoxib group discontinued celecoxib during chemotherapy and 27% (17/63) of those who started maintenance treatment discontinued treatment, largely due to adverse reactions.

Recurrent epithelial ovarian cancer (EOC)

Thirty-seven included studies evaluated the effect of angiogenesis inhibitors in recurrent EOC. Of these, there were nine studies in women with recurrent platinum-sensitive disease (AVANOVA2 2019; Cong 2019; GOG-0213 2017; ICON6 2021; Li 2019; Liu 2019b; Liu 2022; MITO-16b 2021; OCEANS 2015), 19 studies in women with recurrent platinum-resistant disease (AMBITION 2022; APPROVE 2022; AURELIA 2014; BAROCCO 2022; EORTC-1508 2021; Gotlieb 2012; Li 2021; Liu 2019a; Liu 2021a; McGuire 2018; METRO-BIBF 2020; MITO-11 2015; NICCC 2020; Nishikawa 2020; OCTOVA 2021; Roque 2022; Sharma 2021; SWOG-S0904 2014; TRIAS 2018), and nine studies who recruited participants regardless of platinum-sensitivity status (Duska 2020; Gupta 2019; Karlan 2012; Ledermann 2011; Matulonis 2019; Richardson 2018; TAPAZ 2022; TRINOVA-1 2016; TRINOVA-2 2017).

Eleven studies evaluated the addition of bevacizumab to conventional chemotherapy (AURELIA 2014; Cong 2019; GOG-0213 2017; Li 2019; Li 2021; Liu 2019a; Liu 2021a; MITO-16b 2021; Nishikawa 2020; OCEANS 2015; Roque 2022). Thirteen studies evaluated the addition of TKIs to conventional therapy (APPROVE 2022; Duska 2020; ICON6 2021; Karlan 2012; METRO-BIBF 2020; MITO-11 2015; Richardson 2018; Sharma 2021; SWOG-S0904 2014; TAPAZ 2022; TRIAS 2018; TRINOVA-1 2016; TRINOVA-2 2017). One evaluated the addition of olaratumab to conventional chemotherapy (McGuire 2018). Eleven studies evaluated a combination of TKIs with other agents or on their own (AMBITION 2022; BAROCCO 2022; Ledermann 2011; EORTC-1508 2021; Gotlieb

2012; Gupta 2019; Liu 2019b; Liu 2022; NICCC 2020; Matulonis 2019; OCTOVA 2021). The final study compared the addition of bevacizumab to a PARP inhibitor (niraparib) (AVANOVA2 2019).

We graded the certainty of the evidence of the five most clinically relevant comparisons:

- chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone (Summary of findings 4);
- chemotherapy with TKI followed by TKI maintenance compared to chemotherapy alone (Summary of findings 5);
- chemotherapy with bevacizumab compared to chemotherapy alone (Summary of findings 6);
- chemotherapy with TKI compared to chemotherapy alone (Summary of findings 7); and
- chemotherapy with TKI (peptide-Fc fusion protein) compared to chemotherapy alone (Summary of findings 8).

A. Platinum-sensitive EOC

8. Chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone in recurrent platinum-sensitive EOC

Three included studies (1564 participants) compared chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone in recurrent platinum-sensitive EOC (GOG-0213 2017; MITO-16b 2021; OCEANS 2015). See Summary of findings 4.

Overall survival (OS)

Chemotherapy with bevacizumab followed by maintenance bevacizumab likely results in little to no difference in OS compared to chemotherapy alone (HR 0.90, 95% CI 0.79 to 1.02; moderate-certainty evidence; Analysis 8.1).

Progression-free survival (PFS)

Chemotherapy with bevacizumab followed by maintenance bevacizumab likely increases PFS compared to chemotherapy alone (HR 0.56, 95% CI 0.50 to 0.63; moderate-certainty evidence; Analysis 8.2).

Quality of life (QoL)

Chemotherapy with bevacizumab followed by maintenance bevacizumab compared to chemotherapy alone likely results in little to no difference in QoL at 12 months after the first cycle, measured using the Trial Outcome Index score of the Functional Assessment of Cancer Therapy—Ovarian Cancer questionnaire in one study (GOG-0213 2017) (MD 0.80, 95% CI -2.11 to 3.71; 1 study, 486 participants; low-certainty evidence; Analysis 8.3).

Adverse events

The included studies did not report the effect of chemotherapy with bevacizumab on hypertension (grade ≥ 2), proteinuria (grade ≥ 2), pain (grade ≥ 2), abdominal pain (grade ≥ 2), venous thromboembolic events (any grade), non-CNS bleeding (grade ≥ 3), gastrointestinal adverse events (grade ≥ 2), or bowel fistula or perforation (grade ≥ 3). For reasons described above, presented grades of hypertension, proteinuria, pain, abdominal pain, venous thromboembolic events, non-CNS bleeding, and gastrointestinal perforations are different from those we prespecified.

Chemotherapy with bevacizumab followed by maintenance bevacizumab slightly increases any adverse event (grade ≥3) compared to chemotherapy alone (RR 1.11, 95% CI 1.07 to 1.16; 3 studies, 1538 participants; high-certainty evidence; Analysis 8.4).

The evidence is very uncertain about the effect of chemotherapy with bevacizumab followed by maintenance bevacizumab compared to chemotherapy alone on hypertension (grade ≥ 3) (RR 5.82, 95% CI 3.84 to 8.83; 3 studies, 1538 participants; Analysis 8.5), abdominal pain (grade ≥ 3) (RR 16.88, 95% CI 4.72 to 60.34; 2 studies, 1058 participants; Analysis 8.8), neutropenia (grade ≥ 3) (RR 1.04, 95% CI 0.83 to 1.31; 2 studies, 1058 participants; Analysis 8.9), febrile neutropenia (any grade) (RR 1.20, 95% CI 0.70 to 2.06; 3 studies, 1538 participants; Analysis 8.10), and gastrointestinal perforations (RR 4.96, 95% 0.86 to 28.51; 2 studies, 1058 participants; Analysis 8.14).

Chemotherapy with bevacizumab followed by maintenance bevacizumab likely results in little to no difference in venous thromboembolic events (grade ≥ 3) compared to chemotherapy alone (RR 1.73, 95% 0.65 to 4.60; 1 study, 480 participants; Analysis 8.11).

Chemotherapy with bevacizumab followed by maintenance bevacizumab may result in a large increase in proteinuria (grade ≥ 3) (RR 20.27, 95% CI 6.42 to 64.00; 3 studies, 1538 participants; Analysis 8.6), arterial thromboembolic events (any grade) (RR 3.63, 95% 1.49 to 8.84; 1 study, 657 participants; Analysis 8.12), and non-CNS bleeding (RR 3.77, 95% 2.70 to 5.26; 1 study, 657 participants; Analysis 8.13).

Chemotherapy with bevacizumab followed by maintenance bevacizumab likely results in a large increase in pain (grade ≥ 3) (RR 3.09, 95% CI 1.81 to 5.28; 2 studies, 1058 participants; Analysis 8.7).

9. Chemotherapy with TKI followed by TKI maintenance compared to chemotherapy alone in recurrent platinum-sensitive EOC

One study with 282 participants compared chemotherapy with TKI (cediranib) followed by TKI maintenance compared to chemotherapy alone in recurrent platinum-sensitive EOC (ICON6 2021). See Summary of findings 5.

Overall survival (OS)

Chemotherapy with TKI followed by maintenance TKI likely results in little to no difference in OS compared to chemotherapy alone (HR 0.86, 95% CI 0.67 to 1.11; low-certainty evidence; Analysis 9.1).

Progression-free survival (PFS)

Chemotherapy with TKI followed by maintenance TKI likely increases PFS compared to chemotherapy alone (HR 0.56, 95% CI 0.44 to 0.72; moderate-certainty evidence; Analysis 9.2).

Quality of life (QoL)

Chemotherapy with TKI followed by maintenance TKI compared to chemotherapy alone may result in little to no difference in QoL measured at 12 months using the Global Quality of Life European Organisation for Research and Treatment of Cancer Questionnaire QLQ-C30 (MD 6.10, 95% CI -0.96 to 13.16; 146 participants; low-certainty evidence; Analysis 9.3).

Adverse events

The one included study for this comparison did not report the effect of chemotherapy with TKI followed by maintenance TKI on any adverse events (grade ≥ 3), hypertension (grade ≥ 2), proteinuria (grade ≥ 2), pain (grade ≥ 2), abdominal pain (grade ≥ 2), febrile neutropenia (any grade), venous thromboembolic events (any grade), arterial thromboembolic events (any grade), non-CNS bleeding (grade ≥ 3), gastrointestinal adverse events (grade ≥ 2), and bowel fistula or perforation (grade ≥ 3). For reasons described above, presented grades of hypertension, proteinuria, neutropenia, and febrile neutropenia are different from those we prespecified.

Chemotherapy with TKI followed by maintenance TKI likely results in a large increase in hypertension (grade ≥ 3) (RR 3.32, 95% CI 1.21 to 9.10; 444 participants; Analysis 9.4) and febrile neutropenia (grade ≥ 3) (RR 1.92, 95% CI 0.68 to 5.46; 444 participants; Analysis 9.7) compared to chemotherapy alone.

Chemotherapy with TKI followed by maintenance TKI may increase proteinuria (grade ≥ 3) (RR 1.76, 95% CI 0.09 to 36.34; 444 participants; Analysis 9.5) and increases neutropenia (grade ≥ 3) (RR 1.10, 95% CI 0.75 to 1.60; 444 participants; Analysis 9.6) compared to chemotherapy alone.

B. Platinum-resistant EOC

10. Chemotherapy with bevacizumab compared to chemotherapy alone in recurrent platinum-resistant EOC

Five studies (778 participants) compared chemotherapy with bevacizumab compared to chemotherapy alone in recurrent platinum-resistant EOC (APPROVE 2022; AURELIA 2014; Liu 2019a; Nishikawa 2020; Roque 2022). See Summary of findings 6.

An additional included study (Liu 2021a) also compared chemotherapy with bevacizumab compared to chemotherapy alone in recurrent platinum-resistant EOC but data presented were insufficient for inclusion in the meta-analyses

Overall survival (OS)

Chemotherapy with bevacizumab increases OS compared to chemotherapy alone (HR 0.73, 95% CI 0.61 to 0.86; high-certainty evidence; Analysis 10.1).

There were insufficient data to extract HR data for OS from Liu 2021a. Median OS was 17.2 months in the bevacizumab group and 14.1 months in the control group (P = 0.015).

Progression-free survival (PFS)

Chemotherapy with bevacizumab likely results in a large increase in PFS compared to chemotherapy alone (HR 0.49, 95% CI 0.42 to 0.58; moderate-certainty evidence; Analysis 10.2).

There were insufficient data to extract HR for PFS from Liu 2021a. Median PFS was 10.9 months in the bevacizumab group and 7.8 months in the control group (P = 0.007).

Quality of life (QoL)

None of the included studies for this comparison reported this outcome.

Adverse events

Most of the included studies did not report the effect of chemotherapy with bevacizumab on any adverse events (grade ≥ 3), proteinuria (grade ≥ 2), pain (grade ≥ 2), abdominal pain (grade ≥ 2), febrile neutropenia (any grade), venous thromboembolic events (any grade), arterial thromboembolic events (any grade), non-CNS bleeding (grade ≥ 3), gastrointestinal adverse events (grade ≥ 2), and bowel fistula or perforation (grade ≥ 3). For reasons described above, presented grades of proteinuria, febrile neutropenia, venous thromboembolic events, arterial thromboembolic events and gastrointestinal perforations are different from those we prespecified.

Chemotherapy with bevacizumab may increase any adverse events (grade ≥ 3) slightly (RR 1.68, 95% CI 0.76 to 3.69; 1 study, 101 participants; low-certainty evidence).

Chemotherapy with bevacizumab compared to chemotherapy alone may result in a large increase in hypertension (grade ≥ 2: RR 3.11, 95% CI 1.83 to 5.27; 2 studies, 436 participants; low-certainty evidence; Analysis 10.4; grade ≥ 3: RR 3.24, 95% CI 1.46 to 7.19; 4 studies, 623 participants; Analysis 10.4).

The evidence is very uncertain about the effect of chemotherapy with bevacizumab compared to chemotherapy alone on proteinuria (grade ≥ 3) (RR 6.26, 95% CI 1.13 to 34.70; 4 studies, 683 participants; Analysis 10.5), febrile neutropenia (grade ≥ 3) (RR 0.33, 95% CI 0.04 to 3.04; 1 study, 101 participants; Analysis 10.7); arterial thromboembolic evens (grade ≥ 3) (RR 9.10, 95% CI 0.49 to 167.79; 1 study, 360 participants; Analysis 10.9). Bevacizumab may increase the risk of gastrointestinal perforations (grade ≥ 2) slightly (RR 6.89, 95% CI 0.86 to 55.09; 2 studies, 436 participants; Analysis 10.10).

Chemotherapy with bevacizumab compared to chemotherapy alone may increase the risk of neutropenia (grade ≥ 3) (RR 1.35, 95% CI 1.01 to 1.81; 3 studies, 308 participants; Analysis 10.6). The effect on rates of venous thromboembolic events (grade ≥ 3) is very uncertain (RR 0.58, 95% CI 0.21 to 1.63; 2 studies, 436 participants; Analysis 10.8).

11. Chemotherapy with TKI compared to chemotherapy alone in recurrent platinum-resistant EOC

Nine studies evaluated the effect of TKI agents with similar mechanisms of action, as follows: one study each in apatinib (APPROVE 2022), nintedanib (METRO-BIBF 2020), sorafenib (TRIAS 2018), vandetanib (SWOG-S0904 2014); and five studies in pazopanib (Duska 2020; MITO-11 2015; Richardson 2018; Sharma 2021; TAPAZ 2022). See Summary of findings 7.

Overall survival (OS)

Chemotherapy with TKI likely results in little to no difference in OS compared to chemotherapy alone (HR 0.85, 95% CI 0.68 to 1.08; 8 studies, 940 participants, moderate-certainty evidence; Analysis 11.1). This is based on evidence from trials in apatinib, nintedanib, pazopanib, sorafenib and vandetanib, with no strong evidence of subgroup differences depending on the type of TKI agent (P = 0.05). Sensitivity analysis limited to studies with only platinum-resistant EOC showed a significant difference in OS between chemotherapy with TKI and chemotherapy alone (HR 0.77, 95% CI 0.63 to 0.93; 5 studies, 589 participants; fixed-effect model).

Progression-free survival (PFS)

Chemotherapy with TKI may increase PFS compared to chemotherapy alone (HR 0.70, 95% CI 0.55 to 0.89; 8 studies, 940 participants; low-certainty evidence; Analysis 11.2), based on evidence from trials in apatinib, nintedanib, pazopanib, sorafenib and vandetanib, with evidence of subgroup difference depending on the type of TKI agent (P = 0.009). Findings from a sensitivity analysis limited to studies with only platinum-resistant EOC were consistent with the main analysis (HR 0.67, 95% CI 0.57 to 0.79; 6 studies, 695 participants; fixed-effect model).

Quality of life (QoL)

Chemotherapy with TKI may result in little to no difference in QoL compared to chemotherapy alone, based on evidence from three studies (METRO-BIBF 2020; Sharma 2021; TAPAZ 2022). All studies measured global QoL using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire QLQ-C30 at three different time points: at six weeks (METRO-BIBF 2020), after six cycles (Sharma 2021), and after four months (TAPAZ 2022). The mean difference (MD) ranged from -3.40 (95% CI -13.22 to 6.42) to 17.50 (95% CI 1.11 to 33.89; low-certainty evidence; Analysis 11.3). The evidence was limited to trials in nintedanib and pazopanib.

Adverse events

Included trials did not report the effect of chemotherapy with bevacizumab on hypertension (grade ≥ 2), venous thromboembolic events (any grade), arterial thromboembolic events (any grade), and gastrointestinal adverse events (grade ≥ 2). Presented grades of hypertension and gastrointestinal adverse events are different from the prespecified.

Chemotherapy with TKI may increase any adverse events (grade ≥ 3) slightly compared to chemotherapy alone (RR 1.23, 95% 1.02 to 1.49; 4 studies, 548 participants; low-certainty evidence; Analysis 11.4), based on evidence from trials in apatinib, nintedanib, pazopanib and sorafenib, with no evidence of subgroup difference depending on the type of TKI agent (P = 0.06).

Chemotherapy with TKI may result in a large increase in hypertension (grade ≥ 3) compared to chemotherapy alone (RR 4.20, 95% CI 1.58 to 11.14; 7 studies, 844 participants; Analysis 11.5), based on evidence from trials in apatinib, nintedanib, pazopanib, sorafenib and vandetanib, with evidence of subgroup difference depending on the type of TKI agent (P = 0.02).

The evidence is very uncertain about the effect of chemotherapy with TKI on proteinuria (grade ≥ 2) compared to chemotherapy alone (RR 4.00, 95% CI 0.49 to 32.86; 2 studies, 262 participants; Analysis 11.6), based on evidence from trials in apatinib and vandetanib, with no evidence of subgroup difference depending on the type of TKI agent (P = 0.86).

Chemotherapy with TKI may result in little to no difference in pain (grade ≥ 2) compared to chemotherapy alone (RR 0.97, 95% CI 0.44 to 2.15; 3 studies, 361 participants; Analysis 11.7), based on evidence from trials in pazopanib and sorafenib, with no evidence of subgroup difference depending on the type of TKI agent (P = 0.72).

Chemotherapy with TKI may result in little to no difference in abdominal pain (grade ≥ 2) compared to chemotherapy alone (RR 0.78, 95% CI 0.20 to 3.09; 1 study, 116 participants; Analysis 11.8), based on evidence from a trial in pazopanib.

Chemotherapy with TKI may increase neutropenia (grade ≥ 3) compared to chemotherapy alone (RR 1.73, 95% CI 1.15 to 2.61; 9 studies, 1069 participants; Analysis 11.9), based on evidence from trials in apatinib, nintedanib, pazopanib, sorafenib and vandetanib, with evidence of subgroup difference depending on the type of TKI agent (P = 0.008).

Chemotherapy with TKI may result in little to no difference in febrile neutropenia (any grade) compared to chemotherapy alone (RR 1.49, 95% CI 0.68 to 3.30; 6 studies, 748 participants; Analysis 11.10), based on evidence from trials in nintedanib, pazopanib, sorafenib and vandetanib, with no evidence of subgroup difference depending on the type of TKI agent (P = 0.94).

Chemotherapy with TKI may result in little to no difference in non-CNS bleeding (grade ≥ 3) compared to chemotherapy alone (RR 1.07, 95% CI 0.07 to 17.44; 1 study, 172 participants; Analysis 11.11), based on evidence from one trial in sorafenib.

Chemotherapy with TKI likely results in little to no difference in gastrointestinal adverse events (grade ≥ 3) compared to chemotherapy alone (RR 1.08, 95% CI 0.46 to 2.53; 3 studies, 386 participants; Analysis 11.12), based on evidence from trials in nintedanib, pazopanib and sorafenib, with no evidence of subgroup difference depending on the type of TKI agent (P = 0.09).

The evidence is very uncertain about the effect of chemotherapy with TKI on bowel fistula or perforation (grade ≥ 3) compared to chemotherapy alone (RR 2.74, 95% CI 0.77 to 9.75; 5 studies, 557 participants; very low-certainty evidence; Analysis 11.13), based on evidence from trials in nintedanib and pazopanib, with no evidence of subgroup difference depending on the type of TKI agent (P = 0.99).

12. Chemotherapy with olaratumab compared to chemotherapy alone in recurrent platinum-resistant EOC

One trial (with 123 participants) evaluated the effect of the platelet-derived growth factor alpha (PDGFRα)-targeting monoclonal antibody olaratumab in addition to chemotherapy (McGuire 2018).

Overall survival (OS)

Chemotherapy with olaratumab may result in little to no difference in OS (HR 1.10, 95% CI 0.71 to 1.71; Analysis 12.1).

Progression-free survival (PFS)

Chemotherapy with olaratumab may result in little to no difference in PFS (HR 1.04, 95% CI 0.70 to 1.56; Analysis 12.2).

Quality of life (QoL)

McGuire 2018 did not report on QoL.

Adverse events

The evidence from the McGuire 2018 study is very uncertain about the effect of chemotherapy with olaratumab on incidence of pain (grade ≥ 3) (RR 0.33, 95% CI 0.01 to 7.90; Analysis 12.4), abdominal pain (grade ≥ 3) (RR 0.25, 95% CI 0.05 to 1.11; Analysis 12.5), or neutropenia (grade ≥ 3) (RR 1.57, 95% CI 0.55 to 4.54; Analysis 12.6).

McGuire 2018 did not formally report on incidence of hypertension, febrile neutropenia, venous thromboembolism, arterial thromboembolism, non-central nervous system bleeding (grade ≥ 3), or gastrointestinal perforation (grade ≥ 3) by trial arm. There were no cases of proteinuria (grade ≥ 3) (Analysis 12.3).

Other comparisons in platinum-resistant recurrent EOC

The following included studies were not included in meta-analyses.

In the recurrent platinum-resistant setting, two studies had an experimental design and compared a combination of anti-programmed death-ligand 1 (PD-L1) antibody and aspirin with and without bevacizumab (EORTC-1508 2021), and TKI with placebo (Gotlieb 2012). Another two studies compared a combination of PARP inhibitor with TKI to chemotherapy or to PARP inhibitor alone (OCTOVA 2021), and to PARP inhibitor with durvalumab (immunotherapy agent) (AMBITION 2022). None of the studies found evidence of a beneficial effect of the evaluated interventions on survival outcomes.

NICCC 2020 enrolled participants with clear cell cancer of either EOC or endometrial origin. It was a phase II study powered to detect an improvement in PFS from three to five months (HR 0.6), with greater than 90% power, with single agent nintedanib, to determine whether a phase III study was warranted. There was no significant difference in either OS (HR 0.77, 95% CI 0.46 to 1.28) or PFS (HR 0.79, 95% CI 0.5 to 1.125), although there was evidence of non-proportionality of hazards for OS. The study authors concluded that there was insufficient evidence of activity with nintedanib alone, but that combination treatment was worth further examination.

C. Mixed platinum-sensitive, platinum-resistant and unclear recurrent EOC

13. Chemotherapy with TKI (peptide-Fc fusion protein) compared to chemotherapy alone in recurrent mixed platinum-resistance EOC

Three trials evaluated the effect of the TKI agent trebananib, a peptide-Fc fusion protein (Karlan 2012; TRINOVA-1 2016; TRINOVA-2 2017). In the synthesis, we used the 10 mg dose of trebananib data from the Karlan 2012 study. See Summary of findings 8.

Overall survival (OS)

Chemotherapy with TKI (trebananib) likely results in little to no difference in OS (HR 0.92, 95% CI 0.80 to 1.06; 3 studies, 1250 participants; moderate-certainty evidence; Analysis 13.1).

Progression-free survival (PFS)

Chemotherapy with TKI (trebananib) increases PFS (HR 0.73, 95% CI 0.65 to 0.82; 3 studies, 1250 participants; high-certainty evidence; Analysis 13.2).

Quality of life (QoL)

Chemotherapy with TKI (trebananib) may result in little to no difference in QoL measured at 25 weeks using the Functional Assessment of Cancer Therapy Ovarian Cancer questionnaire (MD -0.80, 95% CI -4.31 to 2.71; 1 study, 315 participants; low-certainty evidence; Analysis 13.3) compared to chemotherapy alone.

Adverse events

Included trials did not report the effect of chemotherapy with bevacizumab on any adverse events (grade ≥ 3), hypertension (grade ≥ 2), pain (grade ≥ 2), abdominal pain (grade ≥ 2) and gastrointestinal adverse events (grade ≥ 2). Presented grades of hypertension, pain and abdominal pain are different from those prespecified.

Compared to chemotherapy alone, chemotherapy with TKI (trebananib) may result in little to no difference in hypertension (grade ≥ 3) (RR 2.92, 95% CI 0.70 to 12.18; 3 studies, 1242 participants; Analysis 13.4), febrile neutropenia (any grade) (RR 0.49, 95% CI 0.04 to 5.39; 1 study, 913 participants; Analysis 13.9) and gastrointestinal perforation (grade ≥ 3) (RR 0.35, 95% CI 0.01 to 8.30; 1 study, 108 participants; low-certainty evidence; Analysis 13.13).

Compared to chemotherapy alone, chemotherapy with TKI (trebananib) likely results in little to no difference in abdominal pain (grade ≥ 3) (RR 0.99, 95% CI 0.60 to 1.65; 3 studies, 1242 participants; Analysis 13.7) and venous thromboembolism event (any grade) (RR 0.68, 95% CI 0.25 to 1.85; 2 studies, 1021 participants; Analysis 13.10).

Chemotherapy with TKI (trebananib) increases neutropenia (grade ≥ 3) compared to chemotherapy alone (RR 0.60, 95% CI 0.40 to 0.89; 2 studies, 1134 participants; Analysis 13.8).

The evidence is very uncertain about the effect of chemotherapy with TKI (trebananib) compared to chemotherapy alone on proteinuria (grade ≥ 3) (RR 6.86, 95% CI 0.36 to 132.5; 1 study, 913 participants; Analysis 13.5), pain (grade ≥ 3) (RR 2.94, 95% CI 0.12 to 72.02; 1 study, 913 participants; Analysis 13.6), arterial thromboembolic event (any grade) (RR 3.11, 95% CI 0.13 to 74.72; 1 study, 108 participants; Analysis 13.11) and non-CNS bleeding (grade ≥ 3) (RR 3.11, 95% CI 0.13 to 74.72; 1 study, 108 participants; Analysis 13.12).

Other comparisons in mixed platinum-sensitive, platinum-resistant and unclear recurrent EOC

The following included studies were not included in meta-analyses because of the diversity of the comparisons: Gupta 2019; Ledermann 2011; Matulonis 2019.

We included three studies in recurrent EOC that recruited participants with mixed platinum-sensitivity status: Matulonis 2019 compared a TKI with chemotherapy; Ledermann 2011 compared a TKI with placebo; and Gupta 2019 compared a combination of chemotherapy with celecoxib with chemotherapy alone. Only one study reported an effect on survival outcomes (overall survival) that was statistically significant (HR 2.27, 95% CI 1.17 to 4.41), favouring the comparator (chemotherapy) (Matulonis 2019).

DISCUSSION

Summary of main results

The five studies which were included in the previous version of this review (Gaitskell 2011), using data from conference abstracts, have now all been published in more detail as full papers (GOG-0218 2019; Karlan 2012; Ledermann 2011; ICON7 2015; Gotlieb 2012). Additionally, we identified 45 new studies published within the last ten years.

Our systematic review identified 50 randomised trials with 14,836 individuals diagnosed with epithelial ovarian cancer (EOC): 13

trials (7708 participants) in newly-diagnosed EOC and 37 trials (7128 participants) in recurrent disease. The studies examined the effects of various angiogenesis inhibitors (e.g. bevacizumab, sorafenib, trebananib) in a range of clinical scenarios. Where possible, we grouped and synthesised the evidence by the type of population (newly-diagnosed EOC, recurrent platinum-sensitive EOC, recurrent platinum-resistant EOC) and according to the angiogenesis inhibitor mechanism of action (bevacizumab, tyrosine kinase inhibitors (TKIs) and the TKI agent trebananib, a peptide-Fc fusion protein). We performed quantitative synthesis for thirteen comparisons (as specified below). We graded the certainty of the evidence for the eight most clinically relevant comparisons (indicated with a * in the list below) and the six most critically important outcomes (overall survival (OS), progression-free survival (PFS), quality of life (QoL), any adverse events grade ≥ 3, hypertension grade ≥ 2, and bowel fistula/perforation grade ≥ 3).

Newly-diagnosed EOC

- Chemotherapy with bevacizumab versus chemotherapy alone with placebo for all in the maintenance phase (one study, 1250 participants)
- Chemotherapy with bevacizumab followed by bevacizumab as maintenance versus chemotherapy alone (two studies, 2776 participants)*
- Chemotherapy with TKI followed by TKI as maintenance versus chemotherapy alone (three studies, 2639 participants)*
- Chemotherapy with TKI (peptide-Fc fusion protein) followed by TKI as maintenance versus chemotherapy alone (one study, 1015 participants)*
- Maintenance with TKI versus placebo after first-line chemotherapy (two studies, 1186 participants)
- Neoadjuvant chemotherapy with bevacizumab versus chemotherapy alone followed by adjuvant chemotherapy with bevacizumab and bevacizumab maintenance for all (two studies, 167 participants)
- Chemotherapy with celecoxib versus chemotherapy alone (one study; 196 participants)

Recurrent platinum-sensitive EOC

- Chemotherapy with bevacizumab followed by maintenance bevacizumab versus chemotherapy alone (seven studies, 1893 participants)*
- Chemotherapy with TKI followed by TKI maintenance versus chemotherapy alone (one study, 486 participants)*

Recurrent platinum-resistant EOC

- Chemotherapy with bevacizumab versus chemotherapy alone (seven studies, 894 participants)*
- Chemotherapy with TKI versus chemotherapy alone (seven studies, 810 participants)*
- Chemotherapy with olaratumab versus chemotherapy alone (one study, 123 participants)

Recurrent EOC

- Chemotherapy with TKI (peptide-Fc fusion protein) versus chemotherapy alone (three studies, 1250 participants)*

Eighteen included trials (1850 participants) evaluated the effect of angiogenesis inhibitors in combination with or in comparison to other treatments, such as poly(ADP-ribose) polymerase inhibitors (PARPi), anti PD-L1 antibody, aspirin and celecoxib, in cohorts of participants with mixed populations (newly-diagnosed and/or platinum-sensitive and platinum-resistant recurrent disease). We only briefly summarised the findings of these studies due to their experimental and proof-of-concept nature. Future updates will include an analysis of PARPi-anti-angiogenesis combination treatment.

Newly-diagnosed EOC

Based on available evidence, bevacizumab given with chemotherapy and then continued as a maintenance treatment results in little to no difference in OS and a slight reduction in QoL compared to chemotherapy alone. The combination likely results in little to no difference in any adverse events (grade ≥ 3). The evidence on the effect on PFS and hypertension (grade ≥ 2) is very uncertain.

Equally, TKIs (nintedanib, pazopanib, sorafenib) given with chemotherapy and continued as maintenance treatment likely result in little to no difference in OS compared to chemotherapy alone. However, the combination likely slightly increases PFS and slightly reduces global QoL compared to chemotherapy alone. The combination increases any adverse events (grade ≥ 3) and may result in a large increase in hypertension (grade ≥ 3).

Chemotherapy with a peptide-Fc fusion protein (trebananib) given with chemotherapy and continued as maintenance treatment likely results in little to no difference in OS and PFS compared to chemotherapy alone. The combination increases any adverse events (grade ≥ 3).

Celecoxib plus chemotherapy versus chemotherapy alone may result in little to no difference in OS or PFS in newly-diagnosed ovarian cancer. There may be little to no effect on most adverse events of grade 3 or higher, but 40 of the 97 participants discontinued treatment, mainly due to adverse events.

Recurrent platinum-sensitive EOC

Bevacizumab given with chemotherapy and then continued as a maintenance treatment may have little to no effect on OS; however, the combination may improve PFS. The combination may result in little to no difference in QoL with a slight increase in the rate of any adverse events (grade ≥3). Included trials reported only rate of events of hypertension of grade 3 or above, which were higher in arms with bevacizumab.

The combination of TKIs (cediranib) with chemotherapy likely results in little to no difference in OS; however, it likely increases PFS and may have little to no effect on QoL. Included trials reported only rate of events of hypertension of grade 3 or above, which were higher in arms with TKIs.

Recurrent platinum-resistant EOC

Bevacizumab given with chemotherapy compared to chemotherapy alone, and then continued as a maintenance treatment, increases OS and likely increases PFS. However, the combination may result in a large increase in hypertension (grade ≥ 2).

The combination of TKIs (apatinib, nintedanib, pazopanib, sorafenib, vandetanib) with chemotherapy compared to chemotherapy alone likely results in little to no difference in OS and

may result in little to no meaningful difference in QoL; however, it may increase PFS. The combination slightly increases the rate of any adverse events (grade ≥ 3). The effect on bowel fistula/perforation rates is uncertain as is the effect on hypertension (grade ≥ 2), largely due to the small study size and heterogeneity in the effect between different TKIs.

Chemotherapy with a peptide-Fc fusion protein (trebananib) likely results in little to no difference in OS, although it increased PFS. The combination may result in little to no difference in QoL. The only safety data available were for bowel perforation/fistula (grade ≥ 3), suggesting that trebananib may result in little to no effect on this outcome.

Olaratumab plus liposomal doxorubicin versus liposomal doxorubicin alone did not improve PFS or OS in platinum-resistant or platinum-refractory recurrent ovarian cancer. There was little to no effect on any adverse events of grade 3 or higher.

In summary, bevacizumab in combination with chemotherapy seems most beneficial for individuals with the most advanced diseases. The evidence supporting the use of TKI with chemotherapy for the treatment of EOC was not available, except for its use in combination with chemotherapy for recurrent platinum-resistant EOC.

Overall completeness and applicability of evidence

In terms of applicability, the women in the included studies tended to be younger and fitter than the general cohort of women with ovarian cancer. The increased risk of severe adverse events and effects on the quality of life of long-term maintenance treatment may therefore be different in the wider population of women with ovarian cancer. Furthermore, the included studies were generally powered for PFS rather than OS or other patient-reported outcomes, including adverse events, quality of life and time at home. This limits the certainty and full breadth of information available to women, and their caregivers, needed to make fully informed decisions about treatment.

We are relatively confident that we have captured the majority of studies assessing anti-angiogenesis inhibitors in ovarian cancer, having identified ongoing studies in a previous review update and compared included studies to recent systematic reviews. In addition, this review has been performed alongside other reviews of biological agents and pegylated liposomal doxorubicin (PLD) in ovarian cancer (Morrison 2018; Newhouse 2023; Tattersall 2022). Studies have been shared between review teams, where there was found to be overlap, so the search net has effectively been wider than the search strategy of each individual review. However, this is a fast-moving field with multiple new studies, drugs and drug combinations included in this update, as well as several ongoing studies; we acknowledge that relevant studies may have been missed.

Certainty of the evidence

This is a comprehensive review of literature on the effect of angiogenesis inhibitors in the treatment of epithelial ovarian cancer. Nevertheless, the quality of the evidence is not always satisfactory. The main difficulty in the assessment of the study quality was suboptimal or inadequate reporting of important features of trial design, such as randomisation procedure (in 23 studies, we assessed this domain as unclear) or allocation concealment (in 25 studies, we assessed this domain as unclear). Another indicator of the quality of the evidence, a clinical trial registration number, was unavailable for several studies.

Over half of the included studies (28 out of 50) had an open-label design, which put the studies at high risk of bias for blinding for all outcomes except OS (Figure 4). Overall, we deemed only two studies to be at low risk of bias in all evaluated domains (ICON6 2021; Richardson 2018), and five studies to be at low risk in six domains (AGO-OVAR 12 2020; GOG-0218 2019; TRIAS 2018; TRINOVA-1 2016; TRINOVA-3 2019).

For an informative analysis of the primary outcome of this review (overall survival (OS)), the most commonly used statistical model relies on the assumption of proportional hazards (Schemper 2009), in order to yield an informative effect estimate (hazard ratio). Unfortunately, in a number of key trials in this area (e.g. Duska 2020; ICON6 2021; ICON7 2015; TRINOVA-2 2017), there was evidence of non-proportionality. However, in the final summary of the evidence, we did not downgrade certainty due to this finding. A formal assessment of non-proportionality was infrequently reported, and we perceived it more as a mark of the study's quality rather than its weakness.

Potential biases in the review process

We aimed to reduce any potential biases in the review process by adhering to Cochrane methodology as much as possible. We performed a comprehensive search, including a thorough search of the grey literature. At least two review authors sifted and independently extracted data for all studies. However, we recognise that some studies - published in non-indexed journals or in less accessible languages (e.g. Chinese) - could have been missed. However, studies in Chinese were identified by the search (as they had English language abstracts) and we were able to obtain and translate full text articles with assistance where necessary (see Acknowledgements) (e.g. Liu 2021a).

None of the review authors have any links to drug companies, any financial interest in the prescription of chemotherapeutic agents, nor were we involved in the conduct of the included studies.

Agreements and disagreements with other studies or reviews

We conducted a systematic search for other recent systematic reviews on randomised controlled trials of angiogenesis inhibitors in ovarian cancer, published since January 2020 (see Appendix 4 for search strategy). This identified 15 references, with an additional reference identified in a further search to October 2022. We limited our search to systematic reviews published in the last two years, as many of the primary studies included in this review were only published in the last few years, and thus older systematic reviews would not be comparable.

We excluded seven of these references on the basis of the abstract, and two on the basis of a full-text review. We considered six systematic reviews to be at least partially relevant, and have summarised these below.

Helali 2022 is a comprehensive systematic review and network meta-analysis of anti-angiogenic agents in advanced epithelial ovarian cancer. The authors identified 23 relevant randomised controlled trials (RCTs) and looked separately at newly diagnosed,

recurrent platinum-sensitive, and recurrent platinum-resistant ovarian cancer, focusing on the outcomes of overall survival (OS; primary outcome) and progression-free survival (PFS; secondary outcome). The authors concluded that the best interventions for improving overall survival were likely to be: chemotherapy with concurrent bevacizumab followed by maintenance bevacizumab for high-risk (defined as FIGO stage IV or inoperable/suboptimally-resected stage III) newly-diagnosed (chemotherapy-naive) advanced ovarian cancer; and pazopanib combined with chemotherapy for platinum-resistant recurrent ovarian cancer. They concluded that the evidence was less convincing for a benefit in OS with angiogenesis inhibitors in a setting of non-high-risk, newly-diagnosed, or platinum-sensitive recurrent, ovarian cancer. One author reported being employed in industry; the other authors reported no conflicts of interest.

Hirte 2021 is a systematic review of consolidation or maintenance systemic therapy for newly-diagnosed stage II-IV ovarian cancer. This included a review of studies of VEGF-R TKIs (pazopanib and sorafenib, four studies), anti-VEGF monoclonal antibodies (bevacizumab, two studies), triple angiokinase inhibitors (nintedanib, two studies), and angiopoietin inhibitors (trebananib, one study), in addition to other agents. The authors described the results of the trials but did not conduct a meta-analysis. Their overall conclusion was that, compared with placebo, maintenance therapy with bevacizumab improves PFS for certain patients with newly-diagnosed stage III-IV EOC, but that there is thus far no evidence of a benefit in OS. The authors declared no conflicts of interest.

Chilimoniuk 2022 is a systematic review covering RCTs for a variety of new therapies in ovarian cancer, including 15 studies of angiogenesis inhibitors. The authors concluded that bevacizumab was beneficial for the treatment of recurrent ovarian cancer; that there was some promising evidence for cediranib, apatinib, ramucirumab and nintedanib, but that further studies were needed; and that cabozantinib and motesanib could not be recommended for treatment of ovarian cancer because of toxicity. The authors declared no conflicts of interest.

Broekman 2021 is a systematic review of licenced systemic therapies for ovarian cancer, which aimed to assess their benefits according to the European Society of Medical Oncology Magnitude of Clinical Benefit Scale. This review included the angiogenesis inhibitor, bevacizumab, which has been licensed. The authors concluded that the addition of bevacizumab to chemotherapy in the platinum-resistant setting was one of only three treatments assessed which showed a substantial benefit. One of the authors declared some financial links to two relevant companies; the other authors declared no conflicts of interest.

Liu 2021b is a systematic review of phase II-III clinical trials of bevacizumab in advanced ovarian cancer. The review included 35 studies, of which eight were included in a quantitative synthesis. This review included single-arm phase II studies, as well as randomised phase II and III studies, and included studies in which the comparison was not chemotherapy with, versus without, bevacizumab. The authors found that patients with newly-diagnosed ovarian cancer who were treated with bevacizumab combined with chemotherapy, compared to chemotherapy alone, had improved PFS, but no significant difference in OS. They found that patients with recurrent ovarian cancer treated with regimes including bevacizumab had both improved PFS and improved OS, compared to treatment regimes without bevacizumab. The authors declared no conflicts of interest.

Trillsch 2021 is a meta-analysis of three studies which included participants with platinum-resistant ovarian cancer. One of the included studies involved anti-angiogenesis inhibitors (TRIAS 2018); the two other studies randomised participants to two different topotecan schedules (Sehouli 2011), or oral versus intravenous treosulphan (Sehouli 2017). Datasets were provided by authors of the original studies, who were included as authors of the meta-analysis. They compared prognoses in participants with platinum-resistance developed after first-line chemotherapy (primary platinum resistance (PPR)) versus those who developed platinum resistance after subsequent lines of chemotherapy (secondary platinum resistance (SPR)). They found that PPR had a negative prognostic impact compared with SPR on PFS, although the clinical significance was minimal (3.9 months versus 3.1 months), and the difference in overall survival was not statistically significant. Retrospective subgroup analysis of the TRIAS 2018 study suggested that sorafenib was more effective in those with PPR, where statistically significant improvements in OS (PPR median survival 13.2 months (sorafenib) versus 8.6 months (placebo) (HR 0.52, 95% CI 0.33 to 0.85) compared to those with SPR (median survival 18.6 months (sorafenib) versus 13.5 months (placebo); HR 0.82, 95% CI 0.48 to 1.41) were observed. Similar results were observed for PFS (PPR = 6.9 months (sorafenib) versus 3.8 months (placebo); HR 0.40, 95% CI 0.26 to 0.64); SPR = 5.8 months (sorafenib) versus 4.9 months (placebo) HR 0.83 (95% CI 0.51 to 1.36)). They recognised the need for effective treatments in those with PR disease, especially PPR disease, but also the need to consider reducing treatment burden and introducing palliative care in this cohort, given their poorer prognosis.

Qi 2021 is a systematic review and meta-analysis focused on evaluating the safety and efficacy of apatinib combined with chemotherapy for treatment of advanced ovarian cancer. This review included 12 studies, all conducted in China. The authors reported that patients treated with apatinib combined with chemotherapy, compared to chemotherapy alone, had higher risk of proteinuria, but did not find a significant difference in risk of other adverse events. This review reported on disease control rates and objective response rates, but did not report on progression-free survival or overall survival outcomes. The authors declared no conflicts of interest.

These recent systematic reviews were mostly narrower in scope than the current review, and included fewer studies. Where the scopes overlapped, the conclusions of these other reviews were broadly in keeping with the findings of this review. For example, the finding that bevacizumab was beneficial in the setting of recurrent platinum-resistant ovarian cancer was fairly consistent between reviews, while the evidence of benefit from other agents and in other settings was more variable.

AUTHORS' CONCLUSIONS

Implications for practice

This review's findings suggest that there appears to be a role for anti-angiogenesis treatment. However, given the treatment and economic burden of maintenance treatment, when individuals would not otherwise be on treatment, the benefits and risks of anti-

angiogenesis treatments should be carefully considered and timing of use in the EOC treatment journey optimised for individuals.

The magnitude and certainty of evidence for the different agents investigated varied between the different populations. In platinum-resistant EOC, bevacizumab likely improves both overall survival (OS) and progression-free survival (PFS). Bevacizumab and tyrosine kinase inhibitors (TKIs) probably improve PFS, but may or may not improve OS in platinum-sensitive relapsed disease, with similar results for TKIs in platinum-resistant relapsed epithelial ovarian cancer (EOC) and for trebananib in relapsed EOC. The results in newly-diagnosed EOC are less certain, and there may be little to no effect on OS or PFS, with a decrease in quality of life and increase in adverse events of grade 3 or higher. Overall, adverse event and quality of life data were more variably reported than PFS data.

When the last version of the review was performed, OS data were largely lacking. The subsequent OS results may be immature in areas, but so far are somewhat disappointing, given promising PFS results. They reminds us of the need for caution: PFS improvements may not automatically lead to improvements in OS.

The variable reporting of patient-reported outcomes, especially those concerning quality of life measures, is very disappointing in this setting. Many women, especially those with recurrent disease, will have a limited prognosis. Decisions about treatments that require more frequent hospital visits, and significant cost implications for healthcare systems and individuals (depending on the healthcare system), require more balanced reporting in order for women to make the best decisions for their individual care.

Implications for research

This systematic review and others highlight the variable reporting of results from clinical studies and the focus on the surrogate, more rapidly generated, outcomes (e.g. PFS) rather than ones which may be more meaningful to individuals. Uncertain correlation between PFS and OS has been discussed at length previously (Tattersall 2022). We hope that further data will be available to update OS outcomes for studies as these data mature. The profile of study participants also suggests that they are generally younger and fitter than the general cohort of women with ovarian cancer.

The majority of Ongoing studies aim to recruit participants with recurrent EOC and will be powered for PFS; none appear to have OS as their primary outcome. Some studies are exploring the role of the combination of maintenance angiogenesis inhibitors and poly(ADP-ribose) polymerase (PARP) inhibitors in participants with: newly-diagnosed (NCT05009082; NCT05183984); platinum-sensitive relapsed EOC (ICON9 2021; NCT03462212); platinum-resistant relapsed EOC (NCT05170594); or relapsed EOC with specific tumour mutations (NCT05523440). Several others studies are in participants with platinum-resistant EOC, exploring the role of new angiogenesis inhibitors (NCT00635193; NCT02584478; NCT03262545; NCT04908787; NCT05043402). Some of these studies compare agents with/without, and/or against, bevacizumab (NCT02839707), and some compare the addition of bevacizumab to immunotherapy (NCT04919629). Other studies are comparing intraperitoneal administration of bevacizumab and chemotherapy against intraperitoneal chemotherapy in newly-diagnosed EOC and/or recurrent disease (NCT03095001). One study compared bevacizumab maintenance in treatment of newly-diagnosed EOC (NCT03635489). Updates of this review should therefore aim to consider combination angiogenesis inhibitor treatment with PARP inhibitors and different routes of administration of treatment.

In conducting this review, there have been difficulties with extracting adverse event data and quality of life data, where made available, so they could be combined in meta-analyses. This limited our ability to inform individuals and other decision-makers, and highlights the urgent need for agreed, minimum and standardised patient-reported outcomes measures, time points and reporting for quality of life outcomes in ovarian cancer trials, to allow comparison across studies.

The 'CoRe Outcomes in Women's and Newborn health' (CROWN 2022) initiative aims to "produce, disseminate, and implement" core outcome sets (COS) across a range of conditions in women's and neonatal healthcare. The aim is to define a set of core outcome measures, to improve research quality and usefulness. This would improve research reporting, reduce reporting bias, facilitate evidence synthesis and enable more robust evidence to be presented to patients and healthcare decision-makers, allowing truly informed decision-making. Core outcome measures should be agreed upon and defined by consensus, involving all stakeholders, including patients, charities, clinicians and researchers. Others have already noted variability in, and the need for alignment of, patient-reported outcomes for quality of life assessment in ovarian cancer studies (Donovan 2014; Mercieca-Bebber 2016), so that data can be more readily combined and compared between studies. One measure that should be considered in assessing treatments for advanced cancers would be days at home, since this measure demonstrates a mix of both quantity and quality of life outcomes and also might also better reflect the burden of treatment, for both patients and carers (Chesney 2020). Funders, health research regulators and journal editors should increasingly require standardised data collection and reporting, especially of patient-reported outcomes, to reduce bias and improve the relevance and usefulness of research in ovarian cancer.

Finally, there has been an explosion of research in angiogenesis inhibitors, especially in the development of TKIs and combination therapy with other biological agents (e.g. PARP inhibitors). Despite a great number of trials and randomised participants, few are adequately powered and/or executed randomised controlled trials to enable information for clinical practice. Furthermore, this plethora of studies and combination therapy make it challenging to tease out how we can best treat people with advanced ovarian cancer. The volume of work in this area means that a network meta-analysis approach would be needed to adequately compare different treatments and combinations of treatments in a range of clinical scenarios, requiring dedicated funding and expertise to perform.

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REFERENCES

References to studies included in this review

AGO-OVAR 12 2020 *{published data only}*

Du Bois A, Kristensen G, Ray-Coquard I, Reus A, Pignata S, Colombo N, et al. AGO-OVAR 12: A randomized placebo-controlled GCIG/ENGOT-Intergroup phase III trial of standard frontline chemotherapy +/-nintedanib for advanced ovarian cancer. In: International Journal of Gynecological Cancer. Vol. Conference Abstracts of the 18th International Meeting of the European Society of Gynaecological Oncology. 2013:7-8.

Harter P, Kimmig R, De Gregorio N, Reuss A, Pfisterer J, Cibula D, et al. AGO-OVAR 12: a randomized placebo-controlled GCIG/ENGOT-Intergroup phase III trial of standard frontline chemotherapy +/- nintedanib for advanced ovarian cancer. *Oncology Research and Treatment* 2014;**37**(Suppl 1):74-5.

Kristensen G, Harter P, Trédan O, Sailer MO, Bamias A, Colombo N, et al. Independent review of AGO-OVAR 12, a GCIG/ENGOT-Intergroup phase III trial of nintedanib (N) in first-line therapy for ovarian cancer (OC). *Journal of Clinical Oncology* 2014;**32**(15):5556.

NCT01015118. LUME-Ovar 1: BIBF 1120 or placebo in combination with paclitaxel and carboplatin in first line treatment of ovarian cancer. www.clinicaltrials.gov/ct2/show/NCT01015118 (first posted 18 November 2009).

* Ray-Coquard I, Cibula D, Mirza MR, Reuss A, Ricci C, Colombo N, et al, AGO Study Group-led GCIG/ENGOT Intergroup Consortium. Final results from GCIG/ENGOT/AGO-OVAR 12, a randomised placebo-controlled phase III trial of nintedanib combined with chemotherapy for newly diagnosed advanced ovarian cancer. *International Journal of Cancer* 2020;**146**:439-48.

du Bois A, Kristensen G, Ray-Coquard I, Reuss A, Pignata S, Colombo N, et al. Standard first-line chemotherapy with or without nintedanib for advanced ovarian cancer (AGO-OVAR 12): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Oncology* 2016;**17**(1):78-89.

AGO-OVAR 16 2019 *{published and unpublished data}*

Del Campo J M, Kurzeder C, Berton-Rigaud D, Kim B G, Friedlander M, Zamagni C, et al. Progression-free survival by GCIG criteria: analysis of the secondary endpoint of the AGO-OVAR16 trial. In: 18th International Meeting of the European Society of Gynaecological Oncology. 2013.

Du Bois A, Floquet A, Kim JW, Rau J, Del Campo JM, Friedlander M, et al. Randomized, double-blind, phase III trial of pazopanib versus placebo in women who have not progressed after first-line chemotherapy for advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (AEOC): results of an international Intergroup trial (AGO-OVAR16). *Journal of Clinical Oncology, ASCO Annual Meeting Abstracts* 2013;**31**:LBA5503.

Floquet A, Vergote I, Colombo N, Fiane B, Monk B J, Reinthaller A, et al. Progression-free survival by local investigator versus independent central review: comparative analysis of the AGO-OVAR16 trial. In: 18th International Meeting of the European Society of Gynaecological Oncology. 2013.

Floquet A, Vergote I, Colombo N, Fiane B, Monk BJ, Reinthaller A, et al. Progression-free survival by local investigator versus independent central review: comparative analysis of the AGO-OVAR16 Trial. *Gynecologic Oncology* 2015;**136**:37-42. [DOI: 10.1016/j.ygyno.2014.11.074]

Friedlander M, Knoll S, Meier W, Lesoin A, Kim JW, Poveda A, et al. Quality of life in patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (AEOC) receiving either pazopanib monotherapy or placebo after first-line chemotherapy: AGO-OVAR16 results. In: European Cancer Congress. 2013.

Friedlander M, Rau J, Lee CK, Meier W, Lesoin A, Kim JW, et al. Quality of life in patients with advanced epithelial ovarian cancer (EOC) randomized to maintenance pazopanib or placebo after first-line chemotherapy in the AGO-OVAR 16 trial. Measuring what matters - patient-centered end points in trials of maintenance therapy. *Annals of Oncology* 2018;**29**(3):737-43.

Harter P, Johnson T, Berton-Rigaud D, Park SY, Friedlander M, Del Campo JM, et al. BRCA1/2 mutations associated with progression-free survival in ovarian cancer patients in the AGO-OVAR 16 study. *Gynecologic Oncology* 2016;**140**(3):443-9.

Kim J-W, Mahner S, Wu L-Y, Shoji T, Kim B-G, Zhu J-Q, et al. Pazopanib maintenance therapy in East Asian women with advanced epithelial ovarian cancer: results from AGO-OVAR16 and an East Asian study. *International Journal of Gynecologic Cancer* 2018;**28**(1):2-10.

NCT00866697. Efficacy and safety of pazopanib monotherapy after first line chemotherapy in ovarian, fallopian tube, or primary peritoneal cancer. www.clinicaltrials.gov/ct2/show/NCT00866697 (first posted 20 March 2009).

NCT01227928. Efficacy and safety of pazopanib monotherapy after first-line chemotherapy in ovarian, fallopian tube, or primary peritoneal cancer in Asian women. www.clinicaltrials.gov/ct2/show/NCT01227928 (first posted 25 October 2010).

* Vergote I, du Bois A, Floquet A, Rau J, Kim J-W, Del Compa JM, et al. Overall survival results of AGO-OVAR16: a phase 3 study of maintenance pazopanib versus placebo in women who have not progressed after first-line chemotherapy for advanced ovarian cancer. *Gynecologic Oncology* 2019;**155**(2):186-91.

Zang R, Wu L, Zhu J, Kong B, Kim BG, Yao Y, et al. Pazopanib (Paz) monotherapy in Asian women who have not progressed after first-line chemotherapy for advanced ovarian, Fallopian tube, or primary peritoneal carcinoma. *Journal of Clinical Oncology: ASCO annual meeting proceedings* 2013;**31 Suppl**:Abstract 5512.

du Bois A, Floquet A, Kim JW, Rau J, del Campo JM, Friedlander M, et al. Incorporation of pazopanib in maintenance therapy of ovarian cancer. *Journal of Clinical Oncology* 2014;**32**(30):3374-82. [DOI: 10.1200/JCO.2014.55.7348.]

AMBITION 2022 *{published data only}*

Kim SI, Joung JG, Park E, Lee JY, Choi CH, Kim S, et al. Clinical and molecular characteristics of AMBITION patients who received olaparib plus cediranib or olaparib plus durvalumab for homologous recombination repair mutated, platinum-resistant ovarian cancer (KGOG 3045) (032). *Gynecologic Oncology* 2022;**166**(Suppl 1):S23. [DOI: 10.1016/S0090-8258(22)01250-1]

Lee J-Y, Kim B-G, Kim J-W, Lee JB, Park E, Kim SH, et al. An umbrella study of biomarker-driven targeted therapy in patients with platinum-resistant recurrent ovarian cancer (KGOG 3045, AMBITION). *Journal of Clinical Oncology* 2021;**39**(15 Suppl):5520.

* Lee JY, Kim BG, Kim JW, Lee JB, Park E, Joung JG, et al, Korean Gynecologic Oncology Group investigators. Biomarker-guided targeted therapy in platinum-resistant ovarian cancer (AMBITION; KGOG 3045): a multicentre, open-label, five-arm, uncontrolled, umbrella trial. *Journal of Gynecologic Oncology* 2022;**33**(4):e45.

Lee JY, Yi JY, Kim HS, Lim J, Kim S, Nam BH, et al, KGOG investigators. An umbrella study of biomarker-driven targeted therapy in patients with platinum-resistant recurrent ovarian cancer: a Korean Gynecologic Oncology Group study (KGOG 3045), AMBITION. *Japanese Journal of Clinical Oncology* 2019;**49**(8):789-92.

NCT03699449. An umbrella study of biomarker-driven targeted therapy In patients with platinum-resistant recurrent ovarian cancer (AMBITION). www.clinicaltrials.gov/ct2/show/NCT03699449 (first posted 09 October 2018).

ANTHALYA 2017 *{published data only}*

Joly F, Cottu PH, Gouy S, Lambaudie E, Selle F, Leblanc E, et al. Efficacy and long-term safety with bevacizumab included in neoadjuvant and adjuvant therapies in patients with advanced ovarian cancer: Results of the ANTHALYA trial . *Journal of Clinical Oncology* 2017;**35**(15 Suppl):5538.

NCT01739218. A study of bevacizumab (Avastin) in neoadjuvant therapy in participants with International Federation of Gynecology and Obstetrics (FIGO) Stage IIIC/IV ovarian, tubal, or peritoneal cancer, initially unresectable (ANTHALYA). www.clinicaltrials.gov/ct2/show/NCT01739218 (first posted 03 December 2012).

Rouzier R, Gouy S, Selle F, Guyon F, Lambaudie E, Fourchotte V, et al. 860PD - Complete resection rate at interval debulking surgery after bevacizumab containing neoadjuvant therapy: primary objective of the ANTHALYA trial. *Annals of Oncology* 2016;**27**(6):296-312.

* Rouzier R, Gouy S, Selle F, Lambaudie E, Floquet A, Fourchotte V, et al. Efficacy and safety of bevacizumab-containing neoadjuvant therapy followed by interval debulking surgery in advanced ovarian cancer: results from the ANTHALYA trial. *European Journal of Cancer* 2017;**70**:133-42.

Rouzier R, Gouy S, Selle F, Lambaudie E, Guyon F, Fourchotte V, et al. Complete resection rate at interval debulking surgery after bevacizumab containing neoadjuvant therapy: primary objective of the ANTHALYA trial. *International Journal of Gynecological Cancer* 2017;**26**:871.

Rouzier R, Morice P, Floquet A, Selle F, Lambaudie E, Fourchotte V, et al. A randomized, open-label, phase II study assessing the efficacy and the safety of bevacizumab in neoadjuvant therapy in patients with FIGO stage IIIc/IV ovarian, tubal, or peritoneal adenocarcinoma, initially unresectable. *Journal of Clinical Oncology* 2014;**32**(15 Suppl 1):TPS5614.

APPROVE 2022 *{published data only}*

NCT04348032. Apatinib combined with PLD vs PLD for platinum-resistant recurrent ovarian cancer (APPROVE). www.clinicaltrials.gov/ct2/show/NCT04348032 (first posted 15 April 2020).

Wang T, Li N, Tang J, Yang H, Yin R, Zhang J, et al. Apatinib combined with pegylated liposomal doxorubicin (PLD) versus PLD for platinum-resistant recurrent ovarian cancer (APPROVE): a multicenter, randomized, controlled, open-label, phase II trial. *Gynecologic Oncology* 2021;**162**(Suppl 1):S42.

* Wang T, Tang J, Yang H, Yin R, Zhang J, Zhou Q, et al. Effect of Apatinib plus pegylated liposomal doxorubicin vs pegylated liposomal doxorubicin alone on platinum-resistant recurrent ovarian cancer: the APPROVE randomized clinical trial. *JAMA Oncology* 2022;**8**(8):1169-76. [DOI: 10.1001/jamaoncol.2022.2253]

AURELIA 2014 *{published data only}*

Chappell NP, Miller CR, Fielden AD, Barnett JC. Is FDA-approved bevacizumab cost-effective when included in the treatment of platinum-resistant recurrent ovarian cancer? *Journal of Oncology Practice* 2016;**12**(7):e775-83.

Hilpert F, Fabbro M, Jesus Rubio M, Reuss A, Rosenberg P, Benedetti Panici P, et al. Symptoms and adverse effects with chemotherapy + bevacizumab for platinum-resistant recurrent ovarian cancer: analysis of the phase III AURELIA trial. *Gynecologic Oncology* 2013;**130**(1):E3.

Husain A, Wang Y, Hanker LC, Ojeda B, Anttila M, Breda E, et al. Independent radiologic review of AURELIA, a phase 3 trial of bevacizumab plus chemotherapy for platinum-resistant recurrent ovarian cancer. *Gynecologic Oncology* 2016;**142**(3):465-70.

Kristensen G, Berton-Rigaud D, Hilpert F, Reuss A, Bover I, Raspagliesi F, et al. Effect of bevacizumab (BEV) plus chemotherapy (CT) for platinum-resistant recurrent ovarian cancer (OC) with ascites: analysis of the AURELIA trial. In: International Journal of Gynecological Cancer. 2012:Conference Abstracts: 14th Biennial Meeting of the International Gynecologic Cancer Society.

NCT00976911. AURELIA: A study of Avastin (bevacizumab) added to chemotherapy in patients with platinum-resistant ovarian cancer. www.clinicaltrials.gov/ct2/show/NCT00976911 (first posted 15 September 2009).

Poveda A M, Selle F, Hilpert F, Reuss A, Savarese A, Vergote I, et al. Bevacizumab combined with weekly paclitaxel, pegylated liposomal doxorubicin, or topotecan in platinum-resistant

recurrent ovarian cancer: analysis by chemotherapy cohort of the candomized phase III AURELIA trial. *Journal of Clinical Oncology* 2015;**33**(32):3836-8.

Pujade-Lauraine E, Hilpert F, Weber B, Reus A, Poveda A, Kristensen G, et al. AURELIA: a randomized phase III trial evaluating bevacizumab (BEV) plus chemotherapy (CT) for platinum (PT) resistant recurrent ovarian cancer (OC). *Journal of Clinical Oncology* 2012;**30**:LBA5002.

* Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. *Journal of Clinical Oncology* 2014;**32**(13):1302-8.

Pujade-Lauraine E. Errata: Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. *Journal of Clinical Oncology* 2014;**32**(35):4025.

Sorio R, Roemer-Becuwe C, Hilpert F, Gibbs E, Garcia Y, Kaern J, et al. Safety and efficacy of single-agent bevacizumab-containing therapy in elderly patients with platinum-resistant recurrent ovarian cancer: subgroup analysis of the randomised phase III AURELIA trial. *Gynecologic Oncology* 2017;**144**(1):65-71.

Sorio R, Roemer-Becuwe C, Hilpert F, Reuss A, Garcia Y, Kaern J, et al. Safety and efficacy of single-agent chemotherapy + bevacizumab in elderly patients with platinum-resistant recurrent ovarian cancer: subgroup analysis of Aurelia. *International Journal of Gynecological Cancer* 2013;**23**(8):[no pagination].

Stockler MR, Hilpert F, Friedlander M, King M, Wenzel LB, Lee C, et al. Health-related quality of life (HRQoL) results from the AURELIA trial evaluating bevacizumab (BEV) plus chemotherapy (CT) for platinum-resistant recurrent ovarian cancer (OC). *Journal of Clinical Oncology* 2013;**31 Suppl**:Abstract 5542.

Stockler MR, Hilpert F, Friedlander M, King MT, Wenzel L, Lee C K, et al. Patient-reported outcome results from the open-label phase III AURELIA trial evaluating bevacizumab-containing therapy for platinum-resistant ovarian cancer. *Journal of Clinical Oncology* 2014;**32**:1309-16.

Trillsch F, Mahner S, Hilpert F, Davis L, Garcia-Martinez E, Kristensen G, et al. Prognostic and predictive values of primary versus secondary platinum resistance for bevacizumab treatment in platinum resistant ovarian cancer in the AURELIA trial. *Annals of Oncology* 2016;**27**(9):1733-9.

Witteveen P, Lortholary A, Fehm T, Poveda A, Reuss A, Havsteen H, et al. Final overall survival (OS) results from AURELIA, an open-label randomised phase III trial of chemotherapy (CT) with or without bevacizumab (BEV) for platinum-resistant recurrent ovarian cancer (OC). *European Journal of Cancer* 2013;**49**(Suppl 3):S3-4.

Wysham WZ, Schaffer EM, Coles T, Roque DR, Wheeler SB, Kima KH. Adding bevacizumab to single agent chemotherapy for the treatment of platinum-resistant recurrent ovarian cancer: a cost effectiveness analysis of the AURELIA trial. *Gynecologic Oncology* 2017;**145**(2):340-5.

AVANOVA2 2019 *{published data only}*

* Mirza MR, Avall Lundqvist E, Birrer MJ, dePont Christensen R, Nyvang GB, Malander S, et al. Niraparib plus bevacizumab versus niraparib alone for platinum-sensitive recurrent ovarian cancer (NSGO-AVANOVA2/ENGOT-ov24): a randomised, phase 2, superiority trial. *Lancet Oncology* 2019;**20**(10):1409-19.

Mirza MR, Avall-Lundqvist E, Birrer MJ, DePont Christensen R, Nyvang G-B, Malander S, et al. Combination of niraparib and bevacizumab versus niraparib alone as treatment of recurrent platinum-sensitive ovarian cancer: a randomized controlled chemotherapy-free study-NSGO-AVANOVA2/ENGOT-OV24. *Journal of Clinical Oncology* 2019;**37**(Suppl 15):5505.

Mirza MR, Mortensen CE, Avall-Lundqvist E, Bjorge L, Berek JS, Herrstedt J, et al. ENGOT-OV24-NSGO/ AVANOVA: niraparib versus bevacizumab-niraparib combination versus bevacizumab and niraparib as sequential therapy in women with platinumsensitive epithelial ovarian, fallopian tube, or peritoneal cancer. *Journal of Clinical Oncology* 2015;**33**(15):TPS5607.

Mirza MR, Nyvang G-B, Lund B, DePont Christensen R, Werner TL, Malander S, et al. Final survival analysis of NSGO-AVANOVA2/ ENGOT-OV24: combination of niraparib and bevacizumab versus niraparib alone as treatment of recurrent platinum-sensitive ovarian cancer - a randomized controlled chemotherapy-free study. *Journal of Clinical Oncology* 2020;**38**(15 Suppl):6012.

NCT02354131. Niraparib versus niraparib-bevacizumab combination in women with platinum-sensitive epithelial ovarian cancer (AVANOVA). www.clinicaltrials.gov/ct2/show/NCT02354131 (first posted 03 February 2015).

BAROCCO 2022 *{published data only}*

Colombo N, Nicoletto MO, Benedetti Panici P, Tognon G, Bologna A, Lissoni AA, et al. BAROCCO: a randomized phase II study of weekly paclitaxel vs cediranib-olaparib combination given with continuous or intermittent schedule in patients with recurrent platinum resistant ovarian cancer (PROC). *Annals of Oncology* 2019;**30**(Suppl 5):v896.

Colombo N, Nicoletto O, Benedetti Panici P, Tognon G, Lissoni AA, Bologna A, et al. BAROCCO: a randomized phase II study of weekly paclitaxel vs cediranib-olaparib with continuous schedule vs cediranib-olaparib with intermittent schedule in advanced platinum resistant ovarian cancer. *Annals of Oncology* 2018;**29**(Suppl 8):viii357.

* Colombo N, Tomao F, Benedetti Panici P, Nicoletto MO, Tognon G, Bologna A, et al. Randomized phase II trial of weekly paclitaxel vs. cediranib-olaparib (continuous or intermittent schedule) in platinum-resistant high-grade epithelial ovarian cancer. *Gynecologic Oncology* 2022;**164**(3):505-13. [DOI: 10.1016/j.ygyno.2022.01.015]

NCT03314740. Best approach in recurrent-ovarian-cancer-with cediranib-olaparib (BAROCCO). www.clinicaltrials.gov/ct2/show/NCT03314740 (first posted 19 October 2017).

CHIVA 2019 *{published data only}*

Blanc-Durand F, Yaniz-Galende E, Genestie C, De Saint Basile HG, Chardin L, De Rauglaudre G, et al. Immune tumor microenvironnement (iTME) post-neoadjuvant chemotherapy, beyond PD-L1: novel immune targets in ovarian cancer, data from the CHIVA trial, a GINECO/ GINEGEPS study. *Journal of Clinical Oncology* 2022;**40**(16 Suppl):5554.

* Ferron G, De Rauglaudre G, Chevalier A, et al. Impact of adding nintedanib to neoadjuvant chemotherapy (NACT) for advanced epithelial ovarian cancer (EOC) patients: the CHIVA double-blind randomized phase II GINECO study. *Journal of Clinical Oncology* 2019;**37**(15 Suppl):5512.

Ferron G, De Rauglaudre G, Ray-Coquard IL, Lesoin A, Joly F, Lortholary A, et al. The CHIVA study: a GINECO randomized double blind phase II trial of nintedanib versus placebo with the neo-adjuvant chemotherapy (NACT) strategy for patients (pts) with advanced unresectable ovarian cancer (OC). Report of the interval debulking surgery (IDS) safety outcome. *Annals of Oncology* 2016;**27**(Suppl 6):V1297.

Lecuru F, Pujade-Lauraine E, Hamizi S, Caumont-Prim A, Raban N, Malaurie E, et al. Surrogate endpoint of progression-free (PFS) and overall survival (OS) for advanced ovarian cancer (AOC) patients (pts) treated with neo-adjuvant chemotherapy (NACT): results of the CHIVA randomized phase II GINECO study. *Annals of Oncology* 2019;**30**(Suppl 5):v415.

NCT01583322. Vargatef in addition to first line chemotherapy with interval debulking surgery in patients with ovarian cancer (CHIVA). www.clinicaltrials.gov/ct2/show/NCT01583322 (first posted 24 April 2012).

You B, Robelin P, Tod M, Louvet C, Lotz J-P, Abadie-Lacourtoisie S, et al. CA-125 ELIMination rate constant K (KELIM) Is a marker of chemosensitivity in patients with ovarian cancer: results from the phase II CHIVA trial. *Clinical Cancer Research* 2020;**26**(17):4625-32.

Cong 2019 *{published data only}*

* Cong J, Liu R, Hou J, Wang X, Jiang H, Wang J. Therapeutic effect of bevacizumab combined with paclitaxel and carboplatin on recurrent ovarian cancer. *Journal of the Balkan Union of Oncology (JBUON)* 2019;**24**(3):1003-8.

Duska 2020 *{published data only}*

Duska LR, Brown J, Jelovac D, Moore KN, McGuire WP, Darus C, et al. A randomized phase II evaluation of weekly gemcitabine plus pazopanib versus weekly gemictabine alone in the treatment of persistent or recurrent epithelial ovarian, fallopian tube or primary peritoneal carcinoma. *Journal of Clinical Oncology* 2017;**35** (15 Suppl):5532.

* Duska LR, Petroni GR, Varhegyi N, Brown J, Jelovac D, Moore KN, et al. A randomized phase II evaluation of weekly gemcitabine plus pazopanib versus weekly gemcitabine alone in the treatment of persistent or recurrent epithelial ovarian, fallopian tube or primary peritoneal carcinoma. *Gynecologic Oncology* 2020;**157**(3):585-92.

NCT01610206. A randomized open label phase II study of weekly gemcitabine plus pazopanib versus weekly gemcitabine alone in the treatment of patients with persistent or relapsed epithelial ovarian, fallopian tube or primary peritoneal carcinoma. www.clinicaltrials.gov/ct2/show/NCT01610206 (first posted 01 June 2012).

EORTC-1508 2021 *{published data only}***2015-004601-17**

* Banerjee S, Ottevanger P, Sarivalasis A, Le Scodan R, Montes A, Kroep JR, et al. LBA32 Principal results of the EORTC-1508 trial: a phase II randomised, multicentre study of bevacizumab vs atezolizumab and bevacizumab with acetylsalicylic acid or placebo in recurrent platinum-resistant ovarian, fallopian tube or primary peritoneal adenocarcinoma. *Annals of Oncology* 2021;**32**:S1308.

NCT02659384. Anti-programmed cell death-1 ligand 1 (aPDL-1) antibody atezolizumab, bevacizumab and acetylsalicylic acid in recurrent platinum resistant ovarian cancer. www.clinicaltrials.gov/ct2/show/NCT02659384 (first posted 20 January 2016).

GEICO-1205 2019 *{published data only}*

Garcia Garcia Y, De Juan A, Mendiola C, Barretina-Ginesta P, Vidal L, Santaballa A, et al. Phase II randomized trial of neoadjuvant (NA) chemotherapy (CT) with or without bevacizumab (Bev) in advanced epithelial ovarian cancer (EOC) (GEICO 1205/NOVA TRIAL). *Journal of Clinical Oncology* 2017;**35**:5508.

* Garcia Garcia Y, de Juan Ferre A, Mendiola C, Barretina-Ginesta MP, Gaba Garcia L, Santaballa Bertran A, et al. Efficacy and safety results from GEICO 1205, a randomized phase II trial of neoadjuvant chemotherapy with or without bevacizumab for advanced epithelial ovarian cancer. *International Journal of Gynecological Cancer* 2019;**29**(6):1050-6.

NCT01847677. Neoadjuvant therapy in advanced ovarian cancer with Avastin (NOVA). www.clinicaltrials.gov/ct2/show/NCT01847677 (first posted 07 May 2013).

GOG-0213 2017 *{published data only}*

Coleman R L, Brady M F, Herzog T J, Sabbatini P, Armstrong D K, Walker J L, et al. A phase III randomized controlled clinical trial of carboplatin and paclitaxel alone or in combination with bevacizumab followed by bevacizumab and secondary cytoreductive surgery in platinum sensitive, recurrent ovarian, peritoneal primary and fallopian tube cancer (Gynecologic Oncology Group 0213). *Gynecologic Oncology* 2015;**137**(Suppl 1):3-4.

* Coleman RL, Brady MF, Herzog TJ, Sabbatini P, Armstrong DK, Walker JL, et al. Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncology* 2017;**18**(6):779-91.

NCT00565851. Carboplatin, paclitaxel and gemcitabine hydrochloride with or without bevacizumab after surgery in treating patients with recurrent ovarian epithelial, primary peritoneal, or fallopian tube cancer. www.clinicaltrials.gov/ct2/show/study/NCT00565851 (first posted 30 November 2007).

GOG-0218 2019 *{published and unpublished data}*

Birrer MJ, Lankes H, Burger RA, Mannel R, Homesley H, Henschel V, et al. Biomarker (BM) results from GOG-0218, a phase 3 trial of front-line bevacizumab (BV) + chemotherapy (CT) for ovarian cancer (OC). *Annals of Oncology* 2012;**23**(9 Suppl):IX81-2.

Burger R, Brady M, Bookman M, Monk B, Walker J, Homesley H, et al. Prospective investigation of risk factors for gastrointestinal adverse events in a phase III randomized trial of bevacizumab in first-line therapy of advanced epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer: a Gynecologic Oncology Group study. *Gynecologic Oncology* 2011;**120**:S5 Abstract 7.

* Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *New England Journal of Medicine* 2011;**365**:2473-83.

Burger RA, Brady MF, Bookman MA, Monk BJ, Walker J, Homesley H, et al, Gynaecologic Oncology Group study. Safety and subgroup efficacy analyses in GOG218, a phase III trial of bevacizumab (BEV) in the primary treatment of advanced epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC) or fallopian tube cancer (FTC). *Annals of Oncology* 2010;**21**(Suppl):Abstr 978PD viii307.

Burger RA, Brady MF, Bookman MA, Walker JL, Homesley HD, Fowler J, et al, Gynecologic Oncology Group study. Phase III trial of bevacizumab (BEV) in the primary treatment of advanced epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC). *Journal of Clinical Oncology* 2010;**28**(Suppl):Abstr LBA1.

Burger RA, Brady MF, Rhee J, Sovak MA, Kong G, Nguyen HP, et al. Independent radiologic review of the Gynecologic Oncology Group Study 0218, a phase III trial of bevacizumab in the primary treatment of advanced epithelial ovarian, primary peritoneal, or fallopian tube cancer. *Gynecologic Oncology* 2013;**131**:21-6.

Burger RA, Brady MF, Rhee J, Sovak MA, Nguyen H, Bookman MA. Independent radiologic review of GOG218, a phase III trial of bevacizumab (BEV) in the primary treatment of advanced epithelial ovarian (EOC), primary peritoneal (PPC) or Fallopian tube cancer (FTC). *Journal of Clinical Oncology* 2011;**29**:Abstract 5023.

Chan J, Java J, Monk B, Alvarez-Secord A, Kapp D, Birrer M, et al. A practical prediction model for determining bevacizumab response and toxicity in the treatment of advanced ovarian and peritoneal cancers - an analysis of GOG 218. *Gynecologic Oncology* 2012;**125**(1 Suppl):S31.

Chase DM, Sill W, Monk BJ, Chambers D, Darcy KM, Han ES, et al. Changes in tumor blood flow as measured by Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI) may predict activity of single agent bevacizumab in recurrent epithelial ovarian (EOC) and primary peritoneal cancer (PPC) patients: an exploratory analysis of a Gynecologic Oncology Group Phase II study. *Gynecologic Oncology* 2012;**126**(3):375-80.

Du Pont N, Brady M, Burger R, Monk B. Prognostic significance of ethnicity and age in advanced stage ovarian cancer: an analysis of GOG 218. *Gynecologic Oncology* 2013;**130**(1):E21-22.

Garcia K, Ranganathan A, Coleman RL. Addition of bevacizumab to paclitaxel/carboplatin in first-line management of advanced ovarian cancer: results of the GOG 0218 phase III study (Meeting Highlights: ASCO 2010). *Clinical Ovarian Cancer* 2010;**3**(2):E1-5.

Han ES, Burger RA, Darcy KM, Sill MW, Randall LM, Chase D, et al. Predictive and prognostic angiogenic markers in a gynecologic oncology group phase II trial of bevacizumab in recurrent and persistent ovarian or peritoneal cancer. *Gynecologic Oncology* 2010;**119**(3):484-90.

Monk BJ, Huang H, Burger RA, Mannel RL, Homesley HD, Fowler J, et al. Quality of life outcomes of a randomized, placebo-controlled trial of bevacizumab in the front-line treatment of ovarian cancer: a gynecologic oncology group study. *European Journal of Cancer* 2011;**47**(2):12.

Monk BJ, Huang HQ, Burger RA, Mannel RS, Homesley HD, Fowler J, et al. Patient reported outcomes of a randomized, placebo-controlled trial of bevacizumab in the front-line treatment of ovarian cancer: a Gynecologic Oncology Group Study. *Gynecologic Oncology* 2013;**128**:573-8.

NCT00262847. Carboplatin and paclitaxel with or without bevacizumab in treating patients with stage III or stage IV ovarian epithelial, primary peritoneal, or fallopian tube cancer. www.clinicaltrials.gov/ct2/show/NCT00262847 (first posted 07 December 2005).

Phippen NT, Secord AA, Wolf S, Samsa G, Davidson B, Abernethy AP, et al. Quality of life is significantly associated with survival in women with advanced epithelial ovarian cancer: an ancillary data analysis of the NRG Oncology/Gynecologic Oncology Group (GOG-0218) study. *Gynecologic Oncology* 2017;**147**(1):98-103.

Randall L, Burger R, Nguyen H, Kong G, Bookman M, Fleming G, et al. Outcome differences in patients with advanced epithelial ovarian, primary peritoneal and fallopian tube cancers treated with and without bevacizumab. *Gynecologic Oncology* 2013;**130**(1):e33 .

Randall L, Burger R, Nguyen H, Kong G, Bookman M, Fleming G, et al. Time from completion of chemotherapy to disease progression as a clinically relevant endpoint in women with epithelial ovarian, primary peritoneal, and fallopian tube cancers treated with and without bevacizumab. *Gynecologic Oncology* 2013;**130**(1):e120.

* Tewari KS, Burger RA, Enserro D, Norquist BM, Swisher E, Brady MF, et al. Final overall survival of a randomized trial of bevacizumab for primary treatment of ovarian cancer. *Journal of Clinical Oncology* 2019;**37**(26):2317-28.

You B, Purdy C, Swisher EM, Bookman MA, Fleming GF, Coleman RL, et al. Identification of patients with ovarian cancer who are experiencing the highest benefit from bevacizumab in first-line setting based on their tumor intrinsic chemosensitivity (KELIM): GOG-0218 validation study. *Journal of Clinical Oncology* 2022;**40**(16 Suppl 1):5553.

GOG-0241 2019 *{published data only}***ISRCTN83438782**

* Gore M, Hackshaw A, Brady WE, Penson RT, Zaino R, McCluggage WG, et al. An international, phase III randomized trial in patients with mucinous epithelial ovarian cancer (mEOC/GOG 0241) with long-term follow-up: and experience of conducting a clinical trial in a rare gynecological tumor. *Gynecologic Oncology* 2019;**153**(3):541-8.

Gore ME, Hackshaw A, Brady WE, Penson RT, Zaino RJ, McCluggage WG, et al. Multicentre trial of carboplatin/paclitaxel versus oxaliplatin/capecitabine, each with/without bevacizumab, as first line chemotherapy for patients with mucinous epithelial ovarian cancer (mEOC). *Journal of Clinical Oncology* 2015;**33**(15 Suppl 1):5528.

NCT01081262. Carboplatin and paclitaxel or oxaliplatin and capecitabine with or without bevacizumab as first-line therapy in treating patients with newly diagnosed stage II-IV or recurrent stage I epithelial ovarian or fallopian tube cancer. www.clinicaltrials.gov/ct2/show/NCT01081262 (first posted 05 March 2019).

Gotlieb 2012 *{published data only}***2005-005026-31;**

* Gotlieb W H, Amant F, Advani S, Goswami C, Hirte H, Provencher D, et al. Intravenous aflibercept for treatment of recurrent symptomatic malignant ascites in patients with advanced ovarian cancer: a phase 2, randomised, double-blind, placebo-controlled study. Lancet Oncology 2012;**13**:154-62.

NCT00327444. Study of the effect of intravenous AVE0005 (VEGF Trap) in advanced ovarian cancer patients with recurrent symptomatic malignant ascites. www.clinicaltrials.gov/ct2/show/study/NCT00327444 (first posted 18 May 2006).

Vergote I, Amant F, Advani F, Goswami C, Hirte H, Provencher D et al. Intravenous aflibercept (VEGF Trap) for the treatment of recurrent symptomatic malignant ascites. Personal communication (Abstract to subsequent full published version of the study, received from authors prior to original version of the review).

Vergote I, Amant F, Advani F, Goswani C, Hirte H, Provencher D, et al. Aflibercept (VEGF Trap) in advanced ovarian cancer patients with recurrent symptomatic malignant ascites: results of a randomized, double-blind, placebo-controlled study. In: 16th International Meeting of the European Society of Gynaecological Oncology; 2009 Oct 11-14; Belgrade, Serbia. 2009:Abstract 1428.

Vergote I, Amant F, Advani F, Goswani C, Hirte H, Provencher D, et al. Aflibercept (VEGF Trap) in advanced ovarian cancer patients with recurrent symptomatic malignant ascites: results of a randomized, double-blind, placebo-controlled study. *International Journal of Gynecological Cancer* 2009;**19**:Suppl 2.

Gupta 2019 *{published data only}***NCI-2009-01597CDR0000567043**

* Gupta R, Cristea M, Frankel P, Ruel C, Chen C, Wang Y, et al. Randomized trial of oral cyclophosphamide versus oral cyclophosphamide with celecoxib for recurrent epithelial ovarian, fallopian tube, and primary peritoneal cancer. *Cancer Treatment and Research Communications* 2019;**21**:100155.

NCT00538031. Trial protocol: cyclophosphamide with or without celecoxib in treating patients with recurrent or persistent ovarian epithelial, fallopian tube, or primary peritoneal cancer. www.clinicaltrials.gov/ct2/show/NCT00538031 (first posted 02 October 2007).

Hainsworth 2015 *{published data only}*

* Hainsworth J D, Thompson D S, Bismayer J A, Gian V G, Merritt W M, Whorf R C, et al. Paclitaxel/carboplatin with or without sorafenib in the first-line treatment of patients with stage III/IV epithelial ovarian cancer: a randomized phase II study of the Sarah Cannon Research Institute. *Cancer Medicine* 2015;**4**(5):673-81.

Hainsworth JD, Numnum TM, Rao GG. A randomized phase II study of paclitaxel/carboplatin with or without sorafenib in the first-line treatment of patients with stage III/IV epithelial ovarian cancer. *Journal of Clinical Oncology* 2010;**28**(Suppl 15):TPS257.

NCT00390611. Paclitaxel and carboplatin with or without sorafenib in the first-line treatment of patients with ovarian cancer. www.clinicaltrials.gov/ct2/show/NCT00390611 (first posted 19 October 2006).

Thompson DS, Dudley BS, Bismayer JA, Gian VG, Merritt WM, Whorf RC, et al. Paclitaxel/carboplatin with or without sorafenib in the first-line treatment of patients with stage III/IV epithelial ovarian cancer: A randomized phase II study of the Sarah Cannon Research Institute. *Journal of Clinical Oncology* 2013;**31**(15 Suppl):5513.

Herzog 2013 *{published data only}*

Herzog TJ, Scambia G, Kim BG, Lhomme C, Markowska J, Ray-Coquard I, et al. A randomized, double-blind phase 2 trial of maintenance sorafenib in epithelial ovarian or primary peritoneal cancer. *International Journal of Gynecological Cancer* 2012;**22**(Suppl 3):E99-100.

* Herzog TJ, Scambia G, Kim BG, Lhommé C, Markowska J, Ray-Coquard I, et al. A randomized phase II trial of maintenance therapy with Sorafenib in front-line ovarian carcinoma. *Gynecologic Oncology* 2013;**130**(1):25-30.

NCT00791778. Comparison of nexavar/placebo as maintenance therapy for patients with advanced ovarian or primary peritoneal cancer. www.clinicaltrials.gov/ct2/show/NCT00791778 (first posted 14 November 2008).

ICON6 2021 *{published data only (unpublished sought but not used)}***ISRCTN68510403**

* Ledermann JA, Embleton AC, Raja F, Perren TJ, Jayson GC, Rustin GJ, et al. Cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON6): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016;**387**(10023):1066-74.

Ledermann JA, Embleton-Thirsk AC, Perren TJ, Jayson GC, Rustin GJS, Kaye SB, et al. Cediranib in addition to chemotherapy for women with relapsed platinum-sensitive ovarian cancer (ICON6): overall survival results of a phase III randomised trial. *ESMO Open* 2021;**6**(2):100043.

Ledermann JA, Perren T, Raja F A, Perren T J, Embleton A, Rustin GJS, et al. Randomised double-blind phase iii trial of cediranib (AZD 2171) in relapsed platinum sensitive ovarian cancer: Results of the ICON6 trial. NCRI Cancer Conference (www.abstracts.ncri.org.uk/abstract/) 2013.

Ledermann JA, Perren TJ, Raja FA, Embleton A, Rustin GJ, Jayson G, et al. LBA10: Randomised double-blind phase III trial of cediranib (AZD 2171) in relapsed platinum sensitive ovarian cancer: results of the ICON6 trial. *European Journal of Cancer* 2013;**49**(Suppl 3):S5-6.

NCT00532194. A randomised, placebo-controlled, trial of concurrent cediranib [AZD2171] (with platinum-based chemotherapy) and concurrent and maintenance cediranib in women with platinum-sensitive relapsed ovarian cancer. www.clinicaltrials.gov/ct2/show/NCT00532194 (first posted 20 September 2007).

Raja FA, Griffin CL, Qian W, Hirte H, Parmar MK, Swart AM, et al. Initial toxicity assessment of ICON6: a randomised trial of cediranib plus chemotherapy in platinum-sensitive relapsed ovarian cancer. *British Journal of Cancer* 2011;**105**(7):884-9.

Raja FA, Perren TJ, Embleton A, Rustin GJ, Jayson G, Swart AM, et al. Randomised double-blind phase III trial of cediranib (AZD 2171) in relapsed platinum sensitive ovarian cancer: Results of the ICON6 trial. *International Journal of Gynecological Cancer* 2013;**23**(8):Suppl 1.

Stark DP, Cook A, Brown JM, Brundage MD, Embleton AC, Kaplan RS, et al. Quality of life with cediranib in relapsed ovarian cancer: the ICON6 phase 3 randomized clinical trial. *Cancer* 2017;**123**(14):2752-61.

ICON7 2015 *{published and unpublished data}***ISRCTN91273375**

Gonzalez-Martin A, Oza AM, Embleton AC, Pfisterer J, Ledermann JA, Pujade-Lauraine E, et al. Exploratory outcome analyses according to stage and residual disease in the ICON7 trial of frontline carboplatin/paclitaxel (CP) +/- bevacizumab (BEV) for ovarian cancer (OC). *Journal of Clinical Oncology* 2015;**33**(Suppl 15):5548.

Hinde S, Epstein D, Cook A, Embleton A, Perren T, Sculpher M. The Cost-effectiveness of bevacizumab in advanced ovarian cancer using evidence from the ICON7 Trial. *Value Health* 2016;**19**(4):431-9.

ICON7 - a randomised two-arm, multi-centre Gynaecologic Cancer InterGroup trial of adding bevacizumab to standard chemotherapy (carboplatin and paclitaxel) in patients with epithelial ovarian cancer [abstract]. Proceedings of the Annual Meeting of the British Gynaecological Cancer Society, Manchester, UK 2006 Nov;**1**:92.

ISRCTN91273375. ICON7 - a randomised, two-arm, multi-centre Gynaecologic Cancer InterGroup trial of adding bevacizumab to standard chemotherapy (carboplatin and paclitaxel) in patients with epithelial ovarian cancer. www.isrctn.com/ISRCTN91273375 (first registered 25 January 2006).

Kommoss S, Winterhoff B, Oberg AL, Konecny GE, Wang C, Riska SM, et al. Bevacizumab may differentially improve ovarian cancer outcome in patients with proliferative and mesenchymal molecular subtypes. *Clinical Cancer Research* 2017;**23**(14):3794-801.

Kristensen G, Perren T, Qian W, Pfisterer J, Ledermann JA, Joly F, et al. Result of interim analysis of overall survival in the GCIG ICON7 phase III randomized trial of bevacizumab in women with newly diagnosed ovarian cancer. *Journal of Clinical Oncology* 2011;**29**(18 Suppl):LBA5006.

Morgan RD, Ferreras C, Peset I, Avizienyte E, Renehan AG, Edmondson RJ, et al. c-MET/VEGFR-2 co-localisation impacts on survival following bevacizumab therapy in epithelial ovarian cancer: an exploratory biomarker study of the phase 3 ICON7 trial. *BMC Medicine* 2022;**20**(1):59. [DOI: 10.1186/s12916-022-02270-y]

* Oza A M, Cook AD, Pfisterer J, Embleton A, Ledermann JA, Pujade-Lauraine E, et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *Lancet Oncology* 2015;**16**(8):928-36.

Oza AM, Perren TJ, Swart AM, Schroder W, Pujade-Lauraine E, Havsteen H, et al. LBA6: ICON7: final overall survival results in the GCIG phase III randomized trial of bevacizumab in women with newly diagnosed ovarian cancer. *European Journal of Cancer* 2013;**49**(Suppl 3):S4.

Perren T, Swart AM, Pfisterer J, Ledermann J, Lortholary A, Kristensen G et al. ICON7: A phase III Gynaecologic Cancer InterGroup (GCIG) trial of adding bevacizumab to standard chemotherapy in women with newly diagnosed epithelial ovarian, primary peritoneal or fallopian tube cancer. Powerpoint Presentation from European Society for Medical Oncology 2010 2010.

Perren T, Swart AM, Pfisterer J, Ledermann J, Lortholary A, Kristensen G, et al. ICON7: a phase III randomised Gynaecologic Cancer Intergroup trial of concurrent bevacizumab and chemotherapy followed by maintenance bevacizumab, versus chemotherapy alone in women with newly diagnosed epithelial ovarian (EOC), primary peritoneal (PPC) or fallopian tube cancer (FTC). *Annals of Oncology* 2010;**21**(Suppl 8):LBA4.

* Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, et al. A phase 3 trial of bevacizumab in ovarian cancer. *New England Journal of Medicine* 2011;**365**(26):2484-96.

Pujade-Lauraine E, Oza AM, Perren TJ, Swart AM, Mahner S, Gourley C, et al. ICON7: final overall survival results in the GCIG phase III randomised trial of bevacizumab in newly diagnosed ovarian cancer. *International Journal of Gynecological Cancer* 2013;**23**(8):Suppl 1.

Stark D, Nankivell M, Hilpert F, Elit L, Brown J, Lanceley A, et al. Quality of life in the ICON7 GCIG phase III randomised clinical trial. *European Journal of Cancer* 2011;**47**(Suppl 2):12.

* Stark D, Nankivell M, Pujade-Lauraine E, Kristensen G, Elit L, Stockler M, et al. Standard chemotherapy with or without bevacizumab in advanced ovarian cancer: quality-of-life outcomes from the International Collaboration on Ovarian

Neoplasms (ICON7) phase 3 randomised trial. Lancet Oncology 2013;**14**(3):236-43.

Zhou C, Clamp A, Backen A, Berzuini C, Renehan A, Banks RE, et al. Systematic analysis of circulating soluble angiogenesis-associated proteins in ICON7 identifies tie2 AS a biomarker of vascular progression on bevacizumab. *British Journal of Cancer* 2016;**115**(2):228-35.

Karlan 2012 *{published and unpublished data}*

Karlan B, Lu J, Navale L, Rasmussen E, Sun YN, Vergote IB, et al. Exposure-response relationship of open-label (OL) AMG 386 monotherapy in patients (pts) with recurrent ovarian cancer. *Journal of Clinical Oncology* 2012;**30**(15 Suppl):5072.

Karlan BY, Oza AM, Hansen VL, Richardson GE, Provencher DM, Ghatage P et al. Randomized, double-blind, placebo-controlled phase II study of AMG 386 combined with weekly paclitaxel in patients (pts) with recurrent ovarian carcinoma. *Journal of Clinical Oncology* 2010;**28**(Suppl 15):5000.

* Karlan BY, Oza AM, Richardson GE, Provencher DM, Hansen VL, Buck M, et al. Randomized, double-blind, placebo-controlled phase II study of AMG 386 combined with weekly paclitaxel in patients with recurrent ovarian cancer. *Journal of Clinical Oncology* 2012;**30**(4):362-71.

Lu J, Rasmussen E, Navale L, Kuchimanchi M, Hurh E, Karlan BY, et al. Exposure-response relationships of AMG 386 in combination with weekly paclitaxel in advanced ovarian cancer: Population pharmacokinetic/pharmacodynamic (PK/PD) modelling to facilitate phase III dose selection. *Journal of Clinical Oncology* 2010;**28**(15 Suppl):5042.

Lu J, Rasmussen E, Navale L, Kuchimanchi M, Hurh E, Karlan BY, et al. Exposure-response relationships of AMG 386 in combination with weekly paclitaxel in advanced ovarian cancer: facilitation of phase 3 dose selection by population pharmacokinetic/pharmacodynamic modelling. *Annals of Oncology* 2010;**21**(Suppl 8):viii308.

Lu JF, Rasmussen E, Karlan BY, Vergote IB, Navale L, Kuchimanchi M, et al. Exposure-response relationship of AMG 386 in combination with weekly paclitaxel in recurrent ovarian cancer and its implication for dose selection. *Cancer Chemotherapy and Pharmacology* 2012;**69**(5):1135-44.

NCT00479817. Phase 2, AMG 386 (20060342) in combination with paclitaxel for subjects with advanced recurrent epithelial ovarian or primary peritoneal cancer. www.clinicaltrials.gov/ct2/show/NCT00479817 (first posted 28 May 2007).

Richardson GE, Vergote IB, Oza AM, Hansen VL, Provencher D, Ghatage P, et al. AMG 386 plus weekly paclitaxel for the treatment of advanced ovarian cancer: a randomized, double-blind, placebo-controlled phase 2 study. *Asia-Pacific Journal of Clinical Oncology* 2010;**6**(Suppl 3):122.

Vergote IB, Oza AM, Hansen VL, Richardson GE, Provencher DM, Ghatage P, et al. A randomised, double-blind, placebo-controlled phase 2 study of AMG 386 plus weekly paclitaxel in patients (pts) with advanced ovarian cancer. *Annals of Oncology* 2010;**21**(Suppl 8):viii 305-6.

Ledermann 2011 *{published data only (unpublished sought but not used)}*

* Ledermann JA, Hackshaw A, Kaye S, Jayson G, Gabra H, McNeish I, et al. Randomized phase II placebo-controlled trial of maintenance therapy using the oral triple angiokinase inhibitor BIBF 1120 after chemotherapy for relapsed ovarian cancer. *Journal of Clinical Oncology* 2011;**29**(28):3798-804.

Ledermann JA, Rustin GJ, Hackshaw A, Kaye SB, Jayson G, Gabra H et al. A randomized phase II placebo-controlled trial using maintenance therapy to evaluate the vascular targeting agent BIBF 1120 following treatment of relapsed ovarian cancer (OC). *Journal of Clinical Oncology* 2009;**2**(Suppl 15):5501.

NCT00710762. A randomized placebo-controlled Phase II study of continuous maintenance treatment with BIBF 1120 following chemotherapy in patients with relapsed ovarian cancer. clinicaltrials.gov/ct2/show/NCT00710762 (first posted 04 July 2008).

Li 2019 *{published data only}*

Li C, Cheng W, Yu S, Xuan J. Study on the short-term efficacy and safety of bevacizumab combined with chemotherapy for platinum-sensitive recurrent ovarian cancer. *Basic & Clinical Pharmacology & Toxicology* 2019;**125**:3-224.

Li 2021 *{published data only}*

* Li XL, Zhao JD, Ma JQ. Efficacy of bevacizumab combined with albumin binding paclitaxel in patients with platinum-resistant relapsed and metastatic ovarian cancer and effect on immune function. *Chinese Journal of Pharmaceutical Biotechnology* 2021;**28**(5):491-5. [DOI: 10.19526/j.cnki.1005-8915.20210511]

Liu 2019a *{published data only}*

Liu B, An R, Yu J. Efficacy of bevacizumab combined with albumin-bound paclitaxel in the treatment of platinum-resistant recurrent ovarian cancer. *Journal of B.U.ON.* 2019;**24**(6):2303-9.

Liu 2019b *{published data only}*

Liu J, Barry WT, Birrer MJ. A randomized phase 2 trial comparing efficacy of the combination of the PARP inhibitor olaparib and the antiangiogenic cediranib against olaparib alone in recurrent platinum-sensitive ovarian cancer. *Journal of Clinical Oncology* 2014;**32**(18):LBA5500.

Liu JF, Barry WT, Birrer M, Jung-Min L, Buckanovich RJ, Fleming GF, et al. Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. *Lancet Oncology* 2014;**15**(11):1207-14.

* Liu JF, Barry WT, Birrer M, Lee J-M, Buckanovich RJ, Fleming GF, et al. Overall survival and updated progression-free survival outcomes in a randomized phase II study of combination cediranib and olaparib versus olaparib in relapsed platinum-sensitive ovarian cancer. *Annals of Oncology* 2019;**30**(4):551-7.

Liu JF, Barry WT, Birrer MJ, Lee J-M, Buckanovich RJ, Fleming GF, et al. Overall survival and updated progression-free survival results from a randomized phase 2 trial comparing the

combination of olaparib and cediranib against olaparib alone in recurrent platinum-sensitive ovarian cancer. *Journal of Clinical Oncology* 2017;**35**(15 Suppl 1):5535.

NCT01116648. Cediranib maleate and olaparib in treating patients with recurrent ovarian epithelial cancer, fallopian tube cancer, peritoneal cancer, or recurrent triple-negative breast cancer. www.clinicaltrials.gov/ct2/show/NCT01116648 (first posted 05 May 2010).

Liu 2021a *{published data only}*

Liu M, Lu D, Gao S, Xu X, Zhang Y. Evaluation of the short-term efficacy and safety of bevacizumab combined with doxorubicin liposomes in the treatment of patients with platinum-resistant recurrent epithelial ovarian cancer. *Chinese Journal of Cancer Biotherapy* 2021;**28**(8):818-23.

Liu 2022 *{published data only}*

Liu JF, Brady MF, Matulonis UA, Miller A, Kohn EC, Swisher EM, et al. A phase III study comparing single-agent olaparib or the combination of cediranib and olaparib to standard platinumbased chemotherapy in recurrent platinum-sensitive ovarian cancer. *Journal of Clinical Oncology* 2020;**38**(15 suppl):6003.

* Liu JF, Brady MF, Matulonis UA, Miller A, Kohn EC, Swisher EM, et al. Olaparib with or without cediranib versus platinum-based chemotherapy in recurrent platinum-sensitive ovarian cancer (NRG-GY004): a randomized, open-label, phase III trial. *Journal of Clinical Oncology* 2022;**40**(19):2138-47.

NCT02446600. Testing the use of a single drug (olaparib) or the combination of two drugs (cediranib and olaparib) compared to the usual chemotherapy for women with platinum sensitive ovarian, fallopian tube, or primary peritoneal cancer. www.clinicaltrials.gov/ct2/show/NCT02446600 (first posted: 2021).

Swisher E, Miller A, Kohn E, Brady M, Radke M, Pennil C, et al. Association of homologous recombination deficiency (HRD) with clinical outcomes in a phase III study of olaparib or cediranib and olaparib compared to platinum-based chemotherapy in recurrent platinum-sensitive ovarian cancer (PSOC): Biomarker analyses from NRG-GY004. *Annals of Oncology* 2021;**32**(Suppl 5):S1309.

Matulonis 2019 *{published data only}*

* Matulonis UA, Sill MW, Makker V, Mutch DG, Carlson JW, Darus CJ, et al. A randomized phase II study of cabozantinib versus weekly paclitaxel in the treatment of persistent or recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer: an NRG Oncology/Gynecologic Oncology Group study. *Gynecolic Oncololgy* 2019;**152**(3):548-53.

NCT01716715. Cabozantinib or paclitaxel in treating patients with persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cavity cancer. www.clinicaltrials.gov/ct2/show/NCT01716715 (first posted 30 October 2012).

McGuire 2018 *{published data only}*

* McGuire WP, Penson RT, Gore M, Casado Herraez A, Peterson P, Shahir A, Ilaria R Jr. Randomized phase II study of the PDGFRα antibody olaratumab plus liposomal doxorubicin versus liposomal doxorubicin alone in patients with platinum-refractory or platinum-resistant advanced ovarian cancer. *BMC Cancer* 2018;**18**:1292.

McGuire WP, Shah GD, Loizos N, Youssoufian H, Rowinsky EK, Gore ME. Randomized phase II trial of pegylated liposomal doxorubicin (PLD) with or without anti-platelet-derived growth factor receptor-alpha (PDGFR-alpha) monoclonal antibody IMC-3G3 in platinum-refractory/resistant advanced ovarian cancer. *Journal of Clinical Oncology* 2010;**28**(15 Suppl):TPS256.

NCT00913835. A study of Liposomal Doxorubicin with or without IMC-3G3 in platinum-refractory or resistant advanced ovarian cancer. www.clinicaltrials.gov/ct2/show/NCT00913835 (first posted 04 June 2009).

METRO-BIBF 2020 *{published data only}*

Hall M, Lillywhite R, Nicum S, Lord R, Glasspool R, Feeney M, et al. METRO-BIBF Phase II, randomised, placebo controlled, multicentre, feasibility study of low dose (metronomic) cyclophosphamide (MCy) with and without nintedanib in advanced ovarian cancer (AOC). *Annals of Oncology* 2016;**27**:vi296-312.

* Hall MR, Dehbi HM, Banerjee S, Lord R, Clamp A, Ledermann JA, et al. A phase II randomised, placebo-controlled trial of low dose (metronomic) cyclophosphamide and nintedanib (BIBF1120) in advanced ovarian, fallopian tube or primary peritoneal cancer. *Gynecologic Oncology* 2020;**159**(3):692-8.

NCT01610869. Low dose cyclophosphamide +/-- nintedanib in advanced ovarian cancer (METRO-BIBF). www.clinicaltrials.gov/ct2/show/NCT01610869 (first posted 04 June 2012).

MITO-11 2015 *{published data only}*

NCT01644825. Weekly paclitaxel with or without pazopanib in platinum resistant or refractory ovarian cancer (MITO-11). www.clinicaltrials.gov/ct2/show/NCT01644825) (first posted 19 July 2012).

* Pignata S, Lorusso D, Scambia G, Sambataro D, Tamberi S, Cinieri S, et al. Pazopanib plus weekly paclitaxel versus weekly paclitaxel alone for platinum-resistant or platinum-refractory advanced ovarian cancer (MITO 11): a randomised, open-label, phase 2 trial. *Lancet Oncology* 2015;**16**(5):561-8.

Pignata S, Lorusso D, Scambia G. MITO-11: A randomized multicenter phase II trial testing the addition of pazopanib to weekly paclitaxel in platinum-resistant or -refractory advanced ovarian cancer (AOC). *Journal of Clinical Oncology* 2014;**32**:Abstract 5503.

MITO-16b 2021 *{published data only}***2012-004362-17**

NCT01802749. Bevacizumab beyond progression in platinum sensitive ovarian cancer (MITO16MANGO2b). www.clinicaltrials.gov/ct2/show/NCT01802749 (first posted 01 March 2013).

* Pignata S, Lorusso D, Joly F, Gallo C, Colombo N, Sessa C, et al. Carboplatin-based doublet plus bevacizumab beyond progression versus carboplatin-based doublet alone in patients

with platinum-sensitive ovarian cancer: a randomised, phase 3 trial. *Lancet Oncology* 2021;**22**(2):267-76.

NICCC 2020 *{published data only}***2013-002109-73ISRCTN50772895**

* Glasspool R, McNeish I, Westermann A, Hinsley S, Ledermann J, Ray-Coquard I, et al. A randomised phase II study of nintedanib (BIBF1120) compared to chemotherapy in patients with recurrent clear cell carcinoma of the ovary or endometrium (NICCC/ENGOT-OV36). *International Journal of Gynecological Cancer* 2020;**30**:A127-8.

NCT02866370. Study of nintedanib compared to chemotherapy in patients with recurrent clear cell carcinoma of the ovary or Eedometrium (NiCCC). www.clinicaltrials.gov/ct2/show/NCT02866370 (first posted 15 August 2015).

Nishikawa 2020 *{published data only}*

Nishikawa N, Shoji T, Enomoto T, Abe M, Okamoto A, Saito T, et al. Phase II trial evaluating efficacy and safety of standard of care with or without bevacizumab in platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer. *International Journal of Gynecological Cancer* 2020;**30**(Suppl 3):A10-A11.

* Shoji T, Enomoto T, Abe M, Okamoto A, Nagasawa T, Oishi T, et al. Efficacy and safety of standard of care with/without bevacizumab for platinum-resistant ovarian/fallopian tube/peritoneal cancer previously treated with bevacizumab: the Japanese Gynecologic Oncology Group study JGOG3023. *Cancer Science* 2022;**113**(1):240-50. [DOI: 10.1111/cas.15185]

OCEANS 2015 *{published data only}*

Aghajanian C, Blank S, Goff B, Judson P, Nycum L, Sovak M, et al. Results from a 2nd interim os analysis in oceans: a randomized phase 3 trial of gemcitabine (G), carboplatin (C) and bevacizumab (BV) followed by BV to disease progression in patients with platinum-sensitive recurrent epithelial ovarian (OC), primary peritoneal (PPC), or fallopian tube cancer (FTC). *Gynecologic Oncology* 2012;**125**(3):773.

Aghajanian C, Blank SV, Goff B, Judson PL, Makhija S, Sharma SK, et al. Efficacy in patient subgroups in OCEANS, a randomized, doubleblinded, placebo-controlled, phase 3 trial of chemotherapy +/- bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian (OC), primary peritoneal (PPC), or fallopian tube cancer (FTC). *European Journal of Cancer* 2011;**47**:5.

Aghajanian C, Blank SV, Goff BA, Judson PL, Nycum LR, Sovak MA, et al. An updated safety analysis of OCEANS, a randomized, double-blind, phase III trial of gemcitabine (G) and carboplatin (C) with bevacizumab (BV) or placebo (PL) followed by BV or PL to disease progression (PD) in patients with platinum-sensitive (Plat-S) recurrent ovarian cancer. *Journal of Clinical Oncology* 2012;**30**:5054.

* Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG, Husain A, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *Journal of Clinical Oncology* 2012;**30**:2039-45.

Aghajanian C, Finkler N, Rutherford T, Smith D, Yi J, Parmar H, Nycum R, Sovak MA, et al. Oceans: A randomized, Double-blinded, Placebo-controlled, Phase III trial of chemotherapy+/-bevacizumab (BEV) in platinum-sensitive recurrent epithelial ovarian cancers (EOC), primary peritoneal (PPC), or fallopian tube cancer (FTC). *International Journal of Gynecological Cancer* 2011;**21**:S11.

Aghajanian C, Finkler N, Rutherford T, Smith D, Yi J, Parmar H, et al. OCEANS: A randomized, double-blinded, placebo-controlled phase III trial of chemotherapy with or without bevacizumab (BEV) in patients with platinum-sensitive recurrent epithelial ovarian (EOC), primary peritoneal (PPC), or fallopian tube cancer (FTC). *Journal of Clinical Oncology* 2011;**29**(18):LBA5007.

Aghajanian C, Finkler NJ, Rutherford T, Smith DA, Yi J, Parmar H, et al. OCEANS: a randomized, double-blinded, placebo-controlled phase III trial of chemotherapy with or without bevacizumab (BEV) in patients with platinum-sensitive recurrent epithelial ovarian (EOC), primary peritoneal (PPC), or fallopian tube cancer (FTC). *Journal of Clinical Oncology* 2011;**29**(15):LBA5007.

* Aghajanian C, Goff B, Nycum LR, Wang YV, Husain A, Blank SV. Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. *Gynecologic Oncology* 2015;**139**(1):10-6.

Aghajanian C, Goff BA, Nycum LR, Wang Y, Husain A, Blank SV. Final analysis of overall survival in OCEANS, a randomized phase III trial of gemcitabine, carboplatin, and bevacizumab followed by bevacizumab until disease progression in patients with platinum-sensitive recurrent ovarian cancer. *Gynecologic Oncology* 2014;**133**(Suppl 1):57.

Aghajanian C, Makhija S, Rutherford T, Sharma S, Nycum L, Sovak M, et al. Independent radiologic review of OCEANS, a phase III trial of carboplatin, gemcitabine, and bevacizumab or placebo for the treatment of platinum-sensitive, recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *Gynecologic Oncology* 2012;**125**(Suppl 1):S30-31.

Aghajanian C, Nycum L, Chan JK, Husain A, Yi J, Blank SV. CA-125 in oceans: phase 3 randomized study of gemcitabine/carboplatin + bevacizumab (GC+BV) or placebo (GC+PL) in platinum-sensitive recurrent ovarian cancer. 14th Biennial Meeting of the International Gynecologic Cancer Society 2012.

NCT00434642. A study of carboplatin and gemcitabine plus bevacizumab in patients with ovary, peritoneal, or fallopian tube carcinoma (OCEANS). www.clinicaltrials.gov/ct2/show/NCT00434642 (first posted 13 February 2007).

OCTOVA 2021 *{published data only}***ISRCTN14784018**

Mansouri A, McGregor N, Dunn R, Dobbie S, Holmes J, Collins L, et al. Randomised phase II trial of olaparib, chemotherapy or olaparib and cediranib in patients with platinum-resistant ovarian cancer (OCTOVA): a study protocol. *BMJ Open* 2021;**11**(1):e041463.

NCT03117933. Olaparib +/- cediranib or chemotherapy in patients with platinum-resistant ovarian cancer (OCTOVA).

www.clinicaltrials.gov/ct2/show/NCT03117933 (first posted 18 April 2017).

* Nicum S, Holmes J, McGregor N, Dunn R, Collins L, Kaye S, et al. Randomised phase II trial of olaparib compared to weekly paclitaxel or olaparib plus cediranib in patients with platinum-resistant ovarian cancer (OCTOVA). *Annals of Oncology* 2021;**32**(Suppl 5):S725-6.

Reyners 2012 *{published data only}***https://doi.org/10.1186/ISRCTN30851756ISRCTN30851756**

ISRCTN30851756. A randomized phase II study investigating the addition of the specific cox-2 inhibitor celecoxib to docetaxel plus carboplatin as first-line chemotherapy for stage IC-IV epithelial ovarian fallopian tube or primary peritoneal carcinomas. www.isrctn.com/ISRCTN30851756 (first registered 27 January 2006). [DOI: https://doi.org/10.1186/ISRCTN30851756]

* Reyners AK, de Munck L, Erdkamp FL, Smit WM, Hoekman K, Lalisang RI, et al, DoCaCel Study Group. A randomized phase II study investigating the addition of the specific COX-2 inhibitor celecoxib to docetaxel plus carboplatin as first-line chemotherapy for stage IC to IV epithelial ovarian cancer, fallopian tube or primary peritoneal carcinomas: the DoCaCel study. *Annals of Oncology* 2012;**23**(11):2896-902. [DOI: 10.1093/annonc/mds107] [PMID: PMID: 22689176]

Richardson 2018 *{published data only}*

NCT01468909. Paclitaxel with or without pazopanib hydrochloride in treating patients with persistent or recurrent ovarian epithelial, fallopian tube, or peritoneal cavity cancer. www.clinicaltrials.gov/ct2/show/NCT01468909 (first posted 10 November 2011).

Richardson DL, Sill MW, Cho JK, Pearl ML, Kehoe SM, Hanjani P, et al. A randomized placebo controlled phase IIB trial of weekly paclitaxel plus/minus pazopanib in persistent or recurrent ovarian cancer. *International Journal of Gynecological Cancer* 2014;**24**(9):17.

* Richardson DL, Sill MW, Coleman RL, Sood Aak, Pearl ML, Kehoe SM, et al. Paclitaxel with and without pazopanib for persistent or recurrent ovarian cancer: a randomized clinical trial. *JAMA Oncology* 2018;**4**(2):196-202.

Roque 2022 *{published data only}*

NCT03093155. Evaluation of weekly ixabepilone with or without biweekly bevacizumab. www.clinicaltrials.gov/ct2/show/NCT03093155 (first posted 28 March 2017).

Roque D, Siegel E, Buza N, Bellone S, Silasi D-A, Huang G, et al. Randomized phase II trial of weekly ixabepilone with or without biweekly bevacizumab for platinum-resistant or refractory ovarian/fallopian tube/primary peritoneal cancer. *Gynecologic Oncology* 2021;**162**(Suppl 1):S58.

* Roque DM, Siegel ER, Buza N, Bellone S, Silasi DA, Huang GS, et al. Randomised phase II trial of weekly ixabepilone ± biweekly bevacizumab for platinum-resistant or refractory ovarian/fallopian tube/primary peritoneal cancer. *British Journal of Cancer* 2022;**126**(12):1695-1703. [DOI: 10.1038/s41416-022-01717-6]

Sharma 2021 *{published data only}***CTRI/2017/10/010219**

Sharma A, Khurana S, Malik PS, Singh M, Mathur S, Kumar S, et al. Quality of life, vascular endothelial growth factor inhibition, and survival outcomes with combination oral metronomic therapy in platinum refractory epithelial ovarian carcinoma: results from a randomized study. *Journal of Clinical Oncology* 2020;**38**(15 Suppl):6048.

* Sharma A, Singh M, Chauhan R, Malik PS, Khurana S, Mathur S, et al. Pazopanib based oral metronomic therapy for platinum resistant/refractory epithelial ovarian cancer: a phase II, open label, randomized, controlled trial. *Gynecologic Oncology* 2021;**162**:382-8.

SWOG-S0904 2014 *{published data only}*

Coleman RL, Moon J, Sood A, Branham D, Delmore JE, Bonebrake AJ, et al. Randomized phase II study of docetaxel plus vandetanib (D+V) versus docetaxel followed by vandetanib (D-V) in patients with persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma (OC): SWOG S0904. *Journal of Clinical Oncology* 2012;**30**(15 Suppl):5015.

* Coleman RL, Moon J, Sood AK, Hu W, Delmore JE, Bonebrake AJ, et al. Randomised phase II study of docetaxel plus vandetanib versus docetaxel followed by vandetanib in patients with persistent or recurrent epithelial ovarian, fallopian tube or primary peritoneal carcinoma: SWOG S0904. *European Journal of Cancer* 2014;**50**(9):1638-48.

NCT00872989. Docetaxel with or without vandetanib in treating patients with persistent or recurrent ovarian epithelial cancer, fallopian tube cancer, or primary peritoneal cancer. www.clinicaltrials.gov/ct2/show/NCT00872989 (first posted 01 April 2016).

TAPAZ 2022 *{published data only}*

* Joly F, Fabbro M, Berton D, Lequesne J, Anota A, Puszkiel A, et al. Paclitaxel with or without pazopanib for ovarian cancer relapsing during bevacizumab maintenance therapy: the GINECO randomized phase II TAPAZ study. *Gynecology Oncology* 2022 ;**166**(3):389-96. [DOI: 10.1016/j.ygyno.2022.06.022]

Joly Lobbedez F, Fabbro M, Berton D, Lequesne J, Anota A, Puszkiel A, et al. Paclitaxel with or without pazopanib in ovarian cancer patients with relapse during bevacizumab maintenance therapy: the GINECO randomized phase II TAPAZ study. *Annals of Oncology* 2020;**31**(Suppl 4):S611-S2.

NCT02383251. Paclitaxel/pazopanib for platinum resistant/refractory ovarian cancer (TAPAZ). www.clinicaltrials.gov/ct2/show/NCT02383251 (first posted 09 March 2015).

TRIAS 2018 *{published data only}*

* Chekerov R, Hilpert F, Mahner S, El-Balat A, Harter P, De Gregorio N, et al. Sorafenib plus topotecan versus placebo plus topotecan for platinum-resistant ovarian cancer (TRIAS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncology* 2018;**19**(9):1247-58.

Khalfaoui K, Mahner S, Richter R, Hilpert F, Lorenz R, Harter P, et al. A randomized, double-blind, placebo-controlled, multicenter phase II study to compare the efficacy and safety of sorafenib added to standard treatment with topotecan to

standard treatment alone in patients with platinum-resistant recurrent ovarian cancer (TRIAS): results of a NOGGO-AGO intergroup pilot-study. *Journal of Clinical Oncology* 2011;**29**(15 Suppl):e15548.

NCT01047891. Efficacy and safety study of sorafenib with topotecan in patients with platinum-resistant recurrent ovarian cancer (TRIAS 2009). www.clinicaltrials.gov/ct2/show/NCT01047891 (first posted 13 January 2010).

TRINOVA-1 2016 *{published data only}*

Fujiwara K, Monk BJ, Lhommé C, Coleman RL, Brize A, Oaknin A, et al. Health-related quality of life in women with recurrent ovarian cancer receiving paclitaxel plus trebananib or placebo (TRINOVA-1). *Annals of Oncology* 2016;**27**(6):1006-13. [DOI: 10.1093/annonc/mdw147]

Fujiwara K, Monk BJ, Park SY, Takeuchi S, Nakanishi T, Lim BK, et al. A subgroup analysis of trinova-1: weekly trebananib or placebo plus paclitaxel in Asian women with recurrent ovarian cancer. *International Journal of Gynecological Cancer* 2014;**24**(9 Suppl 4):231-2.

Monk BJ, Poveda A, Vergote I, Raspagliesi F, Fujiwara K, Bae DS, et al. A phase 3, randomized, double-blind trial of weekly paclitaxel plus trebananib or placebo in women with recurrent ovarian cancer: Trinova-1. *International Journal of Gynecological Cancer* 2013;**23**(8):49-50.

* Monk BJ, Poveda A, Vergote I, Raspagliesi F, Fujiwara K, Bae DS, et al. Anti-angiopoietin therapy with trebananib for recurrent ovarian cancer (TRINOVA-1): a randomised, multicentre, double-blind, placebo-controlled phase 3 trial. *Lancet Oncology* 2014;**15**(8):799-808.

* Monk BJ, Poveda A, Vergote I, Raspagliesi F, Fujiwara K, Bae DS, et al. Final results of a phase 3 study of trebananib plus weekly paclitaxel in recurrent ovarian cancer (TRINOVA-1): long-term survival, impact of ascites, and progression-free survival-2. *Gynecologic Oncology* 2016;**143**(1):27-34.

Monk BJ, Poveda A, Vergote I, Raspagliesi F, Fujiwara K, Bae DS, et al. Impact of trebananib plus weekly paclitaxel on overall survival (OS) in patients (pts) with recurrent ovarian cancer and ascites: results from the phase III TRINOVA1 study. *Journal of Clinical Oncology* 2015;**33**(15):5503.

Monk BJ, Poveda A, Vergote I, Raspagliesi F, Fujiwara K, Bae DS, et al. LBA41: A phase III, randomized, double-blind trial of weekly paclitaxel plus the angiopoietin 1 and 2 inhibitor, trebananib, or placebo in women with recurrent ovarian cancer: TRINOVA-1. *European Journal of Cancer* 2013;**49**(Suppl 3):S18.

NCT01204749. TRINOVA-1: a study of AMG 386 or placebo, in combination with weekly paclitaxel chemotherapy, as treatment for ovarian cancer, primary peritoneal cancer and fallopian tube cancer. www.clinicaltrials.gov/ct2/show/NCT01204749 (first posted 17 September 2010).

TRINOVA-2 2017 *{published data only}*

Marth C, Vergote I, Colombo N, Kurzeder C, Lorusso D, Clamp A, et al. ENGOT-ov-6/TRINOVA-2: Randomised, double-blind, phase 3 study of pegylated liposomal doxorubicin plus trebananib or placebo in women with recurrent partially platinum-sensitive or resistant ovarian cancer. *International Journal of Gynecological Cancer* 2015;**25**(Suppl 2):97-8.

* Marth C, Vergote I, Scambia G, Oberaigner W, Clamp A, Berger R, et al. ENGOT-ov-6/TRINOVA-2: Randomised, double-blind, phase 3 study of pegylated liposomal doxorubicin plus trebananib or placebo in women with recurrent partially platinum-sensitive or resistant ovarian cancer. *European Journal of Cancer* 2017;**70**:111-21.

NCT01281254. AMG 386 (Trebananib) in ovarian cancer (TRINOVA-2). www.clinicaltrials.gov/ct2/show/NCT01281254 (first posted 21 January 2011).

TRINOVA-3 2019 *{published data only}*

NCT01493505. TRINOVA-3: a study of AMG 386 or AMG 386 placebo in combination with paclitaxel and carboplatin to treat ovarian cancer. www.clinicaltrials.gov/ct2/show/NCT01493505 (first posted 21 January 2011).

* Vergote I, Scambia G, O'Malley DM, Van Calster B, Sang-Yoon P, Del Campo JM, et al. Trebananib or placebo plus carboplatin and paclitaxel as first-line treatment for advanced ovarian cancer (TRINOVA-3/ENGOT-ov2/GOG-3001): a randomised, double-blind, phase 3 trial. *Lancet Oncology* 2019;**20**(6):862-76.

Zhao 2015 *{published data only}*

NCT01838538. Clinical study in treatment of malignant ascites of ovarian cancer with intraperitoneal injection bevacizumab combined with intraperitoneal hyperthermic perfusion chemotherapy. www.clinicaltrials.gov/ct2/show/NCT01838538 (first posted 24 April 2013).

Zhao H, Du N, Fu Y, Wang H, Fan Z. Clinical study of intraperitoneal injection bevacizumab (BV) combined with intraperitoneal hyperthermic perfusion chemotherapy (CT) in treatment of malignant ascites of ovarian cancer (OC). *Journal of Clinical Oncology* 2013;**31 Suppl**:5558.

* Zhao H, Li X, Chen D, Cai J, Fu Y, Kang H, et al. Intraperitoneal administration of cisplatin plus bevacizumab for the management of malignant ascites in ovarian epithelial cancer: results of a phase III clinical trial. *Medical Oncology* 2015;**32**(2):292.

References to studies excluded from this review

ALIENOR/ENGOT-ov7 2020 *{published data only}*

Ray-Coquard I, Harter P, Lorusso D, et al. Effect of weekly paclitaxel with or without bevacizumab on progression-free rate among patients with relapsed ovarian sex cord-stromal tumors: the ALIENOR/ENGOT-ov7 randomized clinical trial. *JAMA Oncology* 2020;**6**(12):1923-30.

Ray-Coquard IL, Harter P, Lorusso D, Dalban C, Vergote IB, Fujiwara K, et al. Alienor/ENGOT-ov7 randomized trial exploring weekly paclitaxel (wP) + bevacizumab (bev) vs wP alone for patients with ovarian sex cord tumors (SCT) in relapse. *Annals of Oncology* 2018;**29**(Suppl 8):viii333.

Azad 2008 *{published data only}*

Azad N, Annunziata CM, Greenberg L, Minasian L, Kotz H, Sarosy G, et al. Combination therapy with sorafenib and bevacizumab is active in epithelail ovarian cancer. *Gynecologic Oncology* 2008;**108**(3 Suppl 1):S23.

Baumann 2012 *{published data only}*

Baumann KH, du Bois A, Meier W, Rau J, Wimberger P, Sehouli J, et al. A phase II trial (AGO 2.11) in platinum-resistant ovarian cancer: a randomized multicenter trial with sunitinib (SU11248) to evaluate dosage, schedule, tolerability, toxicity and effectiveness of a multitargeted receptor tyrosine kinase inhibitor monotherapy. *Annals of Oncology* 2012;**23**(9):2265-71.

NCT00543049. Randomized multicenter trial with SU11248 evaluating dosage, tolerability, toxicity and effectiveness of a multitargeted receptor tyrosine kinase inhibitor. www.clinicaltrials.gov/ct2/show/NCT00543049 (first posted 12 October 2007).

BOOST 2011 *{published data only}*

NCT01462890. Evaluation of optimal treatment duration of bevacizumab combination with standard chemotherapy in patients with ovarian cancer (BOOST). www.clinicaltrials.gov/ct2/show/study/NCT01462890 (first posted 1 November 2011).

Brown 2014 *{published data only}*

Brown J, Brady WE, Schink J, Van Le L, Leitao M, Yamada SD, et al . Efficacy and safety of bevacizumab in recurrent sex cord-stromal ovarian tumors: results of a phase 2 trial of the Gynecologic Oncology Group. *Cancer* 2014;**120**(3):344-51.

Burger 2010 *{published data only}*

Burger RA. Role of vascular endothelial growth factor inhibitors in the treatment of gynecologic malignancies. *Journal of Gynecologic Oncology* 2010;**21**(1):3-11.

Campos 2013 *{published data only}*

Campos SM, Penson RT, Matulonis U, Horowitz NS, Whalen C, Pereira L, et al. A phase II trial of Sunitinib malate in recurrent and refractory ovarian, fallopian tube and peritoneal carcinoma. *Gynecologic Oncology* 2013;**128**(2):215-20.

Chan 2016 *{published data only}*

Chan J, Brady M, Penson R, Monk B, Boente M, Walker J, et al. Phase III trial of every-3-weeks paclitaxel vs. dose dense weekly paclitaxel with carboplatin +/-bevacizumab in epithelial ovarian, peritoneal, fallopian tube cancer: GOG 262 (NCT01167712). *International Journal of Gynecological Cancer* 2013;**23**:Supp 1.

Chan JK, Brady MF, Penson RT, Huang H, Birrer MJ, Walker JL, et al. Weekly vs. every-3-week paclitaxel and carboplatin for ovarian cancer. *New England Journal of Medicine* 2016;**374**(8):738-48.

NCT01167712. Paclitaxel and carboplatin with or without bevacizumab in treating patients with stage III or stage IV ovarian epithelial cancer, primary peritoneal cancer, or fallopian tube cancer. clinicaltrials.gov/ct2/show/NCT01167712 (first posted 22 July 2010).

Colombo 2012 *{published data only}*

Colombo N, Mangili G, Mammoliti S, Kalling M, Tholander B, Sternas L, et al. A phase II study of aflibercept in patients with advanced epithelial ovarian cancer and symptomatic malignant ascites. *Gynecologic Oncology* 2012;**125**:42-7.

DUO-O 2018 *{published data only}*

NCT03737643. Durvalumab Ttreatment in combination with chemotherapy and bevacizumab, followed by maintenance durvalumab, bevacizumab and olaparib treatment in advanced ovarian cancer patients (DUO-O). www.clinicaltrials.gov/ct2/show/study/NCT03737643 (first posted 09 November 2018).

Okamoto A, Kim JW, Yin R, Trillsch F, Reuss A, Aghajanian C, et al. A randomized phase III trial of durvalumab with chemotherapy and bevacizumab, followed by maintenance durvalumab, bevacizumab and olaparib in newly diagnosed advanced ovarian cancer (DUO-O): updated trial endpoint and inclusion of China cohort (329). *Gynecologic Oncology* 2022;**166**(Suppl 1):S170. [DOI: 10.1016/S0090-8258(22)01551-7]

ENGOT-ov65 2021 *{published data only}*

NCT05116189. Pembrolizumab/placebo plus paclitaxel with or without bevacizumab for platinum-resistant recurrent ovarian cancer (MK-3475-B96/KEYNOTE-B96/ENGOT-ov65). www.clinicaltrials.gov/ct2/show/study/NCT05116189 (first posted 10 November 2021).

GOG-3018 2020 *{published data only}*

Arend RC, Monk BJ, Burger RA, Herzog TJ, Ledermann JA, Moore KN, et al. Clinical trial in progress: pivotal study of VB-111 combined with paclitaxel versus paclitaxel for treatment of platinum-resistant ovarian cancer (OVAL, VB-111-701/GOG-3018). *Journal of Clinical Oncology* 2020;**38**(Suppl 15):TPS6097-TPS6097.

Arend RC, Monk BJ, Herzog TJ, Ledermann JA, Moore KN, Secord AA, et al. Clinical trial in progress: pivotal study of VB-111 combined with paclitaxel versus paclitaxel for treatment of platinum-resistant ovarian cancer (OVAL, VB-111- 701/GOG-3018). *Journal of Clinical Oncology* 2021;**39**(Suppl 15):TPS5599.

Penson RT, Arend RC, Secord AA, Herraez AC, Herzog TJ, Ledermann JA, et al. Pivotal study of ofra-vec (VB-111) combined with paclitaxel versus paclitaxel for treatment of platinum-resistant ovarian cancer (OVAL, VB-111-701/GOG-3018). *Journal of Clinical Oncology* 2022;**40**(16):TPS5606. [DOI: 10.1200/JCO.2022.40.16_suppl.TPS5606]

Hagemann 2013 *{published data only}*

Hagemann AR, Novetsky AP, Zighelboim I, Gao F, Massad LS, Thaker PH, et al. Phase II study of bevacizumab and pemetrexed for recurrent or persistent epithelial ovarian, fallopian tube or primary peritoneal cancer. *Gynecologic Oncology* 2013;**131**(3):545-40.

Harter 2013 *{published data only}*

Harter P, Sehouli J, Kimmig R, Rau J, Hilpert F, Kurzeder C, et al. Addition of vandetanib to pegylated liposomal doxorubicin (PLD) in patients with recurrent ovarian cancer. A randomized

phase I/II study of the AGO Study Group (AGO-OVAR 2.13). *Investigational New Drugs* 2013;**31**(6):1499-504.

Heiss 2010 *{published data only}*

Heiss MM, Murawa P, Koralewski P, Kutarska E, Kolesnik OO, Ivanchenko VV, et al. The trifunctional antibody catumaxomab for the treatment of malignant ascites due to epithelial cancer: results of a prospective randomized phase II/III trial. *International Journal of Cancer* 2010;**127**(9):2209-21.

Ikeda 2013 *{published data only}*

Ikeda Y, Takano M, Oda K, Kouta H, Goto T, Kudoh K, et al. Weekly administration of bevacizumab, gemcitabine, and oxaliplatin in patients with recurrent and refractory ovarian cancer: a preliminary result of 19 cases. *International Journal of Gynecological Cancer* 2013;**23**(2):355-60.

Jones 2019 *{published data only}*

Jones RL, Ratain MJ, O'Dwyer PJ, Sui LL, Jassem J, Medioni J, et al. Phase II randomised discontinuation trial of brivanib in patients with advanced solid tumours. *European Journal of Cancer* 2019;**120**:132-9.

Krasner 2019 *{published data only}*

Krasner CN, Castro C, Penson RT, Roche M, Matulonis UA, Morgan MA, et al. Final report on serial phase II trials of all-intraperitoneal chemotherapy with or without bevacizumab for women with newly diagnosed, optimally cytoreduced carcinoma of Mullerian origin. *Gynecologic Oncology* 2019;**153**(2):223-9.

Ma 2022 *{published data only}*

* Ma, C. Effect of bevacizumab combined with chemotherapy on SDF-1 and CXCR4 in epithelial ovarian cancer and its prognosis. *World Journal of Surgical Oncology* 2022;**20**(1):154. [DOI: 10.1186/s12957-022-02621-2]

Markman 2009 *{published data only}*

Markman M. Antiangiogenic drugs in ovarian cancer. *Expert Opinion on Pharmacotherapy* 2009;**10**(14):2269-77.

Nasu 2022 *{published data only}*

Nasu H, Nishio S, Park J, Yoshimitsu T, Matsukuma K, Tasaki K, et al. Platinum rechallenge treatment using gemcitabine plus carboplatin with or without bevacizumab for platinum-resistant ovarian cancer. *International Journal of Clinical Oncology* 2022;**27**(4):790-801.

NCT00017303 *{published data only}*

NCT00017303. Combination chemotherapy plus IM-862 in treating patients with resected stage III ovarian cancer or primary peritoneal cancer. www.clinicaltrials.gov/ct2/show/NCT00017303 (first posted 27 February 2004).

NCT01972516 *{published data only}*

NCT01972516. A phase II study of tivozanib as maintenance therapy, post-chemotherapy, in patients with platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer. www.clinicaltrials.gov/ct2/show/study/NCT01972516 (first posted 30 October 2013).

OCTAVIA 2014 *{published data only}*

Gonzalez-Martin A, Gladieff L, Tholander B, Stroyakovsky D, Gore M, Scambia G, et al. Efficacy and safety results from OCTAVIA, a single-arm phase II study evaluating front-line bevacizumab, carboplatin and weekly paclitaxel for ovarian cancer. *European Journal of Cancer* 2013;**49**(18):3831-8.

Gonzalez-Martin A, Gladieff L, Tholander B, Stroyakovsky D, Gore M, Scambia G, et al. Updated results from OCTAVIA (front-line bevacizumab, carboplatin and weekly paclitaxel therapy for ovarian cancer). *European Journal of Cancer* 2014;**50**(4):862-3.

Gonzalez-Martin A, Gladieff L, Tholander B, Stroyakovsky D, Gore ME, Oosterkamp HM, et al. Efficacy and safety of front-line bevacizumab (BEV), weekly paclitaxel (wPAC), and q3w carboplatin (C) in elderly patients (pts) with ovarian cancer (OC): subgroup analysis of OCTAVIA. *Journal of Clinical Oncology* 2013;**31**(15 Suppl):5544.

Gonzalez-Martin A, Gladieff L, Tholander B, Stroyakovsky D, Gore ME, Segalla JG, et al. Safety of front-line bevacizumab (BEV) combined with weekly paclitaxel (wPAC) and q3w carboplatin (C) for ovarian cancer (OC): results from OCTAVIA. *Journal of Clinical Oncology* 2012;**30**(15 Suppl):5017.

Ojeda 2011 *{published data only}*

Ojeda B, Casado A, Tibau A, Redondo A, Beltran MGarcia-Martinez E, et al. Bevacizumab alone or with chemotherapy in highly pretreated, relapsed, epithelial ovarian cancer patients. *Journal of Clinical Oncology* 2011;**29**(15 Suppl):e15590.

Osterweil 2010 *{published data only}*

Markman M. Bevacizumab plus chemo extends progression-free survival: comment. Oncology Report 2010;(July-August):25.

Osterweil N. Bevacizumab plus chemo extends progression-free survival: comment. Oncology Report 2010;(July-August):25.

PACOVAR-trial 2011 *{published data only}*

Eichbaum M, Mayer C, Eickhoff R, Bischofs E, Gebauer G, Fehm T, et al. The PACOVAR-trial: A phase I/II study of pazopanib (GW786034) and cyclophosphamide in patients with platinum-resistant recurrent, pre-treated ovarian cancer. *BMC Cancer* 2011;**11**:453.

PAZOFOS 2020 *{published data only}*

* Morgan RD, Banerjee S, Hall M, Clamp AR, Zhou C, Hasan J, et al. Pazopanib and Fosbretabulin in recurrent ovarian cancer (PAZOFOS): a multi-centre, phase 1b and open-label, randomised phase 2 trial. *Gynecologic Oncology* 2020;**156**(3):545-51.

Morgan RD, Jayson GC, Banerjee S, Clamp AR, Lyon AR, Ryder WD, et al. A phase Ib and randomised phase II trial of pazopanib with or without fosbretabulin in advanced recurrent ovarian cancer. *Annals of Oncology* 2018;**29**(Suppl 8):VIII342.

Pfisterer 2021 *{published data only}*

Pfisterer J, Joly F, Kristensen G, Rau J, Mahner S, Pautier P, et al. Optimal treatment duration of bevacizumab (BEV) combined with carboplatin and paclitaxel in patients (pts) with primary epithelial ovarian (EOC), fallopian tube (FTC) or peritoneal

cancer (PPC): a multicenter open-label randomized 2-arm phase 3 ENGOT/GCIG. *Journal of Clinical Oncology* 2021;**39**(15 Suppl):5501.

Ray-Coquard 2019 *{published data only}*

Gonzalez-Martin A, Desauw C, Heitz F, Cropet C, Gargiulo P, Berger R, et al. Maintenance olaparib plus bevacizumab in patients with newly diagnosed advanced high-grade ovarian cancer: main analysis of second progression-free survival in the phase III PAOLA-1/ENGOT-ov25 trial. *European Journal of Cancer* 2022;**174**:221-31. [DOI: 10.1016/j.ejca.2022.07.022]

Joly F, Chabaud S, Cropet C, Anota, A, Demarchi M, Atasevan B, et al. Time without symptoms or toxicity (TWiST) in patients with newly diagnosed advanced ovarian cancer receiving maintenance olaparib or placebo plus bevacizumab: analysis of PAOLA-1/ENGOT-ov25 phase III trial. *Journal of Clinical Oncology* 2022;**40**(16):5562. [DOI: 10.1200/JCO.2022.40.16_suppl.5562]

Montegut C, Falandry C, Cinieri S, Montane L, Rousseau F, Joly F, et al. Safety and quality of life of first-line maintenance olaparib plus bevacizumab in older patients with advanced ovarian cancer in the paola-1 trial. *International Journal of Gynecological Cancer* 2021;**31**(Suppl 1):A201-2. [DOI: 10.1136/ijgc-2021-ESGO.346]

Pujade-Lauraine E, Brown J, Barnicle A, Rowe P, Lao-Sirieix P, Criscione S, et al. Homologous recombination repair mutation gene panels (excluding BRCA) are not predictive of maintenance olaparib plus bevacizumab efficacy in the first-line PAOLA-1/ENGOT-ov25 trial. *Gynecologic Oncology* 2021;**162**:S26-27.

* Ray-Coquard I, Pautier P, Pignata S, Perol D, Gonzalez-Martin A, Berger R, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. *New England Journal of Medicine* 2019;**381**(25):2416-28.

Schilder 2013 *{published data only}*

Schilder RJ, Sill MW, Lankes HA, Gold MA, Mannel RS, Modesitt SC, et al. A phase II evaluation of motesanib (AMG 706) in the treatment of persistent or recurrent ovarian, fallopian tube and primary peritoneal carcinomas: a Gynecologic Oncology Group study. *Gynecologic Oncology* 2013;**129**(1):86-91.

Schwandt 2014 *{published data only}*

A phase II trial Of BAY 43-9006, a novel Raf kinase inhibitor plus paclitaxel/carboplatin in women with recurrent platinum sensitive epithelial ovarian, peritoneal or fallopian tube cancer. www.clinicaltrials.gov/ct2/show/record/NCT00096200 (first posted 9 November 2004).

Schwandt A, von Gruenigen VE, Wenham RM, Frasure H, Eaton S, Fusco N, Fu P, et al. Randomized phase II trial of sorafenib alone or in combination with carboplatin/paclitaxel in women with recurrent platinum sensitive epithelial ovarian, peritoneal, or fallopian tube cancer. *Investigational New Drugs* 2014;**32**(4):729-38.

Sennino 2010 *{published data only}*

Sennino B. Two is better than one: benefits of VEGF and PDGF inhibition in ovarian cancer. *Cancer Biology and Therapy* 2010;**9**(3):183-5.

STAC 2011 *{published data only}*

Campos S, Atkinson T, Berlin S, Roche M, Whalen C, Matulonis U, et al. STAC: A phase II study of carboplatin/paclitaxel/bevacizumab followed by randomization to either bevacizumab alone or erlotinib and bevacizumab in the upfront management of patients with ovarian, fallopian tube or peritoneal cancer. *Gynecologic Oncology* 2011;**120**(1 Suppl 1):S79 Abstract 181.

Tao 2022 *{published data only}*

* Tao Y, Tang XT, Li X, Wu AS, Zhou HS, Zhou CF. Comparison of neoadjuvant chemotherapy efficiency in advanced ovarian cancer patients treated with paclitaxel plus carboplatin and intraperitoneal bevacizumab vs. paclitaxel with carboplatin. *Frontiers in Medicine* 2022;**9**:1-9. [DOI: 10.3389/fmed.2022.807377]

Tew 2014 *{published data only (unpublished sought but not used)}*

NCT00327171. Study of AVE0005 (VEGF Trap) in patients with chemoresistant advanced ovarian cancer. www.clinicaltrials.gov/ct2/show/NCT00327171 (first posted 18 May 2006).

* Tew WP, Colombo N, Ray-Coquard I, Del Campo JM, Oza A, Pereira D, et al. Intravenous aflibercept in patients with platinum-resistant, advanced ovarian cancer: results of a randomized, double-blind, phase 2, parallel-arm study. *Cancer* 2014;**120**(3):335-43.

Tew WP, Colombo N, Ray-Coquard I, Oza A, Del Campo J, Scambia G, et al. VEGF-Trap for patients (pts) with recurrent platinum-resistant epithelial ovarian cancer (EOC): preliminary results of a randomized, multicenter phase II study. *Journal of Clinical Oncology* 2007;**25**(18 Suppl):5508.

Tew 2018 *{published data only}*

NCT00886691. Bevacizumab with or without everolimus in treating patients with recurrent or persistent ovarian epithelial cancer, fallopian tube cancer, or primary peritoneal cancer. www.clinicaltrials.gov/ct2/show/NCT00886691 (first posted 23 April 2009).

* Tew WP, Sill MW, Walker JL, Secord AA, Bonebrake AJ, Schilder JM, et al. Randomized phase II trial of bevacizumab plus everolimus versus bevacizumab alone for recurrent or persistent ovarian, fallopian tube or peritoneal carcinoma: an NRG oncology/gynecologic oncology group study. *Gynecologic Oncology* 2018;**151**(2):257-63.

Tillmans 2012 *{published data only}*

Tillmanns TD, Reed ME, Privett MC, Johns AL, Walker MS, Houts AC. Phase I trial of metronomic oral topotecan in combination with pazopanib utilizing a daily dosing schedule to treat recurrent or persistent gynecologic tumors. *Journal of Clinical Oncology* 2012;**30**(15 Suppl):5014.

Tillmans 2013 *{published data only}*

Tillmanns TD, Lowe MP, Walker MS, Stepanski EJ, Schwartzberg LS. Phase II clinical trial of bevacizumab with albumin-bound paclitaxel in patients with recurrent, platinum-resistant primary epithelial ovarian or primary peritoneal carcinoma. *Gynecologic Oncology* 2013;**128**(2):221-8.

Tredan 2022 *{published data only}*

Tredan O, Provansal Gross M, Abdeddaim C, Chabaud S, Anota A, Treilleux I, et al. Regorafenib (R) or tamoxifen (T) for platinum-sensitive recurrent ovarian cancer (PSROC) with rising CA125 and no evidence of clinical or radiological disease progression: a GINECO randomized phase II trial. *Annals of Oncology* 2020;**31**(Suppl 4):S624-5.

Tredan O, Provansal M, Abdeddaim C, Lardy-Cleaud A, Hardy-Bessard AC, Kalbacher E, et al. Regorafenib or Tamoxifen for platinum-sensitive recurrent ovarian cancer with rising CA125 and no evidence of clinical or RECIST progression: a GINECO randomized phase II trial (REGOVAR). *Gynecologic Oncology* 2022;**164**(1):18-26.

Trillsch 2021 *{published data only}*

* Trillsch F, Mahner S, Czogalla B, Rottmann M, Chekerov R, Braicu EI, et al. Primary platinum resistance and its prognostic impact in patients with recurrent ovarian cancer: an analysis of three prospective trials from the NOGGO study group. *Journal of Gynecologic Oncology* 2021;**32**(3):e372021.

Vergote 2017 *{published data only}*

Buckanovich RJ, Berger R, Sella A, Sikic BI, Shen X, Ramies DA, et al. Activity of cabozantinib (XL184) in advanced ovarian cancer patients (pts): results from a phase II randomized discontinuation trial (RDT). *Journal of Clinical Oncology* 2011;**29**(15 Suppl):5008.

Gordon MS, Edelman G, Galsky MD, Smith DC, Schoffski P, Houggy K et al. An adaptive randomized discontinuation trial of XL184 (BMS-907351) in patients (pts) with advanced solid tumors. *Journal of Clinical Oncology* 2010;**28**(15 Suppl):TPS188.

NCT00940225. Study of cabozantinib (XL184) in adults with advanced malignancies. www.clinicaltrials.gov/ct2/show/NCT00940225 (first posted 15 July 2009).

* Vergote IB, Smith DC, Berger R, Kurzrock R, Vogelzang NJ, Sella A, et al. A phase 2 randomised discontinuation trial of cabozantinib in patients with ovarian carcinoma. *European Journal of Cancer* 2017;**83**:229-36.

Verschraegen 2012 *{published data only}*

Verschraegen CF, Czok S, Muller CY, Boyd L, Lee SJ, Rutledge T, et al. Phase II study of bevacizumab with liposomal doxorubicin for patients with platinum- and taxane-resistant ovarian cancer. *Annals of Oncology* 2012;**23**(12):3104-10.

Wenham 2013 *{published data only}*

Wenham RM, Lapolla J, Lin HY, Apte SM, Lancaster JM, Judson PL, et al. A phase II trial of docetaxel and bevacizumab in recurrent ovarian cancer within 12 months of prior platinum-based chemotherapy. *Gynecologic Oncology* 2013;**130**(1):19-24.

Zhang 2020 *{published data only}*

Zhang H, Chen C, Wang S, Li X, Fan T. Efficacy of bevacizumab combined with nedaplatin in the treatment of ovarian cancer and its effects on tumor markers and immunity of patients. *Journal of B.U.ON.* 2020;**25**(1):80-6.

References to studies awaiting assessment

NCT00744718 *{published data only}*

NCT00744718. Bevacizumab and carboplatin for patients with ovarian cancer. www.clinicaltrials.gov/ct2/show/study/NCT00744718 (first posted 01 September 2008).

NCT03642132 *{published data only}*

NCT03642132. Avelumab and talazoparib in untreated advanced ovarian cancer (JAVELIN OVARIAN PARP 100). www.clinicaltrials.gov/ct2/show/study/NCT03642132 (first posted 22 August 2018).

References to ongoing studies

ICON9 2021 *{published data only}*

* Elyashiv O, Ledermann J, Parmar G, Farrelly L, Counsell N, Feeney A, et al. ICON 9 - an international phase III randomized study to evaluate the efficacy of maintenance therapy with olaparib and cediranib or olaparib alone in patients with relapsed platinum-sensitive ovarian cancer following a response to platinum-based chemotherapy. *International Journal of Gynecological Cancer* 2021;**31**(1):134-8.

NCT03278717. Study evaluating the efficacy of maintenance olaparib and cediranib or olaparib alone in ovarian cancer patients (ICON9). www.clinicaltrials.gov/ct2/show/NCT03278717 (first posted 12 September 2017).

NCT00635193 *{published data only}*

NCT00635193. Efficacy and safety study of M200 (volociximab in combination with liposomal doxorubicin). www.clinicaltrials.gov/ct2/show/NCT00635193 (first posted 13 March 2008).

NCT02584478 *{published data only}*

NCT02584478. Phase 1/2a/3 Evaluation of adding AL3818 to standard platinum-based chemotherapy in subjects with recurrent or metastatic endometrial, ovarian, fallopian, primary peritoneal or cervical carcinoma (AL3818-US-002) (AL3818). www.clinicaltrials.gov/ct2/show/study/NCT02584478 (first posted 22 October 2015).

NCT02839707 *{published data only}*

NCT02839707. Pegylated liposomal doxorubicin hydrochloride with atezolizumab and/or bevacizumab in treating patients with recurrent ovarian, fallopian tube, or primary peritoneal cancer. www.clinicaltrials.gov/ct2/show/study/NCT02839707 (first posted 21 July 2016).

NCT03095001 *{published data only}*

NCT03095001. Intraperitoneal chemotherapy alone or in combination with bevacizumab for ovarian cancer with peritoneal adhesion. www.clinicaltrials.gov/ct2/show/study/NCT03095001 (first posted 29 March 2017).

NCT03262545 *{published data only}*

NCT03262545. Efficacy and safety of apatinib as third line therapy in patients with advanced ovarian cancer. www.clinicaltrials.gov/ct2/show/NCT03262545 (first posted 25 August 2017).

NCT03462212 *{published data only}*

NCT03462212. Carboplatin-paclitaxel-bevacizumab vs carbo-pacli-beva-rucaparib vs carbo-pacli-ruca, selected according to hrd status, in patients with advanced ovarian, primary peritoneal and fallopian tube cancer, preceded by a phase i dose escalation study on ruca-beva combination (MITO25). www.clinicaltrials.gov/ct2/show/NCT03462212 (first posted 12 March 2018).

Scambia G, Salutari V, Musacchio L, Siena S, Pignata S Zavallone L, et al. 45TiP A randomized, molecular driven phase II trial of carboplatin-paclitaxel-bev vs carboplatin-paclitaxel-bev-rucaparib vs carboplatin-paclitaxel-rucaparib, selected according to HRD status, in patients with advanced ovarian cancer. *Annals of Oncology* 2022;**33**(Suppl 5):S401.

NCT03635489 *{published data only}*

NCT03635489. A study of the efficacy and safety of bevacizumab in chinese women with newly diagnosed, previously untreated stage III or stage IV epithelial ovarian, fallopian tube, or primary peritoneal cancer. www.clinicaltrials.gov/ct2/show/NCT03635489 (first posted 17 August 2018).

NCT04908787 *{published data only}*

NCT04908787. A phase III study of BD0801 combined with chemotherapy in recurrent, platinum-resistant epithelial ovarian cancer. www.clinicaltrials.gov/ct2/show/NCT04908787 (first posted 01 June 2021).

NCT04919629 *{published data only}*

NCT04919629. APL-2 and pembrolizumab versus APL-2, pembrolizumab and bevacizumab versus bevacizumab alone for the treatment of recurrent ovarian, fallopian tube, or primary peritoneal cancer and malignant effusion. www.clinicaltrials.gov/ct2/show/study/NCT04919629 (first posted 09 June 2021).

NCT05009082 *{published data only}*

Heitz F, Marth C, Henry S, Reuss A, Cibula D, Gaba L, et al. AGO-OVAR 28/ENGOT-ov57: niraparib versus niraparib in combination with bevacizumab in patients with carboplatin-taxane based chemotherapy in advanced ovarian cancer-A multicenter, randomized, phase III trial. *Journal of Clinical Oncology* 2022;**40**(16):TPS5612. [DOI: 10.1200/JCO.2022.40.16_suppl.TPS5612]

NCT05009082. Niraparib vs niraparib plus bevacizumab in patients with platinum/taxane-based chemotherapy in advanced ovarian cancer. www.clinicaltrials.gov/ct2/show/study/NCT05009082 (first posted 17 August 2021).

NCT05043402 *{published data only}*

NCT05043402. A study of navicixizumab in patients with platinum resistant ovarian cancer. www.clinicaltrials.gov/ct2/show/NCT05043402 (first posted 14 September 2021).

NCT05170594 *{published data only}*

NCT05170594. A study of bevacizumab combined with fluzoparib/chemotherapy or fluzoparib in the treatment of ovarian cancer. www.clinicaltrials.gov/ct2/show/NCT05170594 (first posted 28 December 2021).

NCT05183984 *{published data only}*

NCT05183984. Niraparib with bevacizumab after complete cytoreduction in patients with ovarian cancer (NIRVANA-1). www.clinicaltrials.gov/ct2/show/study/NCT05183984 (first posted 11 January 2022).

NCT05523440 *{published data only}*

NCT05523440. Bevacizumab and/or niraparib in patients with recurrent endometrial and/or ovarian cancer with ARID1A mutation (ARID1A). www.clinicaltrials.gov/ct2/show/study/NCT05523440 (first posted 31 August 2022).

Additional references

Abrams 2003

Abrams TJ, Murray LJ, Pesenti E, Holway VW, Colombo T, Lee LB, et al. Preclinical evaluation of the tyrosine kinase inhibitor SU11248 as a single agent and in combination with "standard of care" therapeutic agents for the treatment of breast cancer. *Molecular Cancer Therapeutics* 2003;**2**(10):1011-21.

Ahmed 2010

Ahmed AA, Etemadmoghadam D, Temple J, Lynch AG, Riad M, Sharma R, et al. Driver mutations in TP53 are ubiquitous in high grade serous carcinoma of the ovary. *Journal of Pathology* 2010;**221**(1):49-56.

Alvarez Secord 2021

Alvarez Secord A, O'Malley DM, Sood AK, Westin SN, Liu JF. Rationale for combination PARP inhibitor and antiangiogenic treatment in advanced epithelial ovarian cancer: a review. *Gynecologic Oncology* 2021;**162**(2):482-95.

Berek 2018

Berek JS, Kehoe ST, Kumar L, Friedlander M. Cancer of the ovary, fallopian tube, and peritoneum. *International Journal of Gynecology & Obstetrics* 2018;**143**(Suppl 2):59-78.

BGCS 2017

Fotopoulou C, Hall M, Cruickshank D, Gabra H, Ganesan R, Hughes C, et al. British Gynaecological Cancer Society (BGCS) epithelial ovarian / fallopian tube / primary peritoneal cancer guidelines: recommendations for practice. *European Journal of Obstetrics, Gynecology and Reproductive Biology* 2017;**213**:123-39. [DOI: 10.1016/j.ejogrb.2017.04.016] [URL: www.rcog.org.uk/en/guidelines-research-services/guidelines/clinical-governance-advice-1a/]

Bhide 2010

Bhide RS, Lombardo LJ, Hunt JT, Cai ZW, Barrish JC, Galbraith S, et al. The antiangiogenic activity in xenograft models of brivanib, a dual inhibitor of vascular endothelial growth factor receptor-2 and fibroblast growth factor receptor-1 kinases. *Molecular Cancer Therapeutics* 2010;**9**(2):369-78.

Brave 2011

Brave SR, Ratcliffe K, Wilson Z, James NH, Ashton S, Wainwright A, et al. Assessing the activity of cediranib, a VEGFR-2/3 tyrosine kinase inhibitor, against VEGFR-1 and

members of the structurally related PDGFR family. *Molecular Cancer Therapeutics* 2011;**10**(5):861-73.

Broekman 2021

Broekman KE, van Kruchten M, van Tinteren H, Sessa C, Jalving M, Reyners AK. Clinical benefit of systemic therapies for recurrent ovarian cancer-ESMO-MCBS scores. *ESMO Open* 2021;**6**(4):100229.

Burger 2007

Burger RA, Sill MW, Monk BJ, Greer BE, Sorosky JI, Gynecologic Oncology Group Study. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer. *Journal of Clinical Oncology* 2007;**25**(33):5165-71.

Cai 2008

Cai ZW, Zhang Y, Borzilleri RM, Qian L, Barbosa S, Wei D, et al. Discovery of brivanib alaninate ((S)-((R)-1-(4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-5-methylpyrrolo[2,1-f][1,2,4] triazin-6-yloxy)propan-2-yl)2-aminopropanoate), a novel prodrug of dual vascular endothelial growth factor receptor-2 and fibroblast growth factor receptor-1 kinase inhibitor (BMS-540215). *Journal of Medicinal Chemistry* 2008;**51**(6):1976-80.

Cancer Research UK 2022

Cancer Research UK. Ovarian cancer five-year net survival by stage, with incidence by stage (all data: adults diagnosed 2013-2017, followed up to 2018). www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer/survival#heading-Three (accessed 22 December 2022).

Cannistra 2007

Cannistra SA, Matulonis UA, Penson RT, Hambleton J, Dupont J, Mackey H, et al. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. *Journal of Clinical Oncology* 2007;**25**(33):5180-6.

Carlomagno 2002

Carlomagno F, Vitagliano D, Guida T, Ciardiello F, Tortora G, Vecchio G, et al. ZD6474, an orally available inhibitor of KDR tyrosine kinase activity, efficiently blocks oncogenic RET kinases. *Cancer Research* 2002;**62**(24):7284-90.

Chesney 2020

Chesney TR, Haas B, Coburn NG, Mahar AL, Zuk V, Zhao H, et al. Patient-centered time-at-home outcomes in older adults after surgical cancer treatment. *JAMA Surgery* 2020;**155**(11):e203754.

Chilimoniuk 2022

Chilimoniuk Z, Rocka A, Stefaniak M, Tomczyk Z, Jasielska F, Madras D, et al. Molecular methods for increasing the effectiveness of ovarian cancer treatment: a systematic review. *Future Oncology* 2022;**18**(13):1627-50.

Choi 2015

Choi HJ, Armaiz Pena GN, Pradeep S, Cho MS, Coleman RL, Sood AK. Anti-vascular therapies in ovarian cancer: moving beyond anti-VEGF approaches. *Cancer Metastasis Rev* 2015;**34**(1):19-40.

Ciombor 2014

Ciombor KK, Berlin J. Aflibercept - a decoy VEGF receptor. *Current Oncology Reports* 2014;**16**(2):368.

Coleridge 2021

Coleridge SL, Bryant A, Kehoe S, Morrison J. Neoadjuvant chemotherapy before surgery versus surgery followed by chemotherapy for initial treatment in advanced ovarian epithelial cancer. *Cochrane Database of Systematic Reviews* 2021, Issue 7. Art. No: CD005343. [DOI: 10.1002/14651858.CD005343.pub6]

Colombo 2019

Colombo N, Sessa C, du Bois A, Ledermann J, McCluggage WG, McNeish I, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. *Annals of Oncology* 2019;**30**(5):672-705.

Covidence [Computer program]

Veritas Health Innovation Covidence. Melbourne, Australia: Veritas Health Innovation, accessed 2019. Available at covidence.org.

CROWN 2022

CROWN Initiative. Core outcomes in women's and newborn health. www.crown-initiative.org. Accessed 3 September 2022.

CTEP 2006

Cancer Therapy Evaluation Program (CTEP). Common terminology criteria for adverse events (CTCAE), version 3.0, DCTD, NCI, NIH, DHHS; August 2006. ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf (accessed prior to 12 April 2023).

Deeks 2001

Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Davey Smith G, Altman DG, editors(s). Systematic Reviews in Health Care: Meta-Analysis in Context. 2nd edition. London, UK: BMJ Publication Group, 2001.

Ding 2019

Ding J, Cheng XY, Liu S, Ji HY, Lin M, Ma R, et al. Apatinib exerts anti-tumour effects on ovarian cancer cells. *Gynecologic Oncology* 2019;**153**(1):165-74.

Donovan 2014

Donovan KA, Donovan HS, Cella D, Gaines ME, Penson RT, Plaxe SC, et al. Recommended patient-reported core set of symptoms and quality-of-life domains to measure in ovarian cancer treatment trials. *Journal of the National Cancer Institute* 2014;**106**(7):dju128. [DOI: 10.1093/jnci/dju128] [PMCID: PMC4110471] [PMID: 25006190]

Engel 2002

Engel J, Eckel R, Schubert-Fritschle G, Kerr J, Kuhn W, Diebold J, et al. Moderate progress for ovarian cancer in the last 20 years: prolongation of survival, but no improvement in the cure rate. *European Journal of Cancer* 2002;**38**(18):2435-45.

Erber 2004

Erber R, Thurnher A, Katsen AD, Groth G, Kerger H, Hammes HP, et al. Combined inhibition of VEGF and PDGF signaling enforces tumor vessel regression by interfering with pericyte-mediated endothelial cell survival mechanisms. *FASEB Journal* 2004;**18**(2):338-40.

Ferrara 2004

Ferrara N, Hillan KJ, Gerber HP, Novotny W. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. *Nature Reviews Drug Discovery* 2004;**3**(5):391-400.

Fidler 1994

Fidler IJ, Ellis LM. The implications of angiogenesis for the biology and therapy of cancer metastasis. *Cell* 1994;**79**(2):185-8.

Folkman 1990

Folkman J. What is the evidence that tumors are angiogenesis dependent? *Journal of National Cancer Institute* 1990;**82**(1):4-6.

GLOBOCAN 2020

Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians* 2021;**71**:209-49. [DOI: 10.3322/caac.21660]

Helali 2022

Helali AE, Wong CH, Choi HC, Chan WW, Dickson N, Siu SW, et al. A comprehensive systematic review and network meta-analysis: the role of anti-angiogenic agents in advanced epithelial ovarian cancer. *Scientific Reports* 2022;**12**(1):3803.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60.

Higgins 2011

Higgins JP, Altman DG, Sterne JA, on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group. Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1/.

Hilberg 2008

Hilberg F, Roth GJ, Krssak M, Kautschitsch S, Sommergruber W, Tontsch-Grunt U, et al. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. *Cancer Research* 2008;**68**(12):4774-82.

Hirte 2021

Hirte H, Yao X, Ferguson SE, May T, Elit L. Consolidation or maintenance systemic therapy for newly diagnosed stage II, III, or IV epithelial ovary, fallopian tube, or primary peritoneal carcinoma: a systematic review. *Critical Reviews in Oncology-Hematology* 2021;**162**:103336.

Kurman 2011

Kurman RJ, Shih IM. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer--shifting the paradigm. *Human Pathology* 2011;**42**(7):918-31.

Kurman 2013

Kurman RJ. Origin and molecular pathogenesis of ovarian high-grade serous carcinoma. *Annals of Oncology* 2013;**24 Suppl 10**:x16-21.

Labidi-Galy 2017

Labidi-Galy SI, Papp E, Hallberg D, Niknafs N, Adleff V, Noe M, et al. High grade serous ovarian carcinomas originate in the fallopian tube. *Nature Communications* 2017;**8**(1):1093.

Ledermann 2013

Ledermann JA, Raja FA, Fotopoulou C, Gonzalez-Martin A, Colombo N, Sessa C, et al. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2013;**24 Suppl 6**:vi24-32.

Lefebvre 2022

Lefebvre C, Glanville J, Briscoe S, Featherstone R, Littlewood A, Marshall C, et al. Chapter 4: Searching for and selecting studies. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.

Liu 2021b

Liu S, Kasherman L, Fazelzad R, Wang L, Bouchard-Fortier G, Lheureux S, et al. The use of bevacizumab in the modern era of targeted therapy for ovarian cancer: A systematic review and meta-analysis. *Gynecologic Oncology* 2021;**161**(2):601-12.

Masferrer 1999

Masferrer JL, Koki A, Seibert K. COX-2 inhibitors. A new class of antiangiogenic agents. *Annals of the New York Academy of Sciences* 1999;**889**:84-6.

Masferrer 2000

Masferrer JL, Leahy KM, Koki AT, Zweifel BS, Settle SL, Woerner BM, et al. Antiangiogenic and antitumor activities of cyclooxygenase-2 inhibitors. *Cancer Research* 2000;**60**(5):1306-11.

McDonald 2002

McDonald DM, Baluk P. Significance of blood vessel leakiness in cancer. *Cancer Research* 2002;**62**(18):5381-5.

Mendel 2003

Mendel DB, Laird AD, Xin X, Louie SG, Christensen JG, Li G, et al. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. *Clinical Cancer Research* 2003;**9**(1):327-37.

Mercieca-Bebber 2016

Mercieca-Bebber R, Friedlander M, Kok P-S, Calvert M, Kyte D, Stockler M, et al. The patient-reported outcome content of international ovarian cancer randomised controlled trial protocols. *Quality of Life Research* 2016;**25**(10):2457-65.

Morrison 2018

Morrison J, Thoma C, Goodall RJ, Lyons TJ, Gaitskell K, Wiggans AJ, Bryant A. Epidermal growth factor receptor blockers for the treatment of ovarian cancer. *Cochrane Database of Systematic Reviews* 2018, Issue 10. Art. No: CD007927. [DOI: 10.1002/14651858.CD007927.pub4]

Mross 2007

Mross K, Steinbild S, Baas F, Gmehling D, Radtke M, Voliotis D, et al. Results from an in vitro and a clinical/pharmacological phase I study with the combination irinotecan and sorafenib. *European Journal of Cancer* 2007;**43**(1):55-63.

NCCN 2022

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: ovarian cancer including fallopian tube cancer and primary peritoneal cancer. NCCN Guidelines. Available from www.nccn.org/guidelines/guidelines-detail?category=1&id=1453 2022;**Version 1**(January 18).

NCI-DCTD-Cediranib 2022

National Cancer Institute: Division of Cancer Treatment and Diagnosis. NCI Formulary: Cediranib (AZD2171, RECENTIN). Available at: nciformulary.cancer.gov/available_agents/Cediranib.htm Last updated: 22 April 2022.

Neal 2010

Neal J, Wakelee H. AMG-386, a selective angiopoietin-1/-2-neutralizing peptibody for the potential treatment of cancer. *Current Opinion in Molecular Therapeutics* 2010;**12**(4):487-95.

Newhouse 2023

Newhouse R, Nelissen E, El-Shakankery K, Rogozińska E, Bain E, Veiga S, Morrison J. Pegylated liposomal doxorubicin for relapsed epithelial ovarian cancer. *Cochrane Database of Systematic Reviews* In press.

NICE 2022

NICE (National Institute for Health and Care Excellence). British National Formulary (BNF). Available from bnf.nice.org.uk/ 2022.

Oehler 2000

Oehler MK, Caffier H. Prognostic relevance of serum vascular endothelial growth factor in ovarian cancer. *Anticancer Research* 2000;**20**(6D):5109-12.

Oliner 2004

Oliner J, Min H, Leal J, Yu D, Rao S, You E, et al. Suppression of angiogenesis and tumor growth by selective inhibition of angiopoietin-2. *Cancer Cell* 2004;**6**(5):507-16.

Prat 2012

Prat J. New insights into ovarian cancer pathology. *Annals of Oncology* 2012;**23**(Suppl 10):x111-7.

Prat 2018

Prat J, D'Angelo E, Espinosa I. Ovarian carcinomas: at least five different diseases with distinct histological features and molecular genetics. *Human Pathology* 2018;**80**:11-27.

Qi 2021

Qi J, Liu E, Yue H, Chen G, Liu Y, Chen J. Evaluation of safety and efficacy of apatinib combination with chemotherapy for ovarian cancer treatment: a systematic review and meta-analysis. *Annals of Palliative Medicine* 2021;**10**(9):9902-13.

Quinn 2001

Quinn M, Babb B, Brock A, Jones J. Cancer Trends in England and Wales. London, UK: The Stationery Office, 2001.

Schemper 2009

Schemper M, Wakounig S, Heinze G. The estimation of average hazard ratios by weighted Cox regression. *Statistics in Medicine* 2009;**28**:2473-89. [DOI: 10.1002/sim.3623]

Schünemann 2017a

Schünemann HJ, Oxman AD, Higgins JP, Vist GE, Glasziou P, Akl E, et al, on behalf of the Cochrane GRADEing Methods Group and the Cochrane Statistical Methods Group. Chapter 11: Completing 'Summary of findings' tables and grading the confidence in or quality of the evidence. In: Higgins JP, Churchill R, Chandler J, Cumpston MS (editors), Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017). Cochrane, 2017. Available from handbook.cochrane.org.

Schünemann 2017b

Schünemann HJ, Oxman AD, Vist GE, Higgins JP, Deeks JJ, Glasziou P, et al, on behalf of the Cochrane Applicability and Recommendations Methods Group. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JP, Churchill R, Chandler J, Cumpston MS (editors), Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017). Available from www.training.cochrane.org/handbook.

Schünemann 2019

Schünemann HJ, Santesso N, Brozek JL. Interactive summary of findings tables: the way to present and understand results of systematic reviews. *JBI Database Systematic Reviews and Implementation Reports* 2019;**17**(3):259-60.

Sehouli 2011

Sehouli J, Stengel D, Harter P, Kurzeder C, Belau A, Bogenrieder T, et al. Topotecan weekly versus conventional 5-day schedule in patients with platinum-resistant ovarian cancer: a randomized multicenter phase II trial of the North-Eastern German Society of Gynecological Oncology Ovarian Cancer Study Group. *Journal of Clinical Oncology* 2011;**29**:242-48.

Sehouli 2017

Sehouli J, Tomè O, Dimitrova D, Camara O, Runnebaum IB, Tessen HW, et al. A phase III, open label, randomized multicenter controlled trial of oral versus intravenous treosulfan in heavily pretreated recurrent ovarian cancer: a study of the

North-Eastern German Society of Gynecological Oncology (NOGGO). *Journal of Cancer Research and Clinical Oncology* 2017;**143**(3):541-50. [DOI: 10.1007/s00432-016-2307-0] [PMID: 27896440]

Shih 2021

Shih I M, Wang Y, Wang T L. The origin of ovarian cancer species and precancerous landscape. *American Journal of Pathology* 2021;**191**(1):26-39.

Siegel 2021

Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. *CA: A Cancer Journal for Clinicians* 2021;**71**:7-33.

Siu 2006

Siu LL, Awada A, Takimoto CH, Piccart M, Schwartz B, Giannaris T, et al. Phase I trial of sorafenib and gemcitabine in advanced solid tumors with an expanded cohort in advanced pancreatic cancer. *Clinical Cancer Research* 2006;**12**(1):144-51.

Sonpavde 2007

Sonpavde G, Hutson TE. Pazopanib: a novel multitargeted tyrosine kinase inhibitor. *Current Oncology Reports* 2007;**9**(2):115-9. [PMID: 17288876]

Stewart 1999

Stewart L, Advanced Ovarian Cancer Trialists Group. Chemotherapy for advanced ovarian cancer. *Cochrane Database of Systematic Reviews* 1999, Issue 1. Art. No: CD001418. [DOI: 10.1002/14651858.CD001418]

Tattersall 2022

Tattersall A, Ryan N, Wiggans AJ, Rogozinska E, Morrison J. Poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of ovarian cancer. *Cochrane Database of Systematic Reviews* 2022, Issue 2. Art. No: CD007929. [DOI: 10.1002/14651858.CD007929.pub4]

Tian 2011

Tian S, Quan H, Xie C, Guo H, Lu F, Xu Y, et al. YN968D1 is a novel and selective inhibitor of vascular endothelial growth factor receptor-2 tyrosine kinase with potent activity in vitro and in vivo. *Cancer Science* 2011;**102**(7):1374-80.

Tierney 2007

Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;**8**:1-16. [DOI: 10.1186/1745-6215-8-16]

Wedge 2002

Wedge SR, Ogilvie DJ, Dukes M, Kendrew J, Chester R, Jackson JA, et al. ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. *Cancer Research* 2002;**62**(16):4645-55.

Wedge 2005

Wedge SR, Kendrew J, Hennequin LF, Valentine PJ, Barry ST, Brave SR, et al. AZD2171: a highly potent, orally bioavailable, vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor for the treatment of cancer. *Cancer Research* 2005;**65**(10):4389-400.

WHO 2020

WHO Classification of Tumours Editorial Board. WHO Classification of Tumours 5th Edition: Female Genital Tumours. Lyon, France: International Agency for Research on Cancer, 2020.

Xue 2021

Xue L, Gao X, Zhang H, Tang J, Wang Q, Li F, et al. Antiangiogenic antibody BD0801 combined with immune checkpoint inhibitors achieves synergistic antitumor activity and affects the tumor microenvironment. *BMC Cancer* 2021;**21**:1134. [DOI: https://doi.org/10.1186/s12885-021-08859-5]

Yakes 2011

Yakes FM, Chen J, Tan J, Yamaguchi K, Shi Y, Yu P, et al. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. *Molecular Cancer Therapeutics* 2011;**10**(12):2298-308.

Zhang 2009

Zhang F, Tang Z, Hou X, Lennartsson J, Li Y, Koch AW, et al. VEGF-B is dispensable for blood vessel growth but critical for their survival, and VEGF-B targeting inhibits pathological angiogenesis. *Proceedings of the National Academy of Sciences* 2009;**106**(15):6152-157.

References to other published versions of this review

Gaitskell 2011

Gaitskell K, Martinek I, Bryant A, Kehoe S, Nicum S, Morrison J. Angiogenesis inhibitors for the treatment of ovarian cancer. *Cochrane Database of Systematic Reviews* 2011, Issue 9. Art. No: CD007930. [DOI: 10.1002/14651858.CD007930.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

AGO-OVAR 12 2020

Study characteristics	
Methods	A two-arm, double-blind, multi-centre, international, phase III randomised placebo-controlled trial

AGO-OVAR 12 2020 *(Continued)*

Participants	1366 women recruited by 9 study groups. Participants were ≥ 18 years old, with advanced-stage (FIGO stage IIB-IV) epithelial ovarian cancer, fallopian tube or primary peritoneal cancer, and upfront debulking surgery. Participants had to have a life expectancy of at least 6 months, and Eastern Cooperative Oncology group (ECOG) performance status 0-2. FIGO stage by intervention groups: Placebo group: FIGO stage IIB-III, N = 344 (75.6%); stage IV, N = 111 (24.4%) Nintedanib group: FIGO stage IIB-III, N = 690 (75.7%); stage IV, N = 221 (24.3%) Macroscopic residual postoperative tumour by intervention groups: Placebo group: no residual tumour, N = 463 (50.8%); Yes, N = 448 (49.2%) Nintedanib group: no residual tumour, N = 230 (50.5%); Yes, N = 225 (49.5%)
Interventions	Participants randomised to one of two arms: Arm I (nintedanib) (n = 911): six courses of paclitaxel (175 mg/m^2)and carboplatin (AUC5 or 6) chemotherapy, plus oral nintedanib (BIBF 1120) 200 mg twice daily, followed by nintedanib monotherapy for up to 120 weeks. Arm II (placebo) (n = 455): six courses of paclitaxel (175 mg/m^2)and carboplatin (AUC5 or 6) chemotherapy, plus oral placebo twice daily, followed by placebo monotherapy for up to 120 weeks.
Outcomes	**Primary**: PFS **Secondary:** • PFS (according to RECIST v1.1) • OS • Time to tumour marker progression • Objective response • Adverse events • Changes in safety laboratory parameters
Notes	This study was included in the previous version of this review, based on results from conference abstracts. The full results have since been published. Industry-sponsored trial (funded by Boehringer Ingelheim) with several authors disclosing a financial conflict of interest. Protocol online at: www.clinicaltrials.gov/show/NCT01015118

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A third-party interactive voice or web-based randomisation system
Allocation concealment (selection bias)	Low risk	A third-party interactive voice or web-based randomisation system
Blinding of participants and personnel (performance bias)	Low risk	Participants, investigators, and independent radiological reviewers were masked to treatment allocation.

AGO-OVAR 12 2020 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, investigators, and independent radiological reviewers were masked to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis
Selective reporting (reporting bias)	Low risk	Analyses as prespecified in the trial protocol
Other bias	Unclear risk	An industry-sponsored trial with several authors disclosing receipt of personal grants and funding from the industry

AGO-OVAR 16 2019

Study characteristics	
Methods	Phase III, randomised, double-blind, multi-centre, international, placebo-controlled trial (14 co-operative study groups, based at sites in 17 countries in Europe, Asia, North America and Australia).
Participants	1114 women were recruited, of whom 940 were randomised (468 allocated to placebo, 472 allocated to pazopanib). Participants were women ≥ 18 years old, with histologically confirmed FIGO stage II-IV epithelial ovarian, fallopian or primary peritoneal carcinoma that was treated with surgical debulking either upfront or as interval debulking, and who had received 5 or more cycles of platinum-taxane-based chemotherapy. Had to have no evidence of disease progression after first-line treatment, no persisting bulky disease (> 2 cm) or no other defined need for imminent second-line therapy. Median age at entry to trial by intervention groups: Placebo group: median age 57 (range 20 to 85) Pazopanib group: median age 56 (range 25 to 85) Eastern Cooperative Oncology group (ECOG) performance status (PS) by intervention groups: Placebo group: ECOG PS 0, n = 359 (76.7%); PS 1, n = 105 (22.4%), PS 2, n = 4 (0.9%). Pazopanib group: ECOG PS 0, n = 361 (76.5%); PS 1, n = 109 (23.1%); PS 2, n = 2 (0.4%). FIGO stage by intervention groups: Placebo group: FIGO stage II, n = 43 (9.2%), stage III, n = 346 (73.9%), stage IV, n = 79 (16.9%) Pazopanib group: FIGO stage II: n = 40 (8.5%), stage III, n = 355 (75.2%), stage IV, n = 77 (16.3%)
Interventions	Randomisation to pazopanib monotherapy (800 mg/day) or matching placebo (800 mg/day), until disease progression (as defined by RECIST version 1.0), unacceptable toxicity, or withdrawal of consent. The study protocol was initially for treatment for 12 months, but this was subsequently changed (via a protocol amendment) to 24 months. A small proportion of participants (6% to 7% of each treatment arm) received planned treatment for only 12 months.
Outcomes	**Primary:** PFS

AGO-OVAR 16 2019 *(Continued)*

Secondary

- OS
- PFS by GCIG criteria
- Safety/adverse events
- Health-related quality of life (HRQoL) assessed by the instruments European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 version 3.0, ovarian cancer module OV-28, and the EuroQOL EQ-5D version 1.

Notes	We contacted study investigators, who kindly provided additional details regarding methods. Protocol online at: clinicaltrials.gov/show/NCT00866697 Extension trial in Asian women: NCT01227928 (see supplementary reference for this study).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The paper states: "Random assignment was performed with a 1:1 ratio and was stratified by (1) first-line treatment outcome … and (2) geographic region." Additional details obtained from trial statistician: "The randomization method was permuted block randomization with block size of 4."
Allocation concealment (selection bias)	Unclear risk	Unclear, potentially high risk (with a permuted block of defined size, could potentially predict future allocation towards end of each block).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial protocol (at ClinicalTrials.gov) specifies that the study is "Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)". Additional info from trial statistician, Karrie Wang: "The study was double-blinded and was un-blinded in Feb of 2013."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The trial protocol (at ClinicalTrials.gov) specifies that the study is "Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)" Additional information from trial statistician: "The efficacy outcome was firewalled to both clinical and statistical members of the study until the clinical cutoff date was reached."
Incomplete outcome data (attrition bias) All outcomes	Low risk	1114 participants screened; 174 did not meet inclusion criteria; 940 randomised; all participants accounted for at end of study and displayed on CONSORT flowchart. Detailed numbers and reasons given for treatment discontinuations, and deviations from protocol or treatment allocation are documented.
Selective reporting (reporting bias)	Low risk	We reviewed the trial protocol at ClinicalTrials.gov. The main outcomes reported in the published paper(s) (PFS, OS, PFS by GCIG criteria, safety and tolerability, and QoL) were all specified in the original protocol.
Other bias	Unclear risk	An industry-sponsored trial with several authors disclosing receipt of personal grants and funding from the industry.

AMBITION 2022

Study characteristics

AMBITION 2022 *(Continued)*

Methods	A randomised, open-label, multi-centre, phase II study for HRD+ patients
Participants	• 70 participants randomised in this study in total; 30 randomised in the comparison relevant to this review. • 20 years or older • Histologically-confirmed high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancers which tested positive for HRD (homologous recombination deficiency) • At least 2 prior lines of anticancer therapy • Disease progression within 6 months of completing platinum-based chemotherapy (i.e. recurrent platinum-resistant) or primary platinum-refractory disease • ECOG performance status 0 to 1 • Median age (range): olaparib + cediranib: 58.00 (57.00 to 76.00); olaparib + durvalumab: 52.50 (45.00 to 72.00)
Interventions	**Intervention** - olaparib 200 mg orally twice daily + cediranib 30 mg orally once daily until disease progression **Control** - olaparib 300 mg orally twice daily until disease progression + durvalumab 1500 mg intravenously every 4 weeks up to 12 months. (The other three arms of this study involved women with HRD-negative disease; their tumour samples were tested for PD-L1 expression, and those with high PD-L1 expression were allocated to durvalumab + chemotherapy (PLD or topotecan or paclitaxel), while those with low PD-L1 expression were allocated to durvalumab + chemotherapy + tremelimumab (with two arms of the latter combination at different doses)).
Outcomes	**Median follow-up** for all 70 participants in 5 arms (only 2 of which are relevant to this review): 8.3 months (IQR 4.6 to 17.3) **Primary**: objective response rate by RECIST 1.1 (time frame: 6 months after treatment initiation) **Secondary** • PFS (time frame: up to 3 years) • OS (time frame: up to 3 years) • Duration of and time to response • Disease control rate • Safety
Notes	Funding statement from 'Acknowledgements' section in main paper (Lee et al 2022): "This study was funded by the Yonsei College of Medicine Research Fund for Clinical Excellence (SHRC). This research was an investigator-initiated trial funded by AstraZeneca." Several authors disclose a financial conflict of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details to assess this domain. Block randomisation with block size 4 was applied after confirmation of patient eligibility and registration with the KGOG (Korean Gynecologic Oncology Group) data centre by telephone, fax, or a web-based system. No details provided about the method of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Insufficient details to assess this domain.

AMBITION 2022 *(Continued)*

		Unclear risk - possibility of allocation being anticipated by investigators if block size is known (see above).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis for all randomised participants (ITT population)
Selective reporting (reporting bias)	Low risk	All analyses as prespecified in the study protocol
Other bias	Unclear risk	An industry-sponsored trial (AstraZeneca)

ANTHALYA 2017

Study characteristics	
Methods	A two-arm, open-label, non-comparative, multi-centre, phase II, randomised trial Participants were randomised in a 2:1 ratio
Participants	• 95 participants • 18 years or older • Histologically-confirmed, initially unresectable FIGO stage IIIC/IV ovarian, tubal or peritoneal adenocarcinoma • No prior chemotherapy, prior radiotherapy, or major surgery (newly diagnosed) • ECOG performance status 0 to 2 • Excluded ovarian tumours with low malignant potential, mucinous or clear cell carcinoma, or carcinosarcoma • Median age: 63 years (range 33 to 87 years)
Interventions	**Intervention:** four cycles of carboplatin-paclitaxel neoadjuvant chemotherapy (carboplatin: AUC 5 mg/mL/min; paclitaxel: 175 mg/m^2) with three cycles of bevacizumab (15 mg/kg in cycles 1 to 3), followed by interval debulking surgery (IDS). **Control:** four cycles of carboplatin-paclitaxel neoadjuvant chemotherapy (carboplatin: AUC 5 mg/mL/min; paclitaxel: 175 mg/m^2), followed by interval debulking surgery. After IDS, all participants received four cycles of adjuvant carboplatin-paclitaxel chemotherapy (carboplatin: AUC 5 mg/mL/min; paclitaxel: 175 mg/m^2; cycles 5 to 8) and up to 20 cycles of bevacizumab (15 mg/kg; cycles 6 to 26).
Outcomes	**Median follow-up time**: not reported **Primary:** percentage of participants with complete resection after IDS **SECONDARY** • ORR

ANTHALYA 2017 *(Continued)*

	• PFS according to RECIST v1.1 • Safety
Notes	Industry-sponsored trial (funded by F. Hoffmann-La Roche Ltd.) with several authors disclosing a financial conflict of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not available
Allocation concealment (selection bias)	Unclear risk	Details not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-lable study. Low risk of bias for OS, high risk of bias for other outcomes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-lable study. Low risk of bias for OS, high risk of bias for other outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data analysis according to modified ITT. Analysis without 4 participants (6%, 4/62) randomised to arm with bevacizumab - 3 randomised by mistake and 1 withdrew consent. None of those participants received the allocated treatment.
Selective reporting (reporting bias)	Low risk	All outcomes analysed as specified in trial registration entry
Other bias	Unclear risk	An industry-sponsored trial with several authors disclosing receipt of personal grants and funding from the industry.

APPROVE 2022

Study characteristics

Methods	An open-label, multi-centre, randomised trial Participants were randomised in a 1:1 ratio, stratified according to prior platinum-sensitive relapsed (yes versus no) and platinum-free interval (< 3 versus 3 to 6 months from last platinum therapy to subsequent progression).
Participants	• 150 participants • Aged 18 years or older • Histologically-confirmed non-mucinous ovarian cancer, fallopian tube cancer or primary peritoneal cancer • Platinum-resistant recurrent disease • Complicated with malignant pleural effusion or ascites, or with recurrent lesions that can be evaluated clinically • ECOG score 0 or 1 • Expected survival time of ≥ 4 months

APPROVE 2022 *(Continued)*

- No previous antivascular targeted therapy
- No more than 2 previous chemotherapy regimens
- Adequare haematological, liver and kidney function

Interventions	**Intervention:** pegylated liposomal doxorubicin ((PLD) 40 mg/m^2 IV every 4 weeks for up to 6 cycles) with apatinib 250 mg orally once daily until disease progression **Control:** pegylated liposomal doxorubicin (40 mg/m^2 IV every 4 weeks for up to 6 cycles)
Outcomes	**Median follow-up:** 8.7 months (IQR 4.7 to 14.1) **Primary**: PFS by RECIST v1.1 **SECONDARY** • OS (immature) • Objective response rate (ORR) • Disease control rate (DCR) • Safety
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned (1:1) to receive treatment with either PLD alone or apatinib plus PLD via an interactive web response system and were stratified by platinum-free interval (PFI, ≤ 3 months versus 3 to 6 months (excluding the boundary values) from last receipt of platinum-based chemotherapy to progression) and prior platinum-sensitive relapse (yes versus no). Treatment was allocated in blocks of 4 or 6 in each stratum.
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis for efficacy. Safety analyses restricted to participants who received at least 1 dose of study medication and had a safety assessment aftewards.
Selective reporting (reporting bias)	Low risk	Outcomes reported (broadly) as per ClinicalTrials.gov protocol, and outcomes in protocol not significantly modified after trial registration
Other bias	Unclear risk	A partly industry-sponsored trial

AURELIA 2014

Study characteristics	
Methods	Phase III, randomised, open-label, two-arm, multi-centre study Participants were randomised in a 1:1 ratio, stratified according to selected chemotherapy (PLD versus paclitaxel versus topotecan), prior antiangiogenic therapy (yes versus no) and platinum-free interval (< 3 months versus 3 to 6 months from last platinum therapy to subsequent progression).
Participants	• 361 participants (179 in intervention arm, 182 in control arm) • 18 years or older • Histologically-confirmed epithelial ovarian, fallopian tube or primary peritoneal cancer • Platinum-resistant recurrent disease (progression within 6 months of completing 4 or more cycles of platinum-based chemotherapy) • No more than 2 prior anticancer regimens, and no refractory disease • ECOG performance status 0 to 2 • Median age (range): chemotherapy alone 61 (25 to 84); bevacizumab + chemotherapy 62 (25 to 80).
Interventions	**Intervention:** chemotherapy (paclitaxel, topotecan or PLD) + bevacizumab (10 mg/kg every 2 weeks, or 15 mg/kg every 3 weeks if receiving topotecan on a 3-weekly schedule) **Control:** chemotherapy - choice of paclitaxel (80 mg/m^2 on days 1, 8, 15 and 22 every 4 weeks), topotecan (4 mg/m^2 on days 1, 8 and 15 every 4 weeks or 1.25 mg/m^2 on days 1 to 5 every 3 weeks), or pegylated liposomal doxorubicin (40 mg/m^2 on day 1 every 4 weeks) Cycles repeated every 4 weeks (or 3-weekly for one schedule of topotecan) and continued until disease progression, unacceptable toxicity, or withdrawal of consent. Participants assigned to chemotherapy could cross over to single-agent bevacizumab (15 mg/kg once every 3 weeks) on clear evidence of progression.
Outcomes	**Median follow-up time**: 13.9 months (chemotherapy alone), 13.0 months (chemotherapy + bevacizumab) (ranges not reported). **Primary:** PFS by RECIST **Secondary** • Objective response rate • Biological PFS • OS • Quality of life: EORTC, Hospital Anxiety and Depression Scale (HADS), FOSI • Safety and tolerability: adverse events, laboratory parameters, ECOG performance status, vital signs
Notes	Protocol online at: clinicaltrials.gov/show/NCT00976911 Industry-sponsored trial (funded by Hoffman La Roche) with several authors disclosing a financial conflict of interest.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Online-based system
Allocation concealment (selection bias)	Low risk	Online-based system

AURELIA 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis
Selective reporting (reporting bias)	Low risk	All analyses as prespecified in the study protocol
Other bias	Unclear risk	An industry-sponsored trial

AVANOVA2 2019

Study characteristics	
Methods	A two-arm, open-label, phase II randomised trial (inferiority study) Participants enrolled by investigators were randomised in a 1:1 ratio using random permuted block randomisation (block sizes 3 and 6 in the original 3-group design; block sizes 2 and 4 in the amended 2-group design) implemented by Sealed Envelope Ltd
Participants	• 97 participants • 18 years or older • Recurrent platinum-sensitive epithelial ovarian, fallopian tube, or peritoneal cancer; high-grade serous or high-grade endometrioid histology • Prior line of platinum-containing therapy for primary disease (up to one non-platinum-based line of therapy in the recurrent setting) • ECOG performance status 0 to 2 • Life expectancy of at least 12 weeks • Median age (IQR) niraparib + bevacizumab group: 67 years (59 to 70); niraparib group: 66 years (58 to 70)
Interventions	**Intervention:** oral niraparib at a starting dose of 300 mg (given as 3 capsules once daily) on days 1 to 21 combined with intravenous bevacizumab 15 mg/kg on day 1 every 3 weeks. **Control** - oral niraparib at a starting dose of 300 mg (given as 3 capsules once daily) on days 1 to 21
Outcomes	**Median follow-up time**: 16.9 months (IQR 15.4 to 20.9) **Primary:** investigator-assessed PFS **Secondary** • Disease control rate (complete response, partial response, or stable disease for ≥12 weeks) • ORR according to RECIST (v1.1) • Patient-reported outcomes • Safety (NCI CTCAE v4.0) and tolerability Overall response according to Gynecological Cancer InterGroup criteria [this outcome was mentioned as a secondary endpoint, which the authors plan to report on in a separate publication]

AVANOVA2 2019 *(Continued)*

	Exploratory subgroup analyses: PFS according to HRD status, *BRCA* mutational status, and chemotherapy-free interval
Notes	Industry-sponsored trial with several authors disclosing a financial conflict of interest. AVANOVA is a proof-of-concept trial which aimed only to identify the more active regimen for phase III evaluation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants enrolled by investigators were randomised in a 1:1 ratio using random permuted block randomisation (block sizes 3 and 6 in the original 3-group design; block sizes 2 and 4 in the amended 2-group design) implemented by Sealed Envelope Ltd
Allocation concealment (selection bias)	Low risk	Participants enrolled by investigators were randomised in a 1:1 ratio using random permuted block randomisation (block sizes 3 and 6 in the original 3-group design; block sizes 2 and 4 in the amended 2-group design) implemented by Sealed Envelope Ltd
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Efficacy and safety data: 97 of 103 randomised participants (94%)
Selective reporting (reporting bias)	Low risk	Outcomes analysed as specified in the National Clinical Trials Network (NCTN) record
Other bias	Unclear risk	An industry-sponsored trial with several authors disclosing receipt of personal grants and funding from the industry. AVANOVA is a proof-of-concept trial which aimed only to identify the more active regimen for phase III evaluation

BAROCCO 2022

Study characteristics

Methods	Participants were randomised in a 1:1:1 ratio, stratified by germline *BRCA*1/2 status, prior chemotherapy, and previous treatment with antiangiogenic drugs.
Participants	• 123 participants (41 in each of the 3 trial arms) • 18 years or older • Pathologically-confirmed high-grade epithelial ovarian cancer • Platinum resistant/refractory disease • ECOG performance status 0-1 • Life expectancy ≥ 16 weeks

BAROCCO 2022 *(Continued)*

- *BRCA* 1/2 mutation status known
- No previous treatment with a PARP inhibitor

Interventions	**Intervention (continuous):** olaparib (600 mg, given as 300 mg twice daily) + cediranib (20 mg daily, every day) **Intervention (intermittent):** olaparib (600 mg, given as 300 mg twice daily) + cediranib (20 mg daily, 5 days a week) **Control:** paclitaxel (80 mg/m^2 weekly)
Outcomes	**Median follow-up:** 29.7 months (IQR 20.7 to 31.2 months) **Primary:** PFS **Secondary** • Treatment compliance • Reasons for discontinuation and treatment modification • Objective response rate • PFS2 (time from first progression to date of second progression or death) • OS • Quality of life assessed with the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) questionnaire • Safety/toxicity
Notes	Protocol at www.clinicaltrials.gov/ct2/show/NCT03314740

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Biased-coin minimisation procedure allowing stratification for factors: g*BRCA*1-2 status (mutated versus wild-type versus unknown); prior chemotherapy (1–2 versus ≥ 3 lines); and previous treatment with antiangiogenic drugs (yes versus no).
Allocation concealment (selection bias)	Unclear risk	Biased-coin minimisation procedure, although details provided regarding allocation concealment are minimal
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All participants accounted for in flow chart, although unequal withdrawal: of the 13 participants who did not receive at least one dose of study treatment, 12 were participants randomised to the control group who withdrew consent after randomisation; overall, 17 participants received less than 4 weeks of treatment.
Selective reporting (reporting bias)	Low risk	Comprehensive outcome reporting and further supplementary data on line. Outcomes reported (broadly) as per ClinicalTrials.gov protocol, and outcomes in protocol not modified after trial registration.

BAROCCO 2022 *(Continued)*

Other bias	Unclear risk	Study partially supported by AstraZeneca

CHIVA 2019

Study characteristics

Methods	A two-arm, multi-centre, randomised, double-blind, placebo-controlled, phase II trial. Participants were randomised by investigators in a 2:1 ratio to the intervention or control arm.
Participants	• 188 participants (124 in intervention arm, 64 in control arm) • Newly diagnosed FIGO stage IIIC-IV ovarian cancer considered as unresectable after laparoscopic evaluation • No previous chemotherapy
Interventions	**Intervention:** nintedanib. Neoadjuvant chemotherapy with carboplatin (AUC 5 mg/mL/min) and paclitaxel (175 mg/m^2) for 3 to 4 cycles before interval debulking surgery followed by 2 to 3 cycles of carboplatin-paclitaxel chemotherapy (total of 6 cycles) + nintedanib (200 mg twice daily) on days 2 to 21 at cycles 1, 2, 5 and 6 and for maintenance therapy for up to 2 years. **Control:** placebo. Neoadjuvant chemotherapy with carboplatin (AUC 5 mg/mL/min) and paclitaxel (175 mg/m^2) for 3 to 4 cycles before interval debulking surgery followed by 2 to 3 cycles of carboplatin-paclitaxel chemotherapy (total of 6 cycles) + placebo (200 mg twice daily) on days 2 to 21 at cycles 1, 2, 5 and 6 and for maintenance therapy for up to 2 years.
Outcomes	**Primary**: median PFS **Secondary** • OS • Response rate • Toxicity
Notes	Industry-sponsored trial (funded by Boehringer Ingelheim)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Masking: double (participant, investigator)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Masking: double (participant, investigator)
Incomplete outcome data (attrition bias)	Unclear risk	Insufficient details to assess this domain

CHIVA 2019 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	Insufficient details to assess this domain
Other bias	Unclear risk	An industry-sponsored trial

Cong 2019

Study characteristics	
Methods	A two-arm, single-centre, randomised controlled trial
Participants	• 164 participants (82 in intervention arm, 82 in control arm) • Histologically-confirmed recurrent platinum-sensitive ovarian cancer • ≥3 weeks of ovarian cancer treatment prior to recurrence
Interventions	**Intervention:** carboplatin (AUC = 5) and paclitaxel (100 mg/m^2) + bevacizumab (15 mg/kg). All given 3 times per week for 3 weeks. **Control:** carboplatin (AUC = 5) and paclitaxel (100 mg/m^2). All given 3 times per week for 3 weeks.
Outcomes	**Median follow-up time**: 15 +/- 5.3 months (control), 15.9 +/- 5.1 months (experimental). **Outcomes** • Objective response rate • Complete response rate • Partial response rate • Stable disease • Progressive disease • PFS • OS • Adverse clinical reactions • Improvement of QoL *Not specified which outcome was primary*
Notes	Work was supported by the Natural Science Fund of Shandong Province, China (No: ZR2016HL37)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details given

Cong 2019 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details given
Selective reporting (reporting bias)	Unclear risk	No details given
Other bias	Unclear risk	Lack of trial registration number or protocol available in public domain

Duska 2020

Study characteristics	
Methods	An open-label, multi-centre, randomised phase II trial Participants were randomised in a 1:1 ratio to intervention or control, stratified by platinum sensitivity and number of prior lines of chemotherapy.
Participants	• 148 participants (151 randomised, but 3 excluded from analysis as never started treatment) • 18 years or older • Persistent or recurrent epithelial ovarian cancer (platinum-sensitive or platinum-resistant) • At least 1 and ≤ 3 prior lines of chemotherapy, but no previous treatment with weekly gemcitabine for recurrent or persistent disease • Measurable/evaluable disease • ECOG performance status 0 to 2 for participants with 1 prior regimen, or 0 to 1 for participants with multiple prior regimens
Interventions	**Intervention:** weekly gemcitabine 1000 mg/m^2 on days 1 and 8 of a 21 day cycle + pazopanib 800 mg daily **Control:** weekly gemcitabine 1000 mg/m^2 on days 1 and 8 of a 21 day cycle
Outcomes	**Primary:** PFS **Secondary** • OS • Adverse events • Preliminary estimates of response • Duration of response • Time to progression
Notes	Industry-supported trial (funded by GlaxoSmithKline/Novartis)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation with 1:1 ratio using a stratified block randomisation scheme with varying block sizes. Randomisation system provided by the University of Virginia Cancer Center Clinical Trials Database

Duska 2020 *(Continued)*

Allocation concealment (selection bias)	Low risk	Randomisation system provided by the University of Virginia Cancer Center Clinical Trials Database
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All attritions and exclusions reported on study flow diagram. Three women randomised to experimental arm were excluded as never started treatment. Six women lost to follow-up for survival (1 in experimental arm and 5 in comparison arm), 6 women withdrew consent (2 in experimental arm and 4 in comparison arm). Analysis for all randomised participants.
Selective reporting (reporting bias)	Low risk	All outcomes reported on ClinicalTrials.gov reported in the publication.
Other bias	Unclear risk	An industry-sponsored trial with several authors disclosing receipt of personal grants and funding from the industry.

EORTC-1508 2021

Study characteristics	
Methods	A five-arm, multi-centre, randomised phase II trial
Participants	• 122 participants randomised in total to 5 arms (several different relevant comparisons for this review) • 18 years or older • Recurrent, histologically-proven, platinum-resistant, epithelial ovarian, fallopian tube and peritoneal cancer • Advanced or metastatic stage • WHO performance status 0 to 2 if ≤ 2 previous lines of therapy; WHO performance status 0 to 1 if > 2 previous lines of therapy • Life expectancy ≥ 12 weeks
Interventions	5 arms: 1. Bevacizumab (15 mg/kg) (n = 33) 2. Atezolizumab (1200 mg) + placebo (n = 11) 3. Atezolizumab (1200 mg) + acetylsalicylic acid (320 mg/day) (n = 13) 4. Atezolizumab (1200 mg) + placebo + bevacizumab (15 mg/kg) (n = 32) 5. Atezolizumab (1200 mg) + acetylsalicylic acid (320 mg/day) + bevacizumab (15 mg/kg) (n = 33) *Comparisons of arms 4 versus 2, and 5 versus 3, would be relevant to this review. However, limited outcome data are available as arms 2 and 3 were closed early.*
Outcomes	**Primary**: PFS rate at 6 months (PFS-6) assessed by RECIST **Secondary**

EORTC-1508 2021 *(Continued)*

	• Tolerability • PFS • Response rate • Time to first subsequent therapy (TFST)
Notes	Funded by EORTC with support from F. Hoffmann-La Roche Ltd. Arms 2 and 3 were closed early (due to results from other studies indicating insufficient activity of PD-L1 inhibitor monotherapy).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details to assess this domain
Allocation concealment (selection bias)	Unclear risk	Insufficient details to assess this domain
Blinding of participants and personnel (performance bias) All outcomes	High risk	Based on information from ClinicalTrials.Gov registration entry, the study was triple-masked (participant, care provider, investigator). However, the trial appears to be open-label for the comparisons we are interested in (i.e. with versus without bevacizumab) - so at high risk of bias for PFS, adverse events, etc., though at low risk of bias for OS.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Based on information from ClinicalTrials.Gov registration entry, the study was triple-masked (participant, care provider, investigator). However, the trial appears to be open-label for the comparisons we are interested in (i.e. with versus without bevacizumab) - so at high risk of bias for PFS, adverse events, etc. though at low risk of bias for OS.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data analysis on all randomised participants
Selective reporting (reporting bias)	Unclear risk	Insufficient details to assess this domain (conference abstract)
Other bias	Unclear risk	Study findings available only in the form of a conference abstract Industry-sponsored trial

GEICO-1205 2019

Study characteristics

Methods	An open-label, multi-centre, randomised phase II trial Participants were randomised in a 1:1 ratio to intervention versus control arm.
Participants	• 68 participants randomised (intervention arm: 35; control arm: 33) • Age 18 years or older • Newly-diagnosed stage III/IV high-grade serous/endometrioid ovarian, fallopian tube or primary peritoneal cancer • Considered a candidate for neoadjuvant chemotherapy followed by interval debulking surgery

GEICO-1205 2019 *(Continued)*

	• ECOG performance status 0 to 2
Interventions	**Intervention:** neoadjuvant chemotherapy with carboplatin (AUC = 6) and paclitaxel (175 mg/m^2) + ≥ 3 cycles of bevacizumab 15 mg/kg, repeated every 3 weeks. **Control:** neoadjuvant chemotherapy with carboplatin (AUC = 6) and paclitaxel (175 mg/m^2), repeated every 3 weeks. After neoadjuvant therapy, participants in both arms were considered for interval debulking surgery followed by 3 cycles of carboplatin-paclitaxel chemotherapy and bevacizumab, followed by 15 months' single-agent bevacizumab.
Outcomes	**Median follow-up**: 19.7 months (range 3.0 to 45.5 months). **Primary:** complete macroscopic response rate at interval debulking surgery **Secondary** • PFS • Safety
Notes	An industry-supported study (Roche Farma SA) with several authors disclosing a financial conflict of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Details not available
Allocation concealment (selection bias)	Unclear risk	Details not available
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study. High risk of bias for PFS and adverse events
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study. High risk of bias for PFS and adverse events
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis
Selective reporting (reporting bias)	Low risk	Outcomes analysed as specified in the protocol
Other bias	Unclear risk	An industry-sponsored trial with several authors disclosing receipt of personal grants and funding from the industry.

GOG-0213 2017

Study characteristics

GOG-0213 2017 *(Continued)*

Methods	An open-label, phase III, randomised, multi-centre study Participants were randomised in a 1:1 ratio to intervention versus control arms, stratified by treatment-free interval and participation in a surgical objective substudy.
Participants	• 674 participants randomised (control arm: 377; intervention arm: 377) • Women ≥ 18 years old, with recurrent platinum-sensitive epithelial ovarian, primary peritoneal or fallopian tube carcinoma • GOG performance status 0 to 2 • ≤ 1 previous chemotherapy regimen
Interventions	All participants had surgical cytoreduction if appropriate. Whether or not they had surgery, participants were then randomised to 1 of 2 treatment arms. **Intervention:** 6 cycles of standard chemotherapy as per control arm, plus bevacizumab (15 mg/kg) every 3 weeks and continued as maintance every 3 weeks until disease progression or unacceptable toxicity **Control:** 6 3-weekly cycles of standard chemotherapy with paclitaxel (175 mg/m^2) and carboplatin (AUC = 5).
Outcomes	**Median follow-up**: 49.6 months in both arms (IQR 41.5 to 62.2 for intervention arm; IQR 40.8 to 59.3 for control arm) **Primary**: OS **Secondary** • PFS • Frequency and severity of adverse events
Notes	Study funded by National Cancer Institute and Genentech. Protocol online at: clinicaltrials.gov/show/NCT00565851

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study treatments were allocated sequentially from lists composed of random permuted blocks of random sizes of the study treatments.
Allocation concealment (selection bias)	Low risk	"An automated electronic web-based procedure was used to enrol patients and randomly assign them to treatments. Each individual's treatment assignment remained concealed until after she was successfully enrolled, and this report includes an account of all individuals who enrolled for the bevacizumab objective."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Incomplete outcome data (attrition bias)	Low risk	Details provided in CONSORT diagram. Looks like participants were analysed as intention-to-treat population for efficacy.

GOG-0213 2017 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Compared reported outcomes to registered protocol on the ClinicalTrials.gov website, and they broadly correspond, including key outcomes of OS, PFS and toxicity.
Other bias	Low risk	Work supported by National Cancer Institute grants to the Gynecologic Oncology Group (GOG) Administrative Office (CA 27469), the Gynecologic Oncology Group Statistical Office (CA 37517), NRG Oncology (1U10 CA180822), and NRG Operations (U10CA180868).

GOG-0218 2019

Study characteristics	
Methods	International, multi-centre, randomised, double-blind, placebo-controlled, phase III trial Participants were randomised in a 1:1:1 ratio to the 2 intervention arms and 1 control arm.
Participants	1873 women were enrolled from 336 sites (in the USA, Canada, South Korea and Japan). 625 participants were treated in arm 1 (chemotherapy + placebo), 625 in arm 2 (chemotherapy + bevacizumab initiation) and 623 in arm 3 (chemotherapy + bevacizumab initiation + maintenance bevacizumab) (see 'Interventions' below for details). All participants had newly-diagnosed (confirmed by histology), previously untreated (i.e. no prior chemotherapy), advanced epithelial ovarian, fallopian tube or primary peritoneal cancer. All participants were within 1 to 12 weeks of initial abdominal surgery for staging and tumour debulking, after which they had stage III optimal (macroscopic residual disease ≤ 1 cm) or suboptimal (> 1 cm) disease or stage IV disease. All participants had a Gynecologic Oncology Group (GOG) Performance Status (PS) of 0 to 2. Participants were excluded if they had a history of significant vascular events, or evidence of intestinal obstruction requiring parenteral support. The median age in each arm was 60 years (range 25 to 86 years in control group; 24 to 88 years in bevacizumab-initiation group; 22 to 89 years in bevacizumab-throughout group). Histology was serous in 1591 (85%) women, endometrioid in 60 (3%), clear cell in 52 (3%), mucinous in 21 (1%) and 149 (8%) women had other histology. 931 (50%) women had GOG performance status 0, 809 (43%) had status 1 and 133 (7%) had status 2. 639 (34%) participants had stage III disease with optimal cytoreduction; 752 (40%) participants had stage III suboptimal and 482 (26%) had stage IV disease. 77 (4%) women had grade 1 disease, 263 (14%) had grade 2, 1277 (68%) had grade 3 disease and grade was not specified in 256 (14%) women. Baseline characteristics were similar between all 3 study arms.
Interventions	Participants were randomised to 1 of 3 treatment arms (in ratio 1:1:1, stratified by GOG performance status and by stage/debulking status), according to a minimisation procedure. Treatment was planned for a total of 22 cycles, over a period of 15 months (each cycle lasted 21 days, with infusions being administered on day 1 of the cycle). **Arm 1 (control group):** paclitaxel/carboplatin chemotherapy for cycles 1 to 6 (IV paclitaxel 175 mg/m^2 + carboplatin AUC 6 (AUC = area under the curve)) + placebo for cycles 2 to 22.

GOG-0218 2019 *(Continued)*

	Arm 2 (bevacizumab-initiation group): paclitaxel/carboplatin chemotherapy as per arm 1 + concurrent bevacizumab (15 mg/kg) for cycles 2 to 6 + placebo for cycles 7 to 22. **Arm 3 (bevacizumab-throughout group):** paclitaxel/carboplatin chemotherapy as per arm 1 + concurrent bevacizumab (15 mg/kg) for cycles 2 to 6 + maintenance bevacizumab for cycles 7 to 22.
Outcomes	**Median follow-up**: 102.9 months **Primary:** PFS (as judged by radiography, CA125, clinical criteria or death) **Secondary:** • OS • Safety • QoL • Correlative laboratory studies
Notes	The key protocol amendments were: a) the inclusion of participants with optimally debulked (macroscopic residual) disease, and b) the change of the primary endpoint from OS to PFS (with unblinding to treatment assignment allowed at the time of disease progression). The primary analysis was performed when 76.3% of participants were alive, with median of 17.4 months follow-up. Analysis for efficacy was by intention-to-treat (ITT) (n = 1873); analysis for safety was for those who actually received the allocated study treatment (n = 1863). Industry-sponsored trial (funded by the National Cancer Institute and Genentech) with several authors disclosing a financial conflict of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Trial protocol states that randomisation was performed by investigators telephoning to a central GOG Statistical and Data Center, or web-based registration and randomisation. Participants were stratified on the basis of GOG performance status, cancer stage, and debulking status, before being randomised according to a minimisation procedure. Have contacted study investigators for more details.
Allocation concealment (selection bias)	Low risk	Trial protocol states that randomisation was performed by investigators telephoning to a central GOG Statistical and Data Center, or web-based registration and randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Trial was double-blinded and placebo-controlled.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding continued until progression, so should be low risk of bias for PFS outcome assessment. OS is a 'hard' (objective) outcome, so arguably little potential for outcome assessment bias, even after unblinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1873 participants enrolled and randomised: 625 to control arm, 625 to bevacizumab-initiation arm, and 623 to bevacizumab-throughout arm. All randomised participants were included in intention-to-treat efficacy analyses. Ten participants did not receive the allocated study treatments, and were exclud-

GOG-0218 2019 *(Continued)*

		ed from safety analyses. All participants accounted for at the end of the study and displayed on CONSORT flowchart.
Selective reporting (reporting bias)	Low risk	Checked original protocol ClinicalTrials.org, and noted original planned outcomes of OS, PFS, incidence of severe toxicity, and QoL – all of which have now been reported. Note: study investigators report that the primary outcome of the study was changed from OS to PFS during the course of the trial. "This change was made because maintaining the blinding of the treatment assignments after disease progression, which was required to protect the integrity of the data on overall survival, was contested by numerous investigators and patients and therefore was deemed infeasible."
Other bias	Unclear risk	The study was supported by the National Cancer Institute and industry (Genentech). Detailed author disclosure forms are available online at www.nejm.org/doi/suppl/10.1056/NEJMoa1104390/suppl_file/nejmoa1104390_disclosures.pdf An industry-sponsored trial. Change of the primary endpoint from overall survival to progression-free survival.

GOG-0241 2019

Study characteristics	
Methods	An open-label, international, randomised, multi-centre, factorial phase III trial Participants were randomised in a ratio of 1:1:1:1 to each of the 2 different chemotherapy-only arms, and each of the 2 intervention arms (2 different chemotherapy regimens + bevacizumab). Randomisation was via an electronic system at the Cancer Trials Centre (UK) or GOG (US), using minimisation stratified by disease status (presence/absence of residual disease) and stage (new/recurrent stages II-IV versus recurrent stage 1) in each country.
Participants	• 50 participants randomised to 4 treatment arms • Histological diagnosis of primary mucinous epithelial ovarian cancer • 18 years or older • FIGO stage II-IV or recurrence after stage I disease • No previous chemotherapy • ECOG performance status 0 to 2
Interventions	**Intervention:** chemotherapy (with either paclitaxel and carboplatin or oxaliplatin and capecitabine) as per the control arms + bevacizumab (15 mg/kg) every 3 weeks for 6 cycles, then continued as maintenance for 12 further cycles. **Control:** chemotherapy with either paclitaxel (175 mg/m^2) and carboplatin (AUC 5/6), or oxaliplatin (130 mg/m^2) and capecitabine (850 mg/m^2), 3-weekly for 6 cycles.
Outcomes	**Median follow-up**: 59 months **Primary:** OS **Secondary** • PFS • Tumour response (assessed using RECIST) • Toxicity

GOG-0241 2019 *(Continued)*

- QoL (assessed using FACT-O TOI and Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity subscale)

Notes	The trial was supported by Cancer Research UK and the National Cancer Institute (in the USA). Bevacizumab was provided by Hoffmann-La Roche Ltd. Note: this trial was included in the previous version of this review as an 'ongoing study', listed under its ClinicalTrials.gov reference (NCT01081262).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned by an electronic system at the Cancer Trials Centre or GOG. Minimisation was used, with two stratification factors (disease status and stage).
Allocation concealment (selection bias)	Low risk	Participants were randomly assigned by an electronic system at the Cancer Trials Centre or GOG. Minimisation was used, with two stratification factors (disease status and stage).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis
Selective reporting (reporting bias)	Low risk	Analysis for all outcomes of interest
Other bias	Low risk	Trial sponsored by National Cancer Institute (NCI)

Gotlieb 2012

Study characteristics

Methods	Multi-centre, international, double-blind, randomised, placebo-controlled, phase II trial
Participants	55 participants randomised (29 to intervention, 26 to control). Participants were women aged ≥18 years with advanced epithelial ovarian cancer (including fallopian tube or primary peritoneal adenocarcinoma) and recurrent symptomatic malignant ascites, which had required 1 to 4 paracenteses in the month prior to randomisation. Other inclusion criteria included: treatment-resistant disease following at least 2 lines of previous chemotherapy (platinum and either topotecan or liposomal doxorubicin), ECOG performance status of ≤ 2, and adequate hepatic, renal and haematological function and no overt proteinuria. Study conducted from July 2006 to October 2009, at 23 sites in 7 countries. 58 women were recruited, of whom 55 were randomised (26 assigned to placebo, 29 assigned to aflibercept). Patients were ex-

Gotlieb 2012 *(Continued)*

	cluded if they had a shunt (e.g. perito-venous) for management of their ascites. They were also excluded if they had had prior treatment with an inhibitor of VEGF or VEGF-R. Median age at entry to trial by intervention groups: Placebo group: median age 53.5 (range 37 to 84) Aflibercept group: median age 60 (range 33 to 88) ECOG performance status by intervention groups: Placebo group: ECOG PS 0, n = 5 (19%); PS 1, n = 11 (42%); PS 2, n = 10 (38%) Aflibercept group: ECOG PS 0, n = 3 (10%); PS 1, n = 12 (41%); PS 2, n = 13 (45%); PS 3, n = 1 (3%) [protocol deviation]
Interventions	**Intervention:** aflibercept (VEGF-Trap) (4 mg/kg IV every 2 weeks) **Control:** placebo Participants were to remain in the double-blind period for minimum 60 days and until at least a repeat paracentesis had occurred. Cross-over was then optional. At 6 months, participants could receive open-label treatment or withdraw from study.
Outcomes	**Primary:** time to repeat paracentesis **Secondary** • Other paracentesis-related parameters • OS (not mentioned as outcome in protocol, but reported) • Tolerability • Safety/adverse events • Quality of life and patient-reported outcomes (both mentioned as outcomes in the original protocol; the participant-assessed Ascites Impact Measure was reported, but other measures of QoL or patient-reported outcomes were not reported).
Notes	The main aim of this study was to look at the effect of VEGF-Trap on the need for paracentesis for malignant ascites (e.g. increasing the length of time until another paracentesis was needed), and hence these are the main outcomes reported by the trialists. However, we have only reported and discussed outcomes relevant to this review; namely, survival and adverse events. Participants were evaluated until the first post-randomisation paracentesis during the double-blind period, study withdrawal, death during the double-blind period or 6 months of double-blind treatment – whichever came first.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation, stratified by time since last paracentesis (≤ 2 versus > 2 weeks). Central randomisation by ICON (well-established service, likely to have reliable random sequence generation). Have contacted authors for details
Allocation concealment (selection bias)	Low risk	Probably done (central randomisation by voice response system provided by ICON, which should ensure allocation concealment)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded, placebo-controlled trial. “Patients, investigators, and sponsor personnel were masked to treatment assignment.”

Gotlieb 2012 *(Continued)*

		At randomisation, participants were assigned to numbered treatment kits (of agent or placebo), which should have concealed intervention from participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Probably low risk during blinded period (up to first repeat paracentesis), but unclear whether survival outcomes were asssessed after blinding stopped. Have emailed authors to ask
Incomplete outcome data (attrition bias) All outcomes	Low risk	58 women were recruited, of whom 55 were randomised (26 assigned to placebo, 29 assigned to aflibercept). Two participants received both aflibercept and placebo during the double-blind period. Efficacy outcomes were reported by assigned groups (intention-to-treat analysis), whilst safety analyses were reported by treatment received. All participants accounted for at the end of the study and displayed on CONSORT diagram.
Selective reporting (reporting bias)	Low risk	Checked study protocol at ClinicalTrials.org. Original protocol (registered May 2006) lists primary outcome as time to repeat paracentesis (as reported in main paper), and secondary outcomes as Ascites Impact Measure (reported), 60-day frequency of paracentesis (reported), and safety/tolerability (reported). The original protocol also listed tumour assessments and quality of life as secondary outcomes, which do not yet seem to have been reported. The main paper also reported survival outcomes (PFS and OS): although these were not listed as outcomes in the original protocol (and the study was not powered with the intention of being able to detect a difference in survival), we agree that it is good practice to report them.
Other bias	Unclear risk	Industry-sponsored study by Sanofi-Aventis, with several authors disclosing financial conflicts of interest. The Principal Investigators are not employed by the organisation sponsoring the study (according to ClinicalTrials.org record). Concern that despite randomisation and stratification methods, slight imbalance at baseline noted: more participants assigned to placebo than to aflibercept had 5 or more paracenteses. Placebo group could have more resistant or aggressive ascites that is more difficult to control – potential bias in favour of aflibercept group.

Gupta 2019

Study characteristics	
Methods	A single-centre, open-label, randomised controlled phase II trial Participants were randomised in a 1:1 ratio to intervention or control.
Participants	• 52 participants randomised • 18 years and older • Histologically-confirmed recurrent or residual epithelial ovarian, fallopian tube or primary peritoneal cancer • Included both platinum-sensitive and platinum-resistant disease • Karnofsky Performance Status of 60% to 100% • Life expectancy of at least 3 months
Interventions	**Intervention:** oral cyclophosphamide (50 mg) once daily + oral celecoxib (400 mg) twice daily. Course repeats every 4 weeks in the absence of disease progression or unacceptable toxicity.

Gupta 2019 *(Continued)*

	Control: oral cyclophosphamide (50 mg) once daily. Course repeats every 4 weeks in the absence of disease progression or unacceptable toxicity.
Outcomes	**Primary**: response rate assessed by RECIST version 1.0 (tumour measurements were done, via imaging, every 2 cycles (every 8 weeks)) **Secondary** • Time to treatment failure (time to discontinuation of therapy, disease progression, or death due to any cause) • OS • PFS • Toxicity (assessed by NCI CTCAE v2.0) In the paper, the authors explain that the original protocol plan was to report on PFS, but that they changed this to report on failure-free survival (time to treatment failure) 'due to follow-up limitations on patients who stopped therapy for reasons other than progression such as toxicities and patient choice'.
Notes	Trial supported by a National Cancer Institute of the National Institutes of Health award [P30CA033572]. Trial protocol at: www.clinicaltrials.gov/ct2/show/NCT00538031

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details to assess this domain
Allocation concealment (selection bias)	Unclear risk	Insufficient details to assess this domain
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	No mention of attrition or exclusions from analysis. All participants randomised appear to be included in results.
Selective reporting (reporting bias)	Unclear risk	Original protocol plan to report on PFS was changed to failure-free survival "due to follow-up limitations on patients who stopped therapy for reasons other than progression such as toxicities and patient choice".
Other bias	Low risk	No industry funding or conflicts of interest.

Hainsworth 2015

Study characteristics

Hainsworth 2015 *(Continued)*

Methods	A multi-centre, randomised, open-label, phase II trial Participants were randomised in a 1:1 ratio to intervention and control arms.
Participants	• 85 participants randomised (43 in intervention arm, 42 in control arm) • 18 years and older • Histologically-confirmed stage III or IV epithelial ovarian cancer • Newly diagnosed (first-line treatment) • Have undergone cytoreductive surgery, and have no residual large volume disease (no tumour nodules > 3 cm in size), bowel involvement or intestinal obstruction
Interventions	**Intervention:** chemotherapy with paclitaxel (175 mg/m^2) and carboplatin (AUC = 6) every 21 days for up to 6 cycles + sorafenib (400 mg orally twice daily) for 52 weeks. **Control:** chemotherapy with paclitaxel (175 mg/m^2) and carboplatin (AUC = 6) every 21 days for up to 6 cycles.
Outcomes	**Primary**: PFS at 2 years **Secondary** • OS • Toxicity • Overall response rate
Notes	Protocol online at: www.clinicaltrials.gov/show/NCT00390611 Trial supported by industry (grant from Bayer Healthcare Pharmaceuticals)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	The study contains a flow chart for the participants. The dropout reasons were reported. ITT analysis has been performed.
Selective reporting (reporting bias)	Low risk	Compared reported outcomes to original study protocol at ClinicalTrials.gov website - outcomes reported mostly correspond to those originally planned.
Other bias	Unclear risk	An industry-sponsored trial. Authors declare no conflicts of interest.

Herzog 2013

Study characteristics	
Methods	Multi-centre, phase II, randomised, double-blind, placebo-controlled trial
Participants	Women ≥ 18 years old, with histologically-confirmed FIGO stage III or IV ovarian epithelial cancer or primary peritoneal cancer, who have achieved a complete clinical response after tumour debulking surgery and only one regimen of standard platinum and taxane-based chemotherapy. Participants were also required to have a life expectancy of ≥ 12 weeks, an ECOG performance status of 0 or 1, normal CA125 levels within 14 days of study entry, and adequate bone marrow, hepatic and renal function. 246 women were enrolled and randomised to maintenance therapy with either sorafenib (n = 123) or placebo (n = 123) Mean age at entry to trial by intervention groups: Placebo group: mean age 54.4 (SD 10.3) Sorafenib group: mean age 56.9 (SD 10.4) Type of cancer by intervention groups: Placebo group: 114 (92.7%) ovarian, 9 (7.3%) peritoneal Sorafenib group: 115 (93.5%) ovarian, 8 (6.5%) peritoneal Eastern Cooperative Oncology group (ECOG) performance status (PS) by intervention groups: Placebo group: ECOG PS 0, n = 92 (74.8%); PS 1, n = 30 (24.4%); PS 2, n = 0 Sorafenib group: ECOG PS 0, n = 89 (72.4%); PS 1, n = 32 (26%); PS 2, n = 1 (0.8%)
Interventions	**Intervention:** sorafenib (400 mg orally twice a day) **Control:** matching placebo Treatment was continued until relapse (determined by CT or MRI imaging), unacceptable toxicity or the endpoint of the study.
Outcomes	**Primary**: PFS, based on time to CT-documented relapse **Secondary** • Time to first pathologic CA125 serum levels • OS • Ovarian cancer symptoms response • General health status
Notes	Protocol online at: www.clinicaltrials.gov/show/NCT00791778

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	“Randomized”, stratified according to the degree of residual disease, surgical debulking, and whether intraperitoneal chemotherapy had been given prior to enrolment - but details of random sequence generation not stated in main paper. Emailed authors on 22/08/2015 to ask for more details.

Herzog 2013 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient details provided for assessment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind"; used sorafenib or "matching placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Double-blind"; used sorafenib or "matching placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants included in the survival and toxicity analyses
Selective reporting (reporting bias)	Low risk	Checked original trial protocol, registered with ClinicalTrials.gov in November 2008. The main outcomes reported (including PFS and OS) were registered as outcomes in the original protocol.
Other bias	Unclear risk	Industry-sponsored study (by Bayer), and 2 of the authors declare employment and stock-ownership with Bayer. However, the Principal Investigators are not employed by the trial sponsors, and the remaining authors declare no conflicts of interest.

ICON6 2021

Study characteristics	
Methods	Phase III, double-blind, placebo-controlled, three-arm, randomised, international, multi-centre study
Participants	456 women were enrolled from 63 centres. Participants were women ≥ 18 years old, with histologically-proven diagnosis of epithelial ovarian carcinoma, fallopian tube carcinoma or primary serous peritoneal carcinoma, with proven relapsed disease occurring more than 6 months since completion of first-line platinum-based chemotherapy ('relapsed platinum sensitive ovarian cancer'). Other requirements included: an ECOG performance status of 0 or 1, life expectancy > 12 weeks, and adequate bone marrow, liver and renal function. The median age at enrolment was 62 years.
Interventions	Randomisation in a 2:3:3 ratio to 1 of 3 different study arms: **Arm A (reference)**: standard platinum-based chemotherapy (6 cycles) plus a daily oral placebo tablet for the duration of the chemotherapy and then for up to 18 months from the time of randomisation, or until protocol-defined disease progression occurs. **Arm B (concurrent cediranib)**: standard chemotherapy plus daily oral cediranib during chemotherapy only, and then an oral daily placebo tablet for up to 18 months from the time of randomisation, or until protocol-defined disease progression or toxicity limiting treatment occurs. **Arm C (concurrent and maintenance cediranib)**: standard chemotherapy plus oral cediranib daily during chemotherapy and then continued for up to 18 months from the time of randomisation, or until protocol-defined disease progression or toxicity limiting treatment occurs. Randomisation was stratified by: GCIG group, first-line chemotherapy (paclitaxel versus no paclitaxel), duration of relapse-free interval (6 to 12 months versus > 12 months), planned chemotherapy regimen (carboplatin/cisplatin versus carboplatin/cisplatin and paclitaxel), and any previous bevacizumab treatment (yes versus no).

ICON6 2021 *(Continued)*

	Carboplatin dose = AUC 5 (glomerular filtration rate measured) or AUC 6 (calculated dose) Paclitaxel dose = 175 mg/m^2 Cisplatin = 75 mg/m^2 (where used - preferred treatment in ICON6 was carcboplatin and paclitaxel, but cisplatin was allowed) Cediranib = 20 mg daily
Outcomes	**Primary**: • stage 1: safety • stage 2: PFS • stage 3: OS and toxicity **Secondary**: • stage 1: none • stage 2: OS • stage 3: PFS, toxicity and QoL
Notes	Protocol online at: www.clinicaltrials.gov/show/NCT00532194 Study website: www.icon6.org/

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was in a 2:3:3 ratio, after stratification for: GCIG group, first-line chemotherapy, duration of relapse-free interval, planned chemotherapy regimen, and previous bevacizumab treatment. Participants were randomised using ClinPhone Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS), via computer key-board data entry for web-based interface or touch-tone phone key pad (www.icon6.org/information-for-patients/randomisation/)
Allocation concealment (selection bias)	Low risk	Participants were randomised using ClinPhone IVRS/IWRS, via computer key-board data entry for web-based interface or touch-tone phone key pad (www.icon6.org/information-for-patients/randomisation/). Automated randomisation via web-based or touch-tone phone key pad should conceal allocations prior to assignment. Randomisation used permuted block sizes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind, placebo-controlled" study – both participants and personnel should be unaware of allocated treatment. "Tablets containing the active drug and placebo were designed to look, taste and smell the same" (ICON6 website).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Triple-masking (participant, investigator, outcomes assessor) according to trial protocol (on ClinicalTrials.gov website)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis for all randomised participants

ICON6 2021 *(Continued)*

Selective reporting (reporting bias)	Low risk	We examined the original study protocol (registered with ClinicalTrials.gov in September 2007). The main outcomes reported (including PFS, OS, toxicity and QoL) were all registered as outcomes in the original protocol.
Other bias	Low risk	The trial is partially supported by industry, but is primarily led by academics/non-industry researchers ("led by the Medical Research Council, UK, funded by Cancer Research UK and partially supported by AstraZeneca") (ICON6 2021, see secondary reference Raja 2011, page 885). Trial had to be redesigned due to discontinuation of cediranib development by AstraZeneca in October 2011. The prospective analysis plan was modified (with no outcome analysis done) to account for shortage in future drug supply.

ICON7 2015

Study characteristics	
Methods	Randomised, two-arm, multi-centre, open-label phase III study
Participants	1528 women were recruited from 263 sites in 7 GCIG (Gynecologic Cancer InterGroup) groups. 764 women were in each of the study arms (chemotherapy + either bevacizumab or placebo) All women had a new, histologically-confirmed diagnosis of EITHER a) high-risk FIGO stage I and IIa epithelial ovarian cancer, with grade 3 or clear cell histology, OR b) FIGO stage IIb-IV epithelial ovarian cancer OR c) fallopian tube or primary peritoneal cancer. All women had previously had surgical debulking, with the aim of maximal surgical cytoreduction, and had no plans for further surgical debulking before disease progression. (Women with inoperable stage III/IV disease were eligible (after biopsy), if no further surgery was planned.) The median age was 57 years (range 18 to 81) in the control group, and 57 years (range 24 to 82) in the bevacizumab group. 692 (45%) women had an ECOG performance status of 0, 720 (47%) had status 1 and 88 (6%) had status 2; data on performance status was unknown/unavailable for 28 (2%) women. 1340 (88%) women had epithelial ovarian cancer, 56 (3%) had fallopian tube cancer, 106 (7%) had primary peritoneal cancer and 26 (2%) women had cancer at multiple sites. Histology was serous in 1054 (69%) women, clear cell in 127 (8%), endometrioid in 117 (8%), mucinous in 34 (2%) and mixed/other in 196 (13%). 97 (6%) women had grade 1 disease, 317 (21%) had grade 2 and 1094 (72%) had grade 3; the grade was unknown for 20 (1%) women. 142 (9%) women had FIGO high-risk stage I/IIA disease (grade 3 or clear cell histology), 315 (21%) had stage IIB-IIIB and 1071 (70%) had stage IIIC/IV disease. 1111 (73%) women had optimal surgery (≤ 1 cm residual disease), 387 (25%) women had suboptimal surgery (> 1 cm residual disease) and 30 (2%) women had not had surgery. Baseline characteristics were similar between the two study arms. **Stratification variables** *FIGO stage and residuum* 1026 (67%) women had stage I-III disease with ≤ 1 cm residual disease, 290 (19%) women had stage I-III disease with > 1cm residual disease and 212 (14%) women had either inoperable stage III disease or stage IV.

ICON7 2015 *(Continued)*

	Intent to start chemotherapy 654 (43%) women intended to start chemotherapy ≤ 4 weeks from surgery; 874 (57%) women intended to start chemotherapy > 4 weeks from surgery.
Interventions	Women were randomised in a 1:1 ratio to cytotoxic chemotherapy (carboplatin and paclitaxel) with or without bevacizumab. Treatment continued until either disease progression or unacceptable toxicity. Randomisation was stratified on 3 variables: the stage and extent of debulking (stage I-III debulked ≤ 1 cm versus stage I-III debulked > 1 cm versus stage IV and inoperable stage III); the timing of starting the intended treatment (≤ 4 versus ≥ 4 weeks after surgery); and GCIG group **Control arm:** carboplatin AUC 6 IV over 30 to 60 minutes + paclitaxel 175 mg/m^2 IV over 3 hours on day 1 of cycle. Treatment repeats once every 3 weeks for up to 6 cycles **Intervention arm:** carboplatin + paclitaxel as in the control arm, plus bevacizumab 7.5 mg/kg IV over 30 to 90 minutes on the same day. Participants may receive the combination of bevacizumab + chemotherapy for up to 6 cycles, and then continue with bevacizumab alone (still once every 3 weeks) for up to 12 cycles. Participants were assessed by CT scan at baseline; CT scans were repeated after cycles 3 and 6, then at 9 and 12 months, then every 6 months in years 2 and 3, and then as indicated in years 4 and 5. Participants had clinical assessments/CA125 measurements at every chemotherapy cycle, then every 6 weeks during the maintenance phase in year 1, then every 3 months in years 2 and 3, and then every 6 months in years 4 and 5.
Outcomes	**Primary**: PFS (disease progression defined by RECIST guidelines on radiological, clinical or symptomatic progression; CA125 elevation alone was not defined as disease progression) **Secondary** • OS • Response rate • Duration of response • Toxicity **Substudies** • Quality of life • Health economics • Translational (biomarker) research
Notes	Trial protocol at: www.controlled-trials.com/isrctn/pf/91273375

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed centrally by computer system based at the Medical Research Council Clinical Trials Unit accessible via the web or telephone. Randomisation was done using 1:1 allocation and a minimisation algorithm with stratification according to grouping, combining FIGO stage and residual disease status, and planned interval between surgery and chemotherapy.
Allocation concealment (selection bias)	Low risk	Randomisation was performed centrally by computer system based at the Medical Research Council Clinical Trials Unit accessible via the web or telephone.

ICON7 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and physicians were not masked to treatment allocation (open-label study). Low risk for OS; high risk for PFS and adverse events
Blinding of outcome assessment (detection bias) All outcomes	High risk	Participants and physicians were not masked to treatment allocation (open-label study). Low risk for OS; high risk for PFS and adverse events
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis
Selective reporting (reporting bias)	Low risk	Outcomes reported (broadly) as per ClinicalTrials.gov protocol, and outcomes in protocol not modified after trial registration
Other bias	Unclear risk	An industry-sponsored trial

Karlan 2012

Study characteristics	
Methods	International, multi-centre, randomised, double-blind, placebo-controlled phase II trial
Participants	161 women were recruited from 38 sites in 5 countries. All had recurrent epithelial ovarian (FIGO stage II-IV), fallopian tube or primary peritoneal cancer (confirmed by histology/cytology). 53 participants were treated in arm 1 (paclitaxel + AMG 386 10 mg/kg), 53 in arm B (paclitaxel + AMG 386 3 mg/kg) and 55 in arm C (paclitaxel + placebo). All participants had radiographically-documented progression, as judged by RECIST or CA125 (GCIG criteria), and ≤ 3 anticancer therapies (but at least 1 platinum-containing regimen). All participants had a GOG performance status of 0 or 1, and adequate renal and hepatic function. The median age was 59 years (range 27 to 80 years) in arm A, 60 years (28 to 85) in arm B and 62 years (38 to 83) in arm C. 137 (85%) women had ovarian cancer; 21 (13%) women had primary peritoneal cancer; 3 (2%) women had fallopian tube cancer. Histology was serous in 87 (54%) women, endometrioid in 16 (10%), clear cell in 3 (2%), mucinous in 2 (1%), unclassified in 46 (29%) and unavailable in 7 (4%) women. 88 (55%) women had GOG performance status 0, 71 (44%) women had status 1, and 2 (1%) women had status 2 to 3. 6 (4%) women had FIGO stage I-II disease, 76 (47%) had stage III, and 41 (25%) had stage IV; the stage of disease was unknown or unavailable for 38 (24%) women. 87 (54%) women had a history of disease progression on or within 6 months of the last chemotherapy regimen. 8 (5%) women had previously been treated with anti-VEGF therapy. 145 (90%) women had measurable disease at baseline. 61 (38%) women had a history of one prior anticancer therapy; 100 (62%) had a history of two or more therapies.

Karlan 2012 *(Continued)*

	86 (53%) women had a history of one prior platinum regimen; 75 (47%) had a history of two or more. 12 (8%) women were platinum-refractory at baseline, 63 (39%) were platinum-resistant (PFI = platinum-free interval < 6 months), 53 (33%) were partially sensitive to platinum (PFI 6 to 12 months), and 31 (19%) women were platinum-sensitive (PFI > 12 months); data were unavailable on platinum-sensitivity status for 2 (1%) women. Baseline characteristics were fairly similar between all three study arms.
Interventions	Participants were stratified, based on whether or not they had had disease progression within 6 months of the last chemotherapy regimen, and on whether or not they had had prior anti-VEGF therapy. They were then randomised (1:1:1) to one of three arms, until disease progression, death or unacceptable toxicity (or withdrawn consent). **Arm A** (n = 53): paclitaxel at 80 mg/m^2 IV once weekly (3 weeks on/1 week off) plus AMG 386 at 10 mg/kg IV once weekly **Arm B** (n = 53): paclitaxel at 80 mg/m^2 IV once weekly (3 weeks on/1 week off) plus AMG 386 at 3 mg/kg IV once weekly **Arm C** (n = 55): paclitaxel at 80 mg/m^2 IV once weekly (3 weeks on/1 week off) plus placebo IV once weekly Participants in arm C who showed disease progression were allowed to have a period of open-label therapy with AMG 386 at 10 mg/kg IV weekly. Participants were assessed by CT or MRI scans of the chest, abdomen and pelvis every 8 weeks. CA125 lab values were obtained centrally every 8 weeks and locally as needed.
Outcomes	Primary: PFS (defined as time from randomisation to disease progression per RECIST, CA125 (GCIG criteria), clinical progression or death) Secondary • Overall survival • Response as per RECIST (ORR) • CA125 response (per GCIG) • Safety • Pharmacokinetics
Notes	The median follow-up time was 66 weeks in arm A (range 40 to 120), 65 weeks in arm B (range 40 to 112), and 64 weeks in arm C (range 40 to 110). One participant in arm A did not receive treatment because of grade 2 asthenia that occurred within 6 days of random assignment; all other randomly assigned participants received ≥1 dose. The analysis of safety data was restricted to treated participants (52 participants in arm A, 53 in arm B and 55 in arm C). The comparison of once-weekly AMG 386 plus paclitaxel for recurrent ovarian cancer is being further investigated in the phase III study TRINOVA-1 (see TRINOVA-1 2016). Trial protocol at www.clinicaltrials.gov/show/NCT00479817

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized… Random assignment was stratified by prior anti-VEGF therapy and disease progression on or within 6 months of the last chemotherapy." Precise method for random sequence generation not specified.

Karlan 2012 *(Continued)*

Allocation concealment (selection bias)	Low risk	Randomization was performed using "an automated voice response telephone system", which should help to ensure allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded and placebo-controlled. "Treatment assignments were blinded to patients and all study site personnel until the primary analysis."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"…data collected from patients after they had started to receive open-label AMG 386 were excluded from all efficacy analyses except overall survival". Restricted analyses to data collected during the double-blinded phase, to ensure blinded outcome assessment (other than for overall survival, which is less susceptible to bias).
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Primary efficacy analyses included the intent-to-treat analysis set (data collected from patients after they had started to receive open-label AMG 386 were excluded from all efficacy analyses except overall survival). Safety analyses included data from the double-blind phase for all patients who received ≥ 1 dose ofAMG386 or placebo." 190 women were assessed for eligibility, of whom 161 were randomised (53 to arm A, 53 to arm B, 55 to arm C). Efficacy analyses included all randomised participants (intention-to-treat). One participant in arm A did not receive any of the allocated treatment, and was excluded from safety analyses. Discontinuations of treatment, with reasons, are given in the detailed CONSORT diagram.
Selective reporting (reporting bias)	Low risk	We checked the study protocol (registered with ClinicalTrials.gov). The main outcomes reported in the paper, including PFS and safety/ tolerability, were present in the version registered in October 2007. Other outcomes (including OS) were registered by March 2008.
Other bias	Unclear risk	This study is at least partially industry-sponsored, with several authors reporting employment or leadership positions, stock ownership, honoraria, or research funding from Amgen.

Ledermann 2011

Study characteristics	
Methods	Randomised, double-blind, placebo-controlled, phase II trial Participants were randomised in a 1:1 ratio with minimisation and stratification by complete versus partial response to the most recent chemotherapy; length of treatment-free interval before entering the trial (< 6 versus ≥ 6 months); and number of lines of previous chemotherapy (2 versus 3 or 4 lines).
Participants	• 84 participants • Chemotherapy-responsive relapsed ovarian cancer (i.e. all women had previously had relapsed ovarian cancer, which had then responded to their last (at least second-line) chemotherapy, according to GCIG criteria). • 44 women were in the intervention (BIBF 1120) arm and 40 in the placebo arm. • The mean age was 60 years (range 27 to 76 years). • 41% of women had had a treatment-free interval before prior chemotherapy of < 6 months; 59% had had an interval of 6 to 12 months. • Life expectancy of at least 3 months

Ledermann 2011 *(Continued)*

	• ECOG performance status 0 to 1
Interventions	**Intervention:** BIBF 1120 (250 mg, oral, twice daily, given for up to 9 months) **Control:** placebo (250 mg, oral, twice daily for up to 9 months)
Outcomes	**Primary**: PFS Rate at 36 weeks (confirmed by CT assessment, performed at 12-week intervals) **Secondary** • Time to tumour progression according to RECIST and the tumour marker CA125 • PFS at 3 and 6 months • Survival at 9 months • Incidence and intensity of adverse events at 9 months
Notes	The median duration of treatment was 116 days (range 2 to 281 days) in the intervention (BIBF 1120) arm and 101 days (range 2 to 239 days) in the placebo arm. The PFS rate at 36 weeks was 15.6% (95% CI 3.8 to 27.3%) for the BIBF 1120 arm and 2.9% (95% CI 0.0 to8.4%) for the placebo arm. The PFS HR was 0.68 (95% CI 0.42 to 1.09) The median time to progression by RECIST criteria was 4.8 months in the BIBF 1120 arm and 2.8 months in the placebo arm. Trial protocol at www.clinicaltrials.gov/show/NCT00710762 This study was included in the previous version of this review, based on information from a conference abstract. The full paper has now been published.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details to assess this domain. The term "randomised" was used in the title, and the Methods section refers to participants being "randomly assigned", with minimisation and stratification, but no further details were provided regarding random sequence generation.
Allocation concealment (selection bias)	Low risk	Participants were randomly assigned to the intervention or control arm using a telephone interactive voice response system. Trial staff and patients were unaware of the allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial. Participants who were alive and progression-free after nine cycles were allowed to continue evaluated drug (treatment allocation unblinded).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data analysis according to intention-to-treat (all randomised participants)

Ledermann 2011 *(Continued)*

Selective reporting (reporting bias)	Low risk	Outcomes broadly reported as specified on ClinicalTrials.gov record
Other bias	Unclear risk	Some participants did not meet the initial criteria for treatment intervals (analysed and reported in a separate analysis). An industry-sponsored trial with several authors disclosing receipt of personal grants and funding from the industry.

Li 2019

Study characteristics	
Methods	A randomised controlled trial Randomisation was via random number table.
Participants	68 participants randomised (34 in intervention arm, 34 in control arm) Platinum-sensitive recurrent ovarian cancer
Interventions	**Intervention:** chemotherapy with paclitaxel and carboplatin + bevacizumab **Control:** chemotherapy with paclitaxel and carboplatin Prior to chemotherapy, both groups were treated with dexamethasone, 5-hydroxytryptamine 3 antagonists, anti-allergic, and anti-emetic treatments.
Outcomes	Somewhat unclear. Abstract reports results for 'Clinical efficacy' and adverse events/ toxicity.
Notes	Only limited information identifiable from an abstract. Attempted to contact authors for further information, but no contact details identifiable. No mention in the abstract of whether study was blinded versus open-label.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation via "the method of random number table"
Allocation concealment (selection bias)	Unclear risk	Details not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	It seems that data from all randomised participants were analysed.

Li 2019 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient details to assess this domain (conference abstract)
Other bias	Unclear risk	Study findings available only in the form of a conference abstract. Unavailable clinical trial registration number

Li 2021

Study characteristics	
Methods	"Divided into observation group and control group by random number table"
Participants	70 participants with recurrent platinum-resistant relapsed and metastatic ovarian cancer
Interventions	Albumin-binding paclitaxel monotherapy (days 1, 8 and 15) versus "observation group was treated with bevacizumab based on the treatment of the control group"
Outcomes	Clinical efficacy (PFS, OS and ORR), adverse reactions and quality of life of participants, immune function
Notes	Unable to get a copy of the full-text paper as it is in Chinese, so data from abstract only. We therefore have minimal information regarding participant characteristics and methodology. High risk of bias and so not yet included in meta-analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants "with recurrent ovarian cancer were divided into observation group and control group by random number table"
Allocation concealment (selection bias)	Unclear risk	No details available in English language abstract
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details available in English language abstract
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details available in English language abstract
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No evidence of published protocol and minimal data available in English language abstract
Selective reporting (reporting bias)	Unclear risk	No evidence of published protocol and minimal data available in English language abstract
Other bias	Unclear risk	No evidence of published protocol and minimal data available in English language abstract

Liu 2019a

Study characteristics	
Methods	A single-centre, randomised controlled trial Participants were randomised in a 1:1 ratio to the intervention or control arms.
Participants	• 86 participants randomised (43 to intervention group, 43 to control group) • Platinum-resistant recurrent ovarian cancer, with clear histological type and TNM stage information • Previous cytoreductive surgery • ECOG performance status ≤ 1 • Positive VEGF expression by immunohistochemistry
Interventions	**Intervention:** albumin-bound paclitaxel (135 to 175 mg/m^2, once a day) + bevacizumab (7.5 mg/kg), for 3 weeks per cycle, for 6 cycles **Control:** albumin-bound paclitaxel (135 to 175 mg/m^2, once a day) for 3 weeks per cycle, for 6 cycles
Outcomes	ORR, disease control rate, safety (NCI CTCAE v3.0), serum CA125 levels at 4 weeks after treatment, median PFS and median OS (not clearly stated which outcome was primary)
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation performed using table of random numbers
Allocation concealment (selection bias)	Unclear risk	Insufficient details to assess this domain
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient details to assess this domain
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient details to assess this domain
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts for the entire follow-up time
Selective reporting (reporting bias)	Unclear risk	Insufficient data to assess this domain (no clinical trial registration number or study protocol)
Other bias	Unclear risk	Unavailable clinical trial registration number

Liu 2019b

Study characteristics

Liu 2019b *(Continued)*

Methods	An open-label, parallel-assignment, multi-centre, randomised, phase II trial Participants were randomised in a 1:1 ratio with permuted blocks, stratified by germline *BRCA* status and previous antiangiogenic therapy.
Participants	90 participants randomised Age 18 or older Relapsed platinum-sensitive ovarian, fallopian tube or primary peritoneal cancer High-grade serous or endometrioid histology or deleterious germline *BRCA1/2* mutation
Interventions	**Intervention:** olaparib (200 mg twice daily) + cediranib (30 mg daily) **Control:** olaparib (400 mg twice daily) Treatment continued until disease progression (by RECIST 1.1), until adverse events meeting discontinuation criteria, or until treatment discontinuation for other reasons.
Outcomes	**Primary:** PFS (assessed by site investigator) **Secondary** • ORR • Toxicity (graded by CTCAE version 4.0) • OS
Notes	This study was mentioned in the previous version of this review as an 'ongoing study', identified by the (now defunct) identifier NCT01115829. Trial protocol at: www.clinicaltrials.gov/ct2/show/NCT01116648 (protocol includes a phase I study as well) Funding: American Recovery and Reinvestment Act grant from the National Institutes of Health (NIH) (3 U01 CA062490-16S2); Intramural Program of the Center for Cancer Research; and the Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomised allocations were generated using the in-house software RANSCH (developed by the Eastern Cooperative Oncology Group Statistical Center). Participants were randomised by the DFHCC (Dana-Farber/Harvard Cancer Center) Quality Assurance Office for Clinical Trials in a 1:1 ratio by permuted blocks stratified by *BRCA* mutation status and by receipt of previous anti-angiogenic therapy in the first-line setting.
Allocation concealment (selection bias)	Low risk	Randomisation was done by the DFHCC Quality Assurance Office for Clinical Trials. Participants, doctors and data analysers were unaware of the randomisation pattern.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Blinding of outcome assessment (detection bias)	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes

Liu 2019b *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Paper includes a flow diagram showing all attritions/exclusions. An intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Outcomes reported are broadly in keeping with those specified in the study protocol on the ClinicalTrials.gov website.
Other bias	Unclear risk	An industry-sponsored trial with several authors disclosing receipt of personal grants and funding from the industry

Liu 2021a

Study characteristics	
Methods	A single-centre, randomised controlled trial. Participants were randomised in a 1:1 ratio to intervention or control by a 'random number grouping' method.
Participants	76 participants randomised (38 in intervention group, 38 in control group) Platinum-resistant recurrent epithelial ovarian cancer **Inclusion criteria** • 18 to 75 years old • KPS ≥ 70 • Expected survival time ≥ 6 months • Previous cytoreductive surgery and platinum-based chemotherapy after surgery, and complete response after chemotherapy • Recurrent disease within 6 months after stopping the planned chemotherapy, no indication for surgery after multi-disciplinary team (MDT) diagnosis and treatment • At least one measurable lesion • No antitumor therapy within 4 weeks **Exclusion criteria** • Heart, brain, lung, liver, kidney or other vital organ dysfunction • Previous splenectomy • Pregnant and lactating women • History of peptic ulcer with unhealed wound • Hypertensive crisis • Allergic constitution • Cachexia or mental disorders and unable to cope with treatment • People with second primary tumour
Interventions	**Intervention:** liposomal doxorubicin chemotherapy for 4 cycles + bevacizumab **Control:** liposomal doxorubicin chemotherapy for 4 cycles
Outcomes	• Changes in serum tumour markers (HE4 and CA125) • Objective response rate

Liu 2021a *(Continued)*

	• Disease control rate • Overall survival • Progression-free survival • Adverse events (CTCAE v4.0) (Unclear which is primary outcome although ORR reported before other outcomes in text)
Notes	Full text kindly translated by Dr Yi Yin

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details to assess this domain; "random number grouping method"
Allocation concealment (selection bias)	Unclear risk	Insufficient details to assess this domain; "random number grouping method"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details to assess this domain. 3 participants withdrawn from study after 4 cycles, but no flow chart for study.
Selective reporting (reporting bias)	Unclear risk	Insufficient details to assess this domain
Other bias	Unclear risk	Funding source not declared

Liu 2022

Study characteristics

Methods	An open-label, parallel-assignment, phase III, randomised controlled trial; participants randomised in a 1:1:1 ratio
Participants	• Randomised 565 (187 standard of care, 189 olaparib, 189 cediranib and olaparib) • 528 participants initiated treatment (166 standard of care; 183 olaparib; 179 cediranib and olaparib); 565 eligible participants enrolled and randomised. 28 participants (20 chemotherapy, six olaparib/cediranib, and two olaparib) did not start assigned study treatment • Platinum-sensitive recurrent high-grade serous or high-grade endometrioid ovarian, primary peritoneal, or fallopian tube cancers; participants with other high-risk histologies were also eligible, provided that they had a known deleterious germline *BRCA*1 or *BRCA*2 mutation • RECIST 1.1 measurable disease OR evaluable disease • Prior chemotherapy must have included a first-line platinum-based regimen with or without intravenous consolidation chemotherapy • ECOG 0 to 2 (Karnofsky ≥ 60%)

Liu 2022 *(Continued)*

Interventions	**Intervention 1**: olaparib 300 mg orally twice daily. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity. **Intervention 2:** olaparib 200 mg orally twice daily and cediranib maleate 30 mg orally four times daily. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity. **Control:** platinum-based chemotherapy (one of the three regimens described below, per investigator choice). **Regimen I:** participants receive paclitaxel IV over 3 hours and carboplatin IV over 30 to 60 minutes on day 1. Treatment repeats every 21 days for at least 4 cycles in the absence of disease progression or unacceptable toxicity. **Regimen II:** participants receive gemcitabine hydrochloride IV over 30 minutes on days 1 and 8, and carboplatin IV over 30 to 60 minutes on day 1. Treatment repeats every 21 days for at least 4 cycles in the absence of disease progression or unacceptable toxicity. **Regimen III:** participants receive pegylated liposomal doxorubicin hydrochloride IV and carboplatin IV over 30 to 60 minutes on day 1. Treatment repeats every 28 days for at least 4 cycles in the absence of disease progression or unacceptable toxicity.
Outcomes	**Median follow-up time:** 29.1 months **Primary:** PFS (investigator-assessed, using RECIST v1.1) **Secondary** • OS • Response • Frequency and severity of adverse effects • Patient-reported scores of disease-related symptoms as measured by the National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Ovarian Symptom Index-18 Disease-Related Symptom-Physical
Notes	28% of participants randomised to the chemotherapy arm received non-protocol therapy, mainly PARP inhibitor maintenance (which was approved by the FDA during the course of the study). OS data not yet mature in paper published in 2022.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participants were enrolled via a web-based registration system. Three protocol treatment regimens were assigned in a 1:1:1 fashion using random permuted blocks, stratified by germline *BRCA*1/2 mutation (yes v no), prior platinum-free interval (6 to 12 months v. 12 months), and prior receipt of antiangiogenic treatment (yes v no)." [Methods]
Allocation concealment (selection bias)	Unclear risk	"Treatment assignment remained concealed until the registration process was completed." [Methods]
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes

Liu 2022 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Performed an intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Outcomes reported (broadly) as per ClinicalTrials.gov protocol
Other bias	Unclear risk	Study partly funded by AstraZeneca

Matulonis 2019

Study characteristics	
Methods	An open-label, multi-centre, randomised, phase II trial Participants were randomised in a 1:1 ratio stratified by platinum-free interval, measurable disease status and prior use of bevacizumab therapy.
Participants	• 111 participants randomised (57 in cabozantinib arm, 54 in paclitaxel arm) • 18 years or older • Persistent or recurrent epithelial ovarian, fallopian tube or primary peritoneal carcinoma (platinum-resistant or platinum-sensitive) • Performance status 0 to 2 • At least 1 but not > 3 prior chemotherapy regimens
Interventions	**Median follow-up time** 13.9 months for cabozantinib arm and 14.5 months for paclitaxel arm **Intervention:** cabozantinib 60 mg orally daily continuously **Control:** paclitaxel 80 mg/m^2 weekly on days 1, 8 and 15 of a 28-day cycle Treatment continued until disease progression or treatment-limiting toxicity.
Outcomes	**Primary**: PFS **Secondary** • OS • Toxicity • Event-free survival • Exploratory translational objectives
Notes	Trial protocol at www.clinicaltrials.gov/ct2/show/NCT01716715 Study supported by grants from the National Cancer Institute.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details to assess this domain
Allocation concealment (selection bias)	Unclear risk	Insufficient details to assess this domain

Matulonis 2019 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled participants are included in the PFS and OS analyses. The toxicity analyses only included participants who received at least one dose of treatment.
Selective reporting (reporting bias)	Unclear risk	Outcomes broadly reported as per trial protocol on ClinicalTrials.gov website. However, the trial protocol lists the primary outcome simply as PFS, whereas in the main paper the authors specify that the primary outcome was whether the difference in PFS between the groups, when ascertained at a specific time, was above a certain statistical magnitude, such as to justify further investigation of the study drug. In the supplementary materials to the main paper, the authors also explain that the statistical analysis method used for the primary outcome of PFS was slightly altered from the initial study protocol, due to an initial misunderstanding of some details of the intended analysis method, which had been previously described by another group.
Other bias	Low risk	Study supported by National Cancer Institute grants to the Gynecologic Oncology Group Administrative Office (CA 27469), the Gynecologic Oncology Group Statistical and Data Center (CA 37517), NRG Oncology (1 U10 CA180822), NRG Operations (U10CA180868) and UG1CA189867 (NCORP)

McGuire 2018

Study characteristics	
Methods	Phase II, open-label, randomised controlled trial
Participants	• Women aged ≥18 years with histologically- or cytologically-confirmed platinum-refractory/resistant ovarian cancer from 22 study sites in 3 countries • 125 randomised, 2 not treated, 123 participants included in the modified intention-to-treat population (62 in intervention arm, 61 in control arm) • ECOG performance status 0 to 1 at study entry
Interventions	Randomisation to either arm A or arm B, continuing until disease progression or other withdrawal criteria. **Intervention:** liposomal doxorubicin (40 mg/m^2 on day 1) + IMC-3G3 (olaratumab) (20 mg/kg on days 1 and 15) on a 28 day cycle **Control:** liposomal doxorubicin (40 mg/m^2) on day 1 of a 28 day cycle Participants in the control arm may receive IMC-3G3 (olaratumab) monotherapy upon disease progression (IMC-3G3 is an inhibitor of PDGF-R-alpha, another tyrosine kinase enzyme involved in angiogenesis, and which is often associated with VEGF-R.)

McGuire 2018 *(Continued)*

Outcomes	**Primary**: PFS **Secondary** • OS • Objective response rate • Median duration of response • Adverse events • IMC-3G3 (olaratumab) antibody and pharmacokinetic assessments
Notes	Protocol online at: www.clinicaltrials.gov/show/NCT00913835 Presented as ongoing trial poster/abstract at American Society of Clinical Oncology (ASCO) 2010 This study was mentioned as an 'ongoing study' in the previous version of this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was performed via an automated interactive system, with stratification based on the previous response to platinum therapy (refractory versus resistant). No further details of random sequence generation
Allocation concealment (selection bias)	Low risk	Randomisation performed by study site personnel via a call-in interactive voice response system or interactive web response system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial. High risk of bias for PFS and adverse events, low risk of bias for OS
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial. High risk of bias for PFS and adverse events, low risk of bias for OS.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis of both primary and secondary endpoints was by a modified intention-to-treat population which included all participants who were randomised and received any quantity of study drug. 125 randomised, 2 not treated, 123 analysed.
Selective reporting (reporting bias)	Low risk	Outcomes reported in the published paper are broadly in keeping with those in the original protocol.
Other bias	Unclear risk	An industry-sponsored trial with several authors disclosing a financial conflict of interest.

METRO-BIBF 2020

Study characteristics

Methods	A randomised, double-blind, parallel-assignment, phase II, controlled trial. Randomisation was performed using an interactive web-based system, with stratified randomisation according to: age (≤ 60 and > 60), previous lines of chemotherapy (≤ 3 or > 3) and previous bevacizumab treatment (yes or no).
Participants	• 117 randomised, 117 analysed

METRO-BIBF 2020 *(Continued)*

- Female participants, ≥ 18 years, histologically-proven recurrent advanced epithelial ovarian, fallopian tube or primary peritoneal carcinomas
- Have either undergone a hysterectomy or bilateral oophorectomy/salpingectomy and/or have been postmenopausal for 24 consecutive months (i.e. who have not had menses at any time in the preceding 24 consecutive months without an alternative medical cause)
- Performance status 0 to 2
- Life expectancy > 6 weeks
- Received 2 or more lines of chemotherapy for ovarian cancer and participant is platinum-resistant or platinum-intolerant or not suitable for any further standard intravenous chemotherapy
- No previous oral cyclophosphamide, nintedanib, or other tyrosine kinase inhibitors but can have received anti-VEGF therapies
- Measurable lesions according to RECIST 1.1 criteria or serum CA125 levels welcomed but not a prerequisite for inclusion
- Previous VEGF (bevacizumab) treatment (Yes): nintedanib 18 (30.5%) placebo 17 (30.9%)
- Number of lines of previous chemotherapy; N (%)
  - 2: nintedanib 7 (11.9%) placebo 7 (12.7%)
  - 3: nintedanib 14 (23.7%) placebo 15 (27.3%)
  - 4: nintedanib 16 (27.1%) placebo 10 (18.2%)
  - ≥ 5: nintedanib 22 (37.3%%) placebo 23 (41.8%)

Interventions	**Intervention:** nintedanib + oral metronomic cyclophosphamide: when the trial began, the starting dose of nintedanib was 200 mg twice daily. The Independent Data Monitoring Committee examined serious adverse events and toxicity data from the initial 61 participants. As a result, a reduced starting dose of nintedanib to 150 mg twice daily was implemented for future recruits. Dose reductions were allowed to a minimum of 100 mg twice daily nintedanib/placebo and 50 mg once daily OMC **Control:** placebo + oral metronomic cyclophosphamide (100 mg once daily), in cycles of 6 weeks
Outcomes	**Median follow-up time**: 1.6 years (IQR: 1.4 to 1.9 years) **Primary:** PFS using RECIST v1.1 **Secondary** • OS • Frequency and severity of adverse effects • Patient-reported scores of disease-related symptoms as measured by the National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Ovarian Symptom Index-18 Disease-Related Symptom-Physical
Notes	Numerous grants and funding received from pharmaceutical companies declared by the study authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was performed using an interactive web-based system, with stratified randomisation according to age, previous lines of chemotherapy and previous use of bevacizumab
Allocation concealment (selection bias)	Low risk	Randomisation was performed using an interactive web-based system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	According to ClinicalTrials.gov record, study had triple masking (participant, care provider, investigator)

METRO-BIBF 2020 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	According to ClinicalTrials.gov record, study had triple masking (participant, care provider, investigator)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis of the data from all randomised participants (intention-to-treat). However, QoL data available for 80/117 participants (68.4%)
Selective reporting (reporting bias)	Low risk	Outcomes are broadly analysed and reported as specified in the ClinicalTrials.gov record
Other bias	Unclear risk	An industry-sponsored trial with several authors disclosing receipt of personal grants and funding from the industry

MITO-11 2015

Study characteristics	
Methods	A multi-centre, open-label, randomised, phase II trial Participants were randomised in a 1:1 ratio to intervention or control, using a computer-generated minimisation procedure stratified by centre, number of previous lines of chemotherapy and platinum-free interval status.
Participants	• 74 participants randomised (37 to intervention arm, 37 to control arm) • Aged 18 to 75 • Cytological or histological diagnosis of epithelial ovarian, fallopian tube or primary peritoneal cancer • FIGO stage IC-IV • Platinum-resistant or platinum-refractory disease • Maximum of 2 previous lines of chemotherapy • ECOG performance status 0 to 1 • No residual peripheral neurotoxicity • Life expectancy of at least 3 months
Interventions	**Intervention:** paclitaxel (80 mg/m^2 on days 1, 8 and 15 in a 28-day cycle) + pazopanib (800 mg daily) **Control:** paclitaxel (80 mg/m^2 on days 1, 8 and 15 in a 28-day cycle)
Outcomes	**Median follow-up**: 16.1 months (IQR 12.5 to 20.8) **Primary**: PFS (assessed in modified ITT population) **Secondary** • OS • Toxicity • Objective response rate
Notes	Study funded by the National Cancer Institute of Naples. GlaxoSmithKline provided the pazopanib free of charge and partly funded the study.
Risk of bias	

MITO-11 2015 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed centrally by a computer-generated minimisation procedure. Random allocation was stratified by centre, number of previous lines of chemotherapy and platinum-free interval status
Allocation concealment (selection bias)	Low risk	Randomisation was performed centrally at the Clinical Trials Unit, National Cancer Institute (Napoli, Italy)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only one person randomised and not included (withdrew consent immediately after randomisation)
Selective reporting (reporting bias)	Low risk	Outcomes broadly analysed and reported as outlined on ClinicalTrials.gov record
Other bias	Unclear risk	An industry co-sponsored trial with two authors disclosing having received research funding from the industry

MITO-16b 2021

Study characteristics	
Methods	An open-label, multi-centre, randomised controlled, phase III trial Participants were randomised in a 1:1 ratio to intervention versus control via the trial website with a minimisation procedure stratified by centre, time of recurrence, performance status and type of second-line chemotherapy.
Participants	• 406 participants randomised • 18 years or older • Histologically-confirmed platinum-sensitive recurrent ovarian, fallopian tube or primary peritoneal carcinoma • FIGO stage IIIB-IV • RECIST-evaluable disease present at baseline • Life expectancy of at least 12 weeks • ECOG performance status 0 to 2
Interventions	**Intervention:** chemotherapy (as in control arm) + bevacizumab (10 mg/kg IV every 14 days if combined with PLD-carboplatin, or 15 mg/kg every 21 days if combined with gemcitabine-carboplatin or paclitaxel-carboplatin). Those who did not progress after combined treatment continued with bevacizumab maintenance therapy (15 mg/kg every 21 days) until disease progression or unacceptable toxicity. **Control:** carboplatin-based chemotherapy with investigators' choice of 1 of 3 different regimens (declared before randomisation), planned for 6 cycles:

MITO-16b 2021 *(Continued)*

- carboplatin (AUC = 5) + paclitaxel (175 mg/m^2) both on day 1, every 21 days
- carboplatin (AUC = 4 on day 1) + gemcitabine (1000 mg/m^2 on days 1 and 8), every 21 days
- carboplatin (AUC = 5 on day 1) + pegylated liposomal doxorubicin (PLD, 30 mg/m^2 on day 1), every 28 days

Outcomes	**Median follow-up**: 20.1 months (IQR 12.9 to 27.8) (as of data cutoff on 28 February 2018) **Primary:** investigator-assessed PFS (the time from randomisation to the first occurrence of either disease progression or death from any cause) **Secondary** • OS (time from randomisation to death from any cause) • Toxicity (CTC AE 4.0) • Centrally reviewed PFS • ORR (RECIST 1.1, defined as the proportion of participants who had a complete response or partial response)
Notes	Hoffmann–La Roche provided bevacizumab and partial funding for trial activities and for the translational project. "Associazione Italiana per la Ricerca sul Cancro supported translational studies with the IG 5776 not reported in this Article. The funders of the study had no role in study design, protocol writing, data collection, data analysis, data interpretation, and writing of the report."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned (1:1) by a web-based central randomisation procedure. Randomisation was done with a minimisation procedure and stratified by centre, time of recurrence, ECOG performance status and type of second-line chemotherapy
Allocation concealment (selection bias)	Low risk	Registration, randomisation and data collection were web-based at the Clinical Trial Unit of the Istituto Nazionale Tumori (Naples, Italy)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open-label study. Low risk of bias for OS and PFS as the analysis used assessment performed by masked independent central review. High risk of bias for adverse events
Incomplete outcome data (attrition bias) All outcomes	Low risk	Efficacy analysis for all randomised participants (ITT population)
Selective reporting (reporting bias)	Low risk	Outcomes broadly reported as specified on the ClinicalTrials.gov record
Other bias	Unclear risk	An industry-sponsored trial with several authors disclosing receipt of personal grants and funding from the industry

NICCC 2020

Study characteristics	
Methods	An international, multi-centre, open-label, phase II, randomised trial
Participants	• 91 participants with ovarian cancer (same study also looked at clear cell endometrial carcinoma) • Histologically-confirmed recurrent clear cell ovarian cancer
Interventions	**Intervention:** nintedanib 200 mg orally twice daily. Treatment until disease progression or unacceptable toxicity. **Control:** chemotherapy with investigators' choice of either paclitaxel (80 mg/m^2 on days 1, 8 and 15), pegylated liposomal doxorubicin (40 mg/m^2) or topotecan (4 mg/m^2 on days 1, 8, 15), on a 28-day cycle, typically for up to 6 cycles.
Outcomes	**Median follow-up**: 20.7 months **Primary**: PFS **Secondary** • OS • Response rate • Disease control rate • QoL • Patient-reported outcomes
Notes	Trial protocol at www.clinicaltrials.gov/ct2/show/NCT02866370 The study was funded by an educational grant from Boehringer Ingelheim and supported by Cancer Research UK Grant ref: C8361/A15600.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details to assess this domain
Allocation concealment (selection bias)	Unclear risk	Insufficient details to assess this domain
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details to assess this domain
Selective reporting (reporting bias)	Unclear risk	Insufficient details to assess this domain

NICCC 2020 *(Continued)*

Other bias	Unclear risk	An industry-sponsored trial

Nishikawa 2020

Study characteristics

Methods	A parallel-assignment, open-label, phase II, randomised controlled trial Clinical trial registration number: JGOG3023; UMIN000017247
Participants	• Target = 106, reported in the abstract = 103 • Age 20 or over • Histologocally-confirmed epithelial ovarian, fallopian tube or primary peritoneal carcinoma • Platinum-resistant disease (defined as progression within < 6 months from completion of a minimum of 3 platinum therapy (including bevacizumab) cycles. • Performance status ECOG 0 to 2 • Participants could be included if they have a RECIST progression, with either measurable or non-measurable disease. Participant who can be evaluated based on GCIG CA125 criteria was allowed • Life expectancy of ≥ 90 days • Exclusion: previous treatment with ≥ 4 anticancer regimens
Interventions	**Intervention:** single-agent chemotherapy (no more details) plus bevacizumab **Control:** single-agent chemotherapy (no more details)
Outcomes	**Primary:** investigator-assessed PFS **Secondary** • OS • ORR • Safety (no details)
Notes	Conference abstract only - minimal details available and preliminary results Industry-sponsored trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient details to assess this domain
Allocation concealment (selection bias)	Unclear risk	Based on clinical trial registration entry, there was a central registration.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes

Nishikawa 2020 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Specified target sample of 106 participants, number given in the conference abstract 103.
Selective reporting (reporting bias)	Unclear risk	Insufficient details to assess this domain
Other bias	Unclear risk	An industry-sponsored trial

OCEANS 2015

Study characteristics	
Methods	Phase III, randomised, double-blind (participant, investigator), placebo-contolled, parallel-assignment, multi-centre study
Participants	Women ≥ 18 years old, with documented ovarian, primary peritoneal or fallopian tube carcinoma that has recurred, with measurable disease, and no prior chemotherapy in the recurrent setting
Interventions	Randomisation to experimental arm (bevacizumab + carboplatin + gemcitabine) or placebo comparator (placebo + carboplatin + gemcitabine)
Outcomes	**Primary:** PFS **Secondary** • Objective response and duration of response • OS • Incidence of gastrointestinal perforation • Characterisation of the safety of bevacizumab in combination with carboplatin and gemcitabine • Incidence of all adverse events
Notes	Protocol online at clinicaltrials.gov/show/NCT00434642

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was via an interactive voice response system in a 1:1 ratio, stratified by time from last platinum treatment to recurrence and cytoreductive surgery for recurrence. No further details
Allocation concealment (selection bias)	Low risk	Randomisation was via an interactive voice response system in a 1:1 ratio, stratified by time from last platinum treatment to recurrrence and cytorediuctive surgery for recurrence.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study sponsor, contract research organisation, investigators, and participants were blinded to treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study sponsor, contract research organisation, investigators, and participants were blinded to treatment assignment.

OCEANS 2015 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Data analysed according to intention-to-treat for efficacy, and per-protocol for toxicity
Selective reporting (reporting bias)	Low risk	Outcomes specified in the ClinicalTrials.gov record reported in the trial publication and broadly correspond with each other.
Other bias	Unclear risk	An industry-sponsored trial

OCTOVA 2021

Study characteristics	
Methods	An open-label, multi-centre, phase II, randomised study Participants were randomised in a 1:1:1 ratio to the 3 arms of the trial, stratified by prior PARP or anti-angiogenic therapy or germline *BRCA*1/2 status.
Participants	• 139 participants randomised to 3 arms • High-grade ovarian, fallopian tube or primary peritoneal cancer • Recurrent platinum-resistant ovarian cancer with relapse within 12 months of previous platinum-based therapy (90% had relapsed within 6 months)
Interventions	**Intervention:** olaparib (300 mg daily) + cediranib (20 mg daily) (n = 47) **Control** (olaparib): olaparib (300 mg daily) (n = 46) **Control** (chemotherapy): paclitaxel (n = 46)
Outcomes	**Primary:** PFS **Secondary** • Safety and tolerability • OS • Objective response rate • Quality of life
Notes	Industry-funded trial (AstraZeneca) with several authors disclosing a financial conflict of interest.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient details to assess this domain
Allocation concealment (selection bias)	Low risk	Site staff completed the trial randomisation form and emailed it to the OCTOVA 2021 Trial Office
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes

OCTOVA 2021 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis for all randomised participants (ITT population)
Selective reporting (reporting bias)	Unclear risk	Insufficient details to assess this domain - conference abstract and presentation
Other bias	Unclear risk	An industry co-sponsored trial

Reyners 2012

Study characteristics	
Methods	An open-label, phase II, randomised trial Participants had an up-front staging laparotomy with or without cytoreductive surgery, then were randomised to the intervention or control arms.
Participants	• 202 participants enrolled and randomised, of whom 6 were excluded for specified reasons. 196 included in analyses - 97 in intervention arm and 99 in control arm • Histologically-confirmed epithelial ovarian, fallopian tube or primary peritoneal cancer • FIGO stage IC to IV
Interventions	**Intervention:** docetaxel (75 mg/m^2) + carboplatin (AUC = 5) + celecoxib (400 mg twice daily) **Control:** docetaxel (75 mg/m^2) + carboplatin (AUC = 5) Chemotherapy (docetaxel + carboplatin) was given on 3-weekly cycles for up to 6 to 9 cycles. Celecoxib could be continued as maintenance treatment for up to 3 years in the absence of progressive disease.
Outcomes	**Median follow-up**: 26 months (2 to 85 months) **Primary** • Response rate • PFS **Secondary** • Safety • OS
Notes	"The study was put on hold 20 December 2004 due to the withdrawal of Food and Drug Administration (FDA) approval of rofecoxib (Vioxx®), another COX-2 inhibitor, for cardiovascular side-effects. Patients were informed by a special letter indicating potential untoward cardiovascular events. In July 2005, the study was continued after adapting the informed consent accorded by the central Medical Ethical Trials Committee." Discontinuation of celecoxib for over 6 months due to wider safety concerns about COX-2 inhibitors. Of intervention-arm participants, 24% (23/97) discontinued celecoxib during chemotherapy and 27% (17/63) of those who started maintenance treatment discontinued treatment, largely due to adverse reactions.

Reyners 2012 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information provided to assess
Allocation concealment (selection bias)	Unclear risk	Insufficient information provided to assess
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial. High risk of bias for PFS and adverse events, low risk of bias for OS
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial. High risk of bias for PFS and adverse events, low risk of bias for OS
Incomplete outcome data (attrition bias) All outcomes	Low risk	202 participants enrolled and randomised, of whom 6 were excluded for specified reasons (no ovarian cancer after pathology review, previous chemotherapy, alcohol abuse and withdrew consent).
Selective reporting (reporting bias)	Unclear risk	The outcomes reported correspond to those in the online protocol, but this was apparently registered retrospectively.
Other bias	Unclear risk	The trial was supported by an unrestricted grant from industry (Pfizer Inc.). Of intervention-arm participants, 24% (23/97) disconinued celecoxib during chemotherapy and 27% (17/63) of those who started maintenance treatment discontinued treatment, largely due to adverse reactions.

Richardson 2018

Study characteristics

Methods	A national, randomised, double-blind, placebo-controlled, phase II trial Participants were randomised in a 1:1 ratio to the intervention or control arms. Randomisation used a permuted block design and was stratified by platinum-free interval, measurable disease status and prior use of bevacizumab therapy.
Participants	• 106 participants randomised (54 to intervention arm, 52 to control arm) • Age 18 years or older • Histologically-confirmed persistent or recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer (both platinum-sensitive and platinum-resistant) • 1 to 3 prior regimens • Performance status 0 to 2
Interventions	**Intervention:** paclitaxel (80 mg/m^2 weekly on days 1, 8 and 15 out of a 28-day cycle) + pazopanib (800 mg daily) **Control:** paclitaxel (80 mg/m^2 weekly on days 1, 8 and 15 out of a 28-day cycle) + placebo (daily) Treatment continued until disease progression or adverse effects prohibited further therapy.
Outcomes	Median follow-up time: 17.7 months (range 0.1 to 26.5)

Richardson 2018 *(Continued)*

	Primary: PFS **Secondary** • OS • Proportion responding • Adverse events • Translational research objectives
Notes	Study supported by grants from the National Cancer Institute (USA). Trial protocol at www.clinicaltrials.gov/ct2/show/NCT01468909

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised 1:1 using a permuted block design (block size, 1) and stratified by their platinum-free interval, measurable disease status, and prior use of bevacizumab therapy. Randomisation was performed by the GOG Statistical and Data Center (Buffalo, New York, USA) using a computer-generated random allocation sequence with an algorithm that required a seed.
Allocation concealment (selection bias)	Low risk	Randomisation was performed by the GOG Statistical and Data Center. (...) The seed was kept at the statistical centre and not communicated to members outside the office (which helped conceal the assignments).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial. Pazopanib and matching placebo were supplied as aqueous film-coated tablets. "Investigators, patients and research personnel will not know whether or not patients have received pazopanib or placebo" (protocol).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind trial. "Investigators, patients and research personnel will not know whether or not patients have received pazopanib or placebo" (protocol).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Efficacy analysis for all randomised participants (ITT population). Safety analysis for all participants who took at least 1 dose of trial drugs (94%, 100/106).
Selective reporting (reporting bias)	Low risk	All outcomes reported and analysed as reported in the protocol (available as appendix with the main publication).
Other bias	Low risk	This study was supported by National Cancer Institute grants to the Gynecologic Oncology Group Tissue Bank (grant No. U10 CA27469, U24 CA114793, U10 CA180868), NRG Oncology (grant No. 1U10 CA180822), and NRG Operations (grant No. U10CA180868).

Roque 2022

Study characteristics

Methods	A randomised, parallel-assignment, open-label, phase II, controlled trial; 1:1 randomisation stratified by study site and previous receipt of bevacizumab
Participants	• 78 randomised, 76 analysed

Roque 2022 *(Continued)*

	• Age 18 or over • Platinum-resistant/refractory (i.e. platinum-free interval < 6 months) recurrent or persistent histologically-confirmed epithelial (non-mucinous) ovarian, fallopian tube or primary peritoneal cancer • All participants must have had measurable disease. Participants must have had at least one "target lesion" to be used to assess response on this protocol as defined by RECIST v1.1 • Performance status ECOG 0 to 2 • Participants must have received prior treatment with taxanes. There was no limit on the number of prior lines of therapy
Interventions	**Intervention**: ixabepilone administered at 20 mg/m^2 intravenously days 1, 8, 15 of a 28-day cycle over 1 hour Bevacizumab administered at 10 mg/kg intravenously days 1, 15 of a 28-day cycle over 1 hour. Bevacizumab was infused after ixabepilone. **Control**: ixabepilone administered at 20 mg/m^2 intravenously days 1, 8, 15 of a 28-day cycle over 1 hour
Outcomes	**Primary:** PFS **Secondary** • OS • Safety (as defined by CTCAE v.4) • Response rates
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned and stratified by (a) study site and (b) previous receipt of bevacizumab prior to randomisation. "Study participants were stratified by study site and previous receipt of BEV with a 1:1 allocation using a dynamic randomisation procedure to minimise stratification-factor imbalance between arms."
Allocation concealment (selection bias)	Unclear risk	Insufficient details to assess this domain
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data analysed for 76 out of 78 randomised participants (97.4%)
Selective reporting (reporting bias)	Low risk	Outcomes reported (broadly) as per ClinicalTrials.gov protocol, and outcomes in protocol not significantly modified after trial registration
Other bias	Unclear risk	Industry collaborator (R-Pharm-US, LLC provided the study drug).

Sharma 2021

Study characteristics	
Methods	A single-centre, open-label, randomised, controlled, phase II trial Participants were randomised in a 1:1 ratio to intervention and control arms
Participants	• 75 participants randomised (37 to intervention arm, 38 to control arm) • Age 18 years or older • Histologically-confirmed platinum-resistant/refractory epithelial ovarian cancer • Performance status 0 to 2 • Life expectancy of at least 12 weeks
Interventions	**Intervention:** etoposide (50 mg, day 1 to 14) + cyclophosphamide (50 mg, day 1 to 28), every 4 weeks + pazopanib (400 mg once daily) **Control:** etoposide (50 mg, day 1 to 14) + cyclophosphamide (50 mg, day 1 to 28), every 4 weeks
Outcomes	Median follow-up: 22.2 months (95% CI 20.3 to 25.4). **Primary**: PFS ("the interval from date of randomization to the date of first documented serological progression (CA125) or start of new antitumor treatment or death, which ever was earlier") **Secondary** • OS ("the interval from date of randomization till last follow up (date of censor) or death") • Toxicity (NCI CTCAE 4.03) • QoL (EORTC QLQ C30 and OV28)
Notes	Funding: Indian Council of Medical Research (ICMR)/Department of Health Research (DHR) Grant in Aid scheme, Government of India (Project no. R.11012/04/2018).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using computer-generated table in blocks (size not given)
Allocation concealment (selection bias)	Low risk	Method of allocation concealment: sequentially-numbered, sealed, opaque envelopes (details from trial registration record)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis for all randomised participants (ITT population) - efficacy and safety analyses
Selective reporting (reporting bias)	Low risk	Outcomes broadly reported as specified in the trial registration record (OS was not listed though reported in paper)

Sharma 2021 *(Continued)*

Other bias	Low risk	Study funded by Indian Council of Medical Research /Department of Health Research grant in Aid scheme, Government of India (Project number R.11012/04/2018). All authors declare no conflicts of interest.

SWOG-S0904 2014

Study characteristics	
Methods	Randomised, open-label, phase II study
Participants	Participants were women with histologically-confirmed ovarian epithelial, fallopian tube or primary peritoneal carcinoma, which was recurrent, refractory or progressive/persistent, and had measurable or non-measurable evaluable disease by imaging. Participants had to have received one prior regimen of platinum-based chemotherapy for management of primary disease, and were allowed up to three additional regimens of cytotoxic chemotherapy for recurrent disease. Other requirements included a Zubrod performance status of 0 to 2, and adequate haematological, renal and liver function. 131 women were randomised, of whom 129 were eligible (66 randomised to docetaxel alone; 63 randomised to docetaxel + vandetanib). Median age at recruitment, by intervention arm: Docetaxel group: median age 61.7, range 32.6 to 80 Docetaxel + vandetanib group: median age 61.9, range 34.3 to 82.5 Type of cancer, by intervention arm: Docetaxel group: ovarian, n = 56 (85%); fallopian tube, n = 3 (5%); peritoneal, n = 7 (11%) Docetaxel + vandetanib group: ovarian, n = 53 (84%); fallopian tube, n = 4 (6%); peritoneal, n = 6 (10%) Zubrod (essentially the same as ECOG) Performance Status (PS), by intervention arm: Docetaxel group: PS 0, n = 37 (56%); PS 1, n = 27 (41%); PS 2, n = 2 (3%) Docetaxel + vandetanib group: PS 0, n = 33 (52%); PS 1, n = 26 (41%); PS 2, n = 4 (6%)
Interventions	Participants were randomised 1:1 using a dynamic balancing algorithm (stratified by prior treatment with antiangiogenesis agents, yes versus no), to one of two arms: **Intervention:** docetaxel, 75 mg/m^2 IV as per arm 1 + vandetanib, 100 mg orally (given daily for 21-day course) **Control:** docetaxel, 75 mg/m^2 IV (given over 1 hour, on day 1 of 21-day course) Courses repeat every 21 days in the absence of a second disease progression or unacceptable toxicity. Participants randomised to arm 1 (docetaxel alone) were allowed to cross-over to single agent vandetanib (100 mg orally daily) upon documented progression. After completion of study treatment, follow-up was at every 3 months for 2 years, and then every 6 months for 3 years.
Outcomes	**Primary**: PFS **Secondary**

SWOG-S0904 2014 *(Continued)*

- Response rate (complete and partial)
- Overall survival
- Adverse events/toxicity

Notes	Because cross-over was allowed from single-agent docetaxel to single-agent vandetanib upon documented progression, the OS comparison is effectively between docetaxel + concurrent vandetanib versus docetaxel + optional sequential vandetanib.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomised centrally 1:1 using a dynamic balancing algorithm with startification".
Allocation concealment (selection bias)	Low risk	Randomisation was performed centrally, at the SWOG Statistical Center. Thus, it is unlikely that intervention allocations could have been foreseen in advance by those recruiting participants.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attritions/exclusions are well-reported in both text and CONSORT diagrams. Intention-to-treat analyses are performed where possible and appropriate. 131 women randomised; 2 excluded due to ineligibility (no baseline imaging, n = 1; uncontrolled hypertension, n = 1); 66 allocated to docetaxel, and 63 to docetaxel + vandetanib. For docetaxel group: • N = 66 for PFS/OS analysis (all those randomised) • N = 57 for response analysis (9 excluded due to non-measurable disease) • N = 64 for toxicity analysis (2 excluded, as did not receive treatment) • 2 lost to follow-up (presumably censored at last follow-up date) For docetaxel + vandetanib group: • N = 63 for PFS/OS analysis (all those randomised) • N = 52 for response analysis (11 excluded due to non-measurable disease) • N = 61 for toxicity analysis (2 excluded, as did not receive treatment) • 1 lost to follow-up (presumably censored at last follow-up date)
Selective reporting (reporting bias)	Low risk	We compared the reported outcomes to those intended (from the online protocol at ClinicalTrials.gov): the published paper covered the main planned outcomes from the protocol. Exploratory analyses, which had not been prespecified, were generally indicated as such.
Other bias	Unclear risk	The study appears to be partially, though not predominantly, sponsored by industry (AstraZeneca).

SWOG-S0904 2014 *(Continued)*

	The author disclosures state that the lead author "has served as an uncompensated scientific advisor to AstraZeneca for developmental programs not involving vandetanib", and there are no other conflicts of interest reported.

TAPAZ 2022

Study characteristics	
Methods	A randomised, parallel-assignment, phase II, open-label controlled trial; randomisation 2:1
Participants	• 125 screened, 118 randomised, 116 treated and analysed as modified ITT • Age 18 or over • Histologically-documented ovarian, tubal or peritoneum carcinoma (stage IC to IV) • Treated at least with 1 line of platinum-based chemotherapy who have relapsed within 6 months after the last administration of platinum-based chemotherapy and taking bevacizumab for maintenance. Note: penultimate line of chemotherapy could have contained chemotherapy without platinum and the last line should have contained platinum-based chemotherapy (followed by bevacizumab for maintenance) • Participants must have had disease that was measurable and/or evaluable according to RECIST criteria and required chemotherapy treatment • Performance status ECOG < 2 • Life expectancy of more than 3 months • **Exclusion:** previous treatment with monotherapy weekly paclitaxel; previous treatment with bevacizumab within three weeks before start of study treatment
Interventions	**Intervention:** weekly paclitaxel 65 mg/m^2 with pazopanib 600 mg to 800 mg daily **Control:** weekly paclitaxel 80 mg/m^2
Outcomes	**Median follow-up:** 13.1 months (range 1.2 to 56.3) **Primary:** PFS at 4 months according to RECIST v1.1 **Secondary** • OS • Rates of overall response and stable disease • QoL • Safety (NCI CTCAE v4.3)
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised (2:1) phase II trial. Randomisation used "a minimization procedure stratified by: number of prior platinum-based treatment lines (1 versus 2), PFI (<6 versus 6–12 months), and baseline HRQoL (European Organisation for Research and Treatment of Cancer [EORTC] global health status/quality of life [GHS/QoL] score <50 versus ≥50)."

TAPAZ 2022 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient details to assess this domain
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study. Low risk of bias for OS, high risk of bias for other outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	118 randomised, then 2 withdrew consent/refused to participate; remaining 116 received the allocated treatment and were analysed as ITT population
Selective reporting (reporting bias)	Low risk	Compared reported outcomes to registered protocol on the ClinicalTrials.gov website, and they broadly correspond, including key outcomes of OS, PFS, QoL and toxicity
Other bias	Unclear risk	An industry-sponsored trial

TRIAS 2018

Study characteristics	
Methods	A double-blind, multi-centre, phase II, randomised controlled trial
Participants	• 174 randomised; 172 analysed • Age 18 years or older • Histologically-confirmed platinum-resistant/refractory epithelial ovarian, fallopian tube or primary peritoneal cancer • No more than 2 prior treatment regimens for recurrent ovarian cancer • ECOG performance status 0 or 1 • Life expectancy of at least 12 weeks
Interventions	**Intervention:** topotecan (1.25 mg/m^2 on days 1–5) + sorafenib (400 mg twice daily on days 6–15), repeated every 21 days for up to 6 cycles, followed by daily maintenance sorafenib for up to 1 year in participants without progression **Control:** topotecan (1.25 mg/m^2 on days 1–5) + placebo (twice daily on days 6–15), repeated every 21 days for up to 6 cycles, followed by daily maintenance placebo for up to 1 year in participants without progression
Outcomes	**Median follow-up**: 10.0 months (IQR 5.0 to 18.4) **Primary**: investigator-assessed PFS (interval between the first treatment cycle and disease progression or death from any cause) **Secondary** • OS (interval between the first treatment cycle and death, censored at last follow-up or end of study in participants without events) • ORR (complete or partial response by RECIST 1.1) • Duration of response from the first assessment of complete or partial response until the date of disease progression or death, whichever occurred first

TRIAS 2018 *(Continued)*

	• Time to progression • Patient-reported outcomes (PROs) • Safety (NCI-CTC v3.0) • Tolerability PROs were assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire core module (QLQ-C30) and ovarian cancer-specific module (QLQ-OV28) at the screening visit, 12 weeks after treatment initiation, 4 weeks after the end of chemotherapy, and every 3 months thereafter.
Notes	Industry-funded trial (Bayer, Amgen and GlaxoSmithKline) with several authors disclosing a financial conflict of interest. Trial protocol at www.clinicaltrials.gov/ct2/show/NCT01047891

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done centrally by a third party with stratification in block sizes of 4 according to the timing of relapse. Randomisation ratio - 1:1.
Allocation concealment (selection bias)	Low risk	Randomisation was done using a web-generated response system. The treatment list was prepared and stored by the third party and remained concealed during the conduct of the trial.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Investigators and participants were masked to allocation of sorafenib or placebo (identical in appearance). Topotecan treatment was open-label.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators and participants were masked to allocation of sorafenib or placebo (identical in appearance). Topotecan treatment was open-label.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis for modified ITT population (all randomly-assigned participants who received at least one dose of study treatment) - 172 out of 174 randomised participants. 83 started sorafenib with topotecan out of 85 randomised. Two participants were excluded due to serious adverse events. No participants were excluded in topotecan with the placebo arm.
Selective reporting (reporting bias)	Low risk	Outcomes broadly reported as specified on the ClinicalTrials.gov record
Other bias	Unclear risk	An industry-sponsored trial with several authors disclosing receipt of personal grants and funding from the industry

TRINOVA-1 2016

Study characteristics

Methods	Phase III, randomised, double-blind, placebo-controlled, multi-centre study
Participants	• 919 participants randomised (461 to intervention arm and 458 to control arm)

TRINOVA-1 2016 *(Continued)*

	• Women ≥ 18 years old with a histo/cytological diagnosis of invasive epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer, for which they have undergone surgery and a platinum-based chemotherapy
Interventions	**Intervention:** paclitaxel (80 mg/m^2 IV weekly) + trebananib (AMG 386) (15 mg/kg IV weekly) **Control:** paclitaxel (80 mg/m^2 IV weekly) + placebo (IV weekly)
Outcomes	**Primary:** PFS **Secondary** • Incidence of the occurrence of anti-AMG 386 antibody formation • Patient-reported health-related quality of life (HRQOL) and ovarian cancer-related symptoms using the Functional Assessment of Cancer Therapy - Ovary questionnaire (FACT-O) • OS • Objective response rate • Duration of esponse • CA125 response rate per Gynecologic Cancer InterGroup (GCIG) and change in CA125 • Incidence of adverse events and significant laboratory abnormalities • Pharmacokinetics of AMG 386 (Cmax and Cmin) • Overall health status using EuroQOL (EQ5D)
Notes	Protocol online at clinicaltrials.gov/show/NCT01204749

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly allocated to trial arms in a 1:1 ratio, using a permuted block method (block size of 4). The randomisation sequence was generated at Amgen by a statistician who had no access to study data and was not involved in the analysis.
Allocation concealment (selection bias)	Low risk	The enrollment and randomisation were performed using a computerised interactive voice response system. Access to the randomisation sequence was restricted throughout the study.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A double-blind trial where all site staff, investigators, pharmacists, participants and study team personnel (including the study statisticians) were masked to the treatment assignments
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A double-blind trial where all site staff, investigators, pharmacists, participants and study team personnel (including the study statisticians) were masked to the treatment assignments
Incomplete outcome data (attrition bias) All outcomes	Low risk	Efficacy analysis using data from all randomised particiapnts (intention-to-treat population); safety using data from all treated and quality of life using data from all randomised participants with available baseline measurements
Selective reporting (reporting bias)	Low risk	Outcomes analysed and reported as specified in a study protocol
Other bias	Unclear risk	An industry-sponsored trial with several authors disclosing receipt of personal grants and funding from the industry

TRINOVA-2 2017

Study characteristics	
Methods	An international, multi-centre, randomised, double-blind, phase III trial Participants were randomised in a 1:1 ratio to intervention or control, stratified by platinum-free interval, measurable disease and geographic region.
Participants	• 223 participants randomised (114 to intervention arm, 109 to control arm) • Originally planned for N = 380 but study modified due to global shortage of PLD, necessitating a period of suspended enrolment • Recurrent partially platinum-sensitive or platinum-resistant (platinum-free interval ≤ 12 months) epithelial ovarian, fallopian tube or primary peritoneal cancer • ECOG performance status 0 or 1 • No previous treatment with pegylated liposomal doxorubicin or anthracycline/mitoxantrone-based chemotherapy • No previous treatment with trebananib or another inhibitor of angiopoietins/Tie2
Interventions	**Intervention:** pegylated liposomal doxorubicin (50 mg/m^2 once every 4 weeks, IV) + trebananib (15 mg/kg once weekly, IV) **Control:** pegylated liposomal doxorubicin (50 mg/m^2 once every 4 weeks, IV) + placebo (once weekly, IV) Treatment continued until disease progression, unacceptable toxicity or withdrawal of consent.
Outcomes	**Median follow-up time**: 12.4 months (IQR 8.2 to 15.5) **Primary**: PFS **Secondary** • OS • Objective response rate • Change in tumour burden • Duration of response • Adverse events
Notes	Contacted authors to seek further methodological information, including on random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants were randomised 1:1 with stratification by platinum-free interval, measurable disease and geographic region.
Allocation concealment (selection bias)	Unclear risk	Insufficient details to assess this domain
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study (participants and investigators)

TRINOVA-2 2017 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study (participants and investigators). PFS was assessed by investigator using RECIST v1.1 criteria
Incomplete outcome data (attrition bias) All outcomes	Low risk	Efficacy analysis for all randomised participants (ITT population). Safety analysis for all participants who took at least 1 dose of trial drugs (99%, 221/223).
Selective reporting (reporting bias)	Low risk	Two outcomes (OS and PFS) listed on the ClinicalTrials.gov broadly analysed and reported as specified in the entry
Other bias	Unclear risk	An industry-sponsored trial with several authors disclosing receipt of personal grants and funding from the industry. Enrolment was temporarily halted for 14 months due to a shortage of PLD. This resulted in two time-separated study cohorts, with different median actual follow-up times. Additionally, the authors mention that there were marked differences in exposure to PLD within treatment arms.

TRINOVA-3 2019

Study characteristics	
Methods	An international, multi-centre, double-blind, phase III trial Participants were randomised in a 2:1 ratio using a permuted block method to intervention or control, stratified by carboplatin dose, FIGO stage, and category of residual disease after primary debulking surgery or with planned interval debulking surgery.
Participants	• 1015 participants randomised (678 to intervention arm, 337 to control arm) • Age 18 years or older • Histologically-confirmed FIGO stage III or IV epithelial ovarian, fallopian tube or primary peritoneal cancer • Newly diagnosed and with an indication for first-line treatment with 6 cycles of carboplatin-paclitaxel chemotherapy • No previous treatment with trebananib or other inhibitors of angiopoietins/Tie2 • Investigators declared prior to randomisation whether or not it was planned to perform interval debulking surgery • ECOG performance status 0 or 1
Interventions	**Median follow-up**: 27.4 months (IQR 17.7 to 34.2) **Intervention:** paclitaxel (175 mg/m^2) + carboplatin (AUC = 5 or 6) every 3 weeks for 6 cycles + trebananib (15 mg/kg, weekly, continued for up to 18 months) **Control:** paclitaxel (175 mg/m^2) + carboplatin (AUC = 5 or 6) every 3 weeks for 6 cycles + placebo (IV, weekly, continued for up to 18 months)
Outcomes	**Primary**: PFS (investigator-assessed) **Secondary** • OS • Adverse events • Pharmacokinetics

TRINOVA-3 2019 *(Continued)*

- Frequency of anti-trebananib antibody formation
- Patient-reported outcomes

Notes	Trial protocol at www.clinicaltrials.gov/ct2/show/NCT01493505

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A web-based randomisation system
Allocation concealment (selection bias)	Low risk	A web-based randomisation system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded study. The sponsor, investigator, site staff, participants and study team personnel (including statistician) were masked to treatment assignement.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded study. The sponsor, investigator, site staff, participants and study team personnel (including statistician) were masked to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis
Selective reporting (reporting bias)	Low risk	Analyses as prespecified in the trial protocol
Other bias	Unclear risk	An industry-sponsored trial

Zhao 2015

Study characteristics

Methods	Randomised, phase III, clinical trial; likely open-label as blinding not mentioned Single-centre study: First Affiliated Hospital of Chinese PLA General Hospital, Beijing, China
Participants	Ovarian epithelial cancer confirmed by pathology and histopathologic stage IIa–IV according to the FIGO system. **Inclusion criteria:** participants with malignant ascites, ECOG PS score 0–2, expected lifetime more than 3 months, and with no major organ dysfunction and with adequate bone marrow, cardiac, hepatic and renal function. All participants were aged from 18 to 75 years old (22/31 (71%) < 60 years in intraperitoneal bevacizumab + cisplatin arm; 19/27 (70.4%) < 60 years in intraperitoneal cisplatin arm). Serous carcinoma: 20/31 (64.5%) in intraperitoneal bevacizumab + cisplatin arm; 17/27 (63%) in intraperitoneal cisplatin arm WHO Performance status 0 to 1: 25/31 (80.7%) in intraperitoneal bevacizumab + cisplatin arm; 21/27 (77.8%) in intraperitoneal cisplatin arm

Zhao 2015 *(Continued)*

	FIGO stage IIc-III: 7/31 (22.6%) in intraperitoneal bevacizumab + cisplatin arm; 6/27 (22.2%) in intraperitoneal cisplatin arm); FIGO stage IV: 24/31 (77.4%) in intraperitoneal bevacizumab + cisplatin arm; 21/27 (77.8%) in intraperitoneal cisplatin arm
Interventions	Intraperitoneal chemotherapy + bevacizumab (31) versus intraperitoneal chemotherapy (27) **Intervention:** cisplatin intraperitoneal injection (40 mg/m^2) and bevacizumab intraperitoneal injection (300 mg in 20 mL saline) **Control:** cisplatin intraperitoneal injection (40 mg/m^2) Participants had ascites drained prior to intraperitoneal administration. To ensure the uniform distribution of drugs in abdomen, participants were advised to change position smoothly every 15 minutes. The drugs were administrated every 2 weeks. All participants received IV chemotherapy in addition (paclitaxel 135 mg/m^2 + carboplatin AUC 5 every 3 weeks).
Outcomes	**Primary:** ORR (by measurement of ascites by USS) **Secondary** • Number of required peritoneal drainages • Speed of peritoneal drainage (mL/hour) • Change of QoL score (Karnofsky Performance Status (KPS)
Notes	All participants were randomly assigned to receive either intraperitoneal administration of cisplatin only (control group, n = 27) or cisplatin plus bevacizumab (study group, n = 31) with use of a random number table. No mention of blinding to treatment. Study was supported by Clinical and Scientific Research Foundation of PLA General Hospital (2012FC-TSYS- 3021), Scientific Research Subject of Clinical Research Department of PLA General Hospital (QN201205) and Beijing Municipal Commission of Science and Technology (2131107002213040)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random allocation using a random number table
Allocation concealment (selection bias)	Unclear risk	Details not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details not available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysed as assigned, no attrition or exclusion
Selective reporting (reporting bias)	Low risk	Reported on all of the prespecified outcomes: overall response rate, QoL and the VEGF level in ascites

Zhao 2015 *(Continued)*

Other bias	Unclear risk	Limited information about the trial

ALT: alanine transaminase; **AMG386:** trebananib; **AST:** aspartate aminotransferase; **AUC:** area under the curve;**BIBF**: BIBF 1120 = nintedanib; ***BRCA*:** breast cancer gene; **CA125:** cancer antigen 125; **COX-2:** cyclo-oxygenase-2; **CT:** computed tomography; **CTCAE:** Common Terminology Criteria for Adverse Events; **ECOG:** Eastern Cooperative Oncology Group; **EORTC:** European Organisation for Research and Treatment of Cancer; **FACT-O (TOI):** Functional Assessment of Cancer Therapy-Ovarian (Trial Outcome Index); **FIGO:** International Federation of Gynecology and Obstetrics; **FOSI:** Functional Assessment of Cancer Therapy (FACT)/National Comprehensive Cancer Network (NCCN) Ovarian Symptom Index; **GCIG:** Gynecological Cancer InterGroup; **GOG:** Gynecologic Oncology Group; **HRD:** homologous recombination deficiency; **ICON**: International Collaborative Ovarian Neoplasm study; **IDS:** interval debulking surgery; **IQR:** interquartile range; **ITT:** intention-to-treat; **IV:** intravenous(ly); **KPS:** Karnofsky Performance Status; **MRI:** magnetic resonance imaging; **NCI:** National Cancer Institute; **ORR:** objective response rate; **OS:** overall survival; **PARP:** poly(ADP-ribose) polymerase; **PD-L1**: Programmed death-ligand 1; **PLD:** pegylated liposomal doxorubicin; **PFS:** progression-free survival; **QoL:** quality of life; **RECIST:** Response Evaluation Criteria in Solid Tumors; **SWOG**: Southwest Oncology Group; **TNM:** tumour nodes metastases; **ULN:** upper limit of normal; **USS:** ultrasound scan; **VEGF:** vascular endothelial growth factor; **VEGF-R:** vascular endothelial growth factor receptor; **WHO:** World Health Organization

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

Study	Reason for exclusion
ALIENOR/ENGOT-ov7 2020	Ineligible population: RCT in ovarian sex cord stromal tumours, not EOC
Azad 2008	Ineligible study design: not an RCT. This was a phase I dose-finding study of sorafenib and bevacizumab for people with multiple tumour types; this report emphasises results for the 15 patients with ovarian cancer.
Baumann 2012	Ineligible comparator: trial compares two different schedules of an angiogenesis inhibitor (sunitinib). Note: in the previous version of this review, this study was mentioned as an excluded ongoing study, identified by the reference NCT00543049.
BOOST 2011	Ineligible intervention. This was a randomised phase III trial evaluating whether the early and continuous addition of bevacizumab, for up to 30 months, to the standard chemotherapy was more effective than the early and continuous addition of bevacizumab, for up to 15 months. Both arms received the angiogenesis inhibitor bevacizumab, and thus the trial does not fulfil our inclusion criteria.
Brown 2014	Ineligible population and ineligible study design: not an RCT. All enrolled participants were meant to receive bevacizumab. Also, the study was in sex cord stromal ovarian tumours, not epithelial ovarian cancer.
Burger 2010	Not a clinical trial. Comprehensive narrative review of literature on VEGF inhibitors for gynaecologic malignancies, including summary tables of completed and ongoing trials. Not a systematic review.
Campos 2013	Ineligible study design: not an RCT. A non-randomised phase II trial, in which all participants were allocated to receive sunitinib.
Chan 2016	Ineligible intervention. Note: study was mentioned in the previous version of this review as an excluded ongoing study, identified as NCT01167712. Full paper published in 2016. This was a phase III RCT, but the aim was to compare different schedules of chemotherapy (paclitaxel and carboplatin). Participants in both arms had the option of receiving bevacizumab.
Colombo 2012	Ineligible study design: not an RCT. This is a phase II single-arm study (in which all participants were allocated to receive aflibercept, with no 'control' group).

Study	Reason for exclusion
DUO-O 2018	Ineligible intervention. This was a randomised trial that aimed to evaluate the addition of durvalumab (an immunotherapy drug) with or without olaparib (a PARP inhibitor) to platinum-based chemotherapy and bevacizumab. All participants received bevacizumab.
ENGOT-ov65 2021	Ineligible intervention. This is an RCT that primarily aimed to evaluate the addition of pembrolizumab (an immunotherapy). It appears that both arms could receive bevacizumab, but whether or not participants received bevacizumab does not appear to have been randomly assigned.
GOG-3018 2020	Ineligible intervention. The intervention being trialled was an anti-cancer gene therapy. While it is described as having a "broad antiangiogenic effect", this is a very different intervention to the typical angiogenesis inhibitors evaluated in this review (which are mostly small-molecule tyrosine kinase inhibitors or antibodies).
Hagemann 2013	Ineligible study design: not an RCT. This is a single-arm phase II study, in which all participants were allocated to receive pemetrexed and bevacizumab (no control group).
Harter 2013	Ineligible study design: not an RCT (did not progress from phase I trial to planned phase II randomised study due to adverse safety data).
Heiss 2010	Ineligible intervention. The antibody used (catumaxomab) was not an angiogenesis inhibitor, instead targeting the cell surface markers CD3 (cluster of differentiation 3) and EPCAM (epithelial cell adhesion molecule). The study used intraperitoneal administration, and was primarily concerned with malignant ascites – though neither of these would definitely be reasons for exclusion.
Ikeda 2013	Ineligible study design: not an RCT. This was a non-randomised study in which all participants were allocated to receive gemcitabine, oxaliplatin and bevacizumab (no control group).
Jones 2019	Ineligible study design. This was a randomised discontinuation trial, in which all participants received the angiogenesis inhibitor (brivanib) for a 12-week lead-in period, after which participants with stable disease were randomised to brivanib or placebo.
Krasner 2019	Ineligible study design: not an RCT (two parallel trials, one of chemotherapy with bevacizumab, the other of chemotherapy alone).
Ma 2022	Ineligible study design: not an RCT. Participants allocated to study arms depending on order of admission. Quasi-randomised and at high risk of bias.
Markman 2009	Not a clinical trial. A narrative review of the literature on angiogenesis inhibitors in ovarian cancer. Not a systematic review.
Nasu 2022	Ineligible study design: not an RCT. This was a single-arm study.
NCT00017303	Ineligible comparator. Ongoing randomised phase II study of IM-862 (a synthetic dipeptide (L-glutamine L-tryptophan) which has anti-angiogenic action) in people with resected stage III ovarian cancer. Study excluded because all participants receive IM-862, randomised to one of three different dosage schedules (i.e. participants were not randomised to therapy with versus without angiogenesis inhibitor). Note: no results posted on ClinicalTrials.gov website as of 17/09/2022.
NCT01972516	Ineligible study design. This appears to be a relevant RCT, based on the protocol and results on the ClinicalTrials.gov website. However, the trial was terminated early due to poor accrual, with only 4 participants. The study therefore does not meet our inclusion criterion of a minimum of 10 participants.
OCTAVIA 2014	Ineligible study design: not an RCT. This was a non-randomised, single-arm, phase II study, in which all participants were allocated to receive carboplatin, paclitaxel and bevacizumab (no control group).

Study	Reason for exclusion
Ojeda 2011	Ineligible comparator: not an RCT of an angiogenesis inhibitor compared to chemotherapy or no treatment. All participants in the study received bevacizumab.
Osterweil 2010	Not a clinical trial. Two different references to a single article, reporting and commenting on a conference abstract about a phase III RCT (GOG-0218 2019).
PACOVAR-trial 2011	Ineligible comparator. This was a phase I/II study regarding dosage and tolerability of pazopanib, in which all participants were meant to be treated with pazopanib (i.e. no control arm).
PAZOFOS 2020	Ineligible comparator. Trial randomised participants to pazopanib versus pazopanib plus fosbretabulin (i.e. an angiogenesis inhibitor in both arms).
Pfisterer 2021	Ineligible comparator. This is an RCT, but participants in both arms received an angiogenesis inhibitor (bevacizumab), and were randomised to either 15 or 30 months of treatment.
Ray-Coquard 2019	Ineligible comparator. Trial compared bevacizumab plus olaparib versus bevacizumab plus placebo (i.e. the trial was in olaparib, and both arms received an angiogenesis inhibitor).
Schilder 2013	Ineligible study design: not an RCT. A single-arm, phase II study in which all participants were allocated to receive motesanib (no control group).
Schwandt 2014	Ineligible comparator. Note: study mentioned in previous version of this review as an ongoing excluded study, identified as NCT00096200. Results published in 2014. A randomised phase II study in people with recurrent ovarian cancer. All participants received sorafenib; one group received sorafenib only, while the other group received sorafenib plus carboplatin and paclitaxel. Study excluded as it does not compare treatment with versus without angiogenesis inhibitor.
Sennino 2010	Not a clinical trial. An article commenting on another paper, which compared the activity of bevacizumab to an inhibitor of PDGF-beta (platelet-derived growth factor beta) in mouse-based models of ovarian cancer.
STAC 2011	Ineligible comparator. Although this is an RCT, all participants were allocated to receive chemotherapy plus bevacizumab. Randomisation only governed whether or not they received erlotinib in addition; therefore, does not fulfil our inclusion criteria.
Tao 2022	Study compared adding two cycles of intraperitoneal bevacizumab to carboplatin-paclitaxel chemotherapy prior to primary debulking surgery and looked at short-term outcomes.
Tew 2014	Ineligible comparator. Phase II study, involving 162 participants with recurrent platinum-resistant ovarian cancer, randomised to either 2 mg/kg VEGF-Trap or 4 mg/kg VEGF-Trap (i.e. no control group, given only standard therapy and/or placebo).
Tew 2018	Ineligible comparator. Note: study was mentioned in previous version of this review as an excluded ongoing study, identified by NCT00886691. Full paper published in 2018. A randomised phase II study in people with recurrent/persistent ovarian cancer, comparing therapy with bevacizumab alone versus bevacizumab plus everolimus (an inhibitor of a serine-threonine kinase). Thus, the trial did not compare therapy with versus without an angiogenesis inhibitor.
Tillmans 2012	Ineligible study design: not an RCT. A single-arm, phase I trial in which all participants were allocated to receive pazopanib and topotecan (no control group).
Tillmans 2013	Ineligible study design: not an RCT. A single-arm, phase II study in which all participants were allocated to receive bevacizumab and albumin-bounded paclitaxel.

Study	Reason for exclusion
Tredan 2022	Ineligible comparator. The trial compared treatment with an angiogenesis inhibitor (regorafenib) to tamoxifen (a drug which is not a standard treatment for ovarian cancer, and is not cytotoxic chemotherapy).
Trillsch 2021	Not a clinical trial: a meta-analysis of included studies.
Vergote 2017	Ineligible study design. This was a randomised discontinuation study: all participants receive the angiogenesis inhibitor (cabozantinib) to begin with, and were then randomised to continue or stop. Note: this study was mentioned in the previous version of this review as a 'study awaiting classification' (under the reference Gordon 2010, based on the conference abstract).
Verschraegen 2012	Ineligible study design: not an RCT. A single-arm, phase II study in which all participants were allocated to receive bevacizumab and liposomal doxorubicin.
Wenham 2013	Ineligible study design: not an RCT. A single-arm, phase II study in which all participants were allocated to receive docetaxel and bevacizumab (no control group).
Zhang 2020	Ineligible comparator. This was an RCT comparing carboplatin versus bevacizumab plus nedaplatin (i.e. there was different chemotherapy in the two arms).

EOC: epithelial ovarian cancer; **RCT:** randomised controlled trial; **VEGF**: vascular endothelial growth factor

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

NCT00744718

Methods	An open-label, phase II trial It is unclear from the online trial protocol whether or not this is a randomised controlled trial Trial is stated to use "factorial assignment" - unclear whether or not this is randomisation
Participants	• 73 participants • Age 18 or older • Histologically-confirmed platinum-resistant ovarian, fallopian tube or primary peritoneal cancer • Stages I-IV • Previously treated with a maximum of 3 different cytostatic regimens • Performance status 0-2
Interventions	• Bevacizumab, 10 mg/kg every 3 weeks • Carboplatin, area under the curve = 5 every 5 weeks It is unclear from the online protocol whether all participants receive both agents, or whether participants are randomised to different agents alone or in combination.
Outcomes	**Primary**: PFS **Secondary** • OS • Response rate • Response duration
Notes	

NCT03642132

Methods	An open-label, randomised, phase III trial Note: this trial is primarily intended to evaluate the efficacy and safety of avelumab (an immune checkpoint inhibitor) and talazoparib (a PARP inhibitor), but also includes a third arm with an angiogenesis inhibitor, and so one or more comparison may be relevant to this review. The trial was ended early, and it is unclear what results will be available.
Participants	• 79 participants randomised • 18 years or older • Histologically-confirmed epithelial ovarian, fallopian tube or primary peritoneal cancer including carcinosarcoma with high-grade serous component • Treatment-naive patients with stage III/IV ovarian cancer • Must have completed a primary surgical debulking procedure or be candidates for neoadjuvant chemotherapy with planned interval debulking surgery • ECOG performance status 0-1
Interventions	3-arm trial: Arm 1: chemotherapy (carboplatin-paclitaxel) + avelumab followed by avelumab + talazoparib Arm 2: chemotherapy (carboplatin-paclitaxel) followed by talazoparib maintenance Arm 3: chemotherapy (carboplatin-paclitaxel) + bevacizumab followed by bevacizumab maintenance
Outcomes	Notes: outcomes listed are now obsolete after protocol amendment. **Primary**: PFS as determined based on blinded independent central review assessment per RECIST v1.1 **Secondary** • OS • Quality of life (assessed by EuroQoL questionnaire EQ-5D-5L) • Self-reported symptom index (assessed by the National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Ovarian Cancer Symptom Index - 18 Item Version (NFOSI-18)) • Anti-drug antibodies against avelumab • PFS after the second line of therapy • Maximum observed plasma concentrations of talazoparib and avelumab
Notes	From ClinicalTrials.gov website: "On March 19, 2019, Sponsors alliance announced the discontinuation of the ongoing Phase III study, and the decision was based on several factors, including previous announced interim results from JAVELIN Ovarian 100 study (B9991010). Patients who remain in B9991030 study will continue receiving their randomized treatment assigned and will be monitored for appropriate safety assessments until treatment discontinuation."

OS: overall survival; **PARP:** poly(ADP-ribose) polymerase; **PFS:** progression-free survival; **RECIST:** Response Evaluation Criteria in Solid Tumors

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

ICON9 2021

Study name	ICON 9 - an international phase III randomized study to evaluate the efficacy of maintenance therapy with olaparib and cediranib or olaparib alone in patients with relapsed platinum-sensitive ovarian cancer following a response to platinum-based chemotherapy
Methods	An international, multi-centre, open-label, randomised, phase III trial Trial is of maintenance therapy after partial or complete response to a minimum of 4 cycles of platinum-based chemotherapy
Participants	• Women with relapsed ovarian cancer whose disease progresses more than 6 months after first-line chemotherapy (recurrent platinum-sensitive ovarian cancer) • Age 18 years and older • CT- or MRI-proven relapsed disease • Evidence of response to chemotherapy mid-treatment (post 3 or 4 cycles) • ECOG performance status 0-1 • Life expectancy of at least 16 weeks
Interventions	**Intervention**: olaparib 300 mg twice daily + cediranib 20 mg once daily **Control**: olaparib 300 mg twice daily
Outcomes	**Primary**: PFS (meaured from date of randomisation; investigator-assessed using RECIST v1.1) **Secondary** • Toxicity • PFS and OS measured from date of starting chemotherapy • Adherence to therapy • Time to start of second subsequent therapy • Quality of life (assessed using EORTC QLQ C30 and OV28) • Cost-effectiveness (assessed using EQ-5D-5L) • Response rate • OS from date of randomisation
Starting date	15 June 2018. Estimated completion date: December 2023
Contact information	
Notes	

NCT00635193

Study name	Efficacy and safety study of M200 (volociximab in combination with liposomal doxorubicin)
Methods	An open-label, parallel-assignment, phase I/II study
Participants	• Estimated 138 participants • People with advanced epithelial ovarian or primary peritoneal cancer who have relapsed after prior therapy with platinum-taxane chemotherapy • 18 years and older
Interventions	**Intervention:** liposomal doxorubicin (40 mg/m^2) + volociximab (an anti-angiogenic integrin inhibitor, at various different dose schedules)

NCT00635193 *(Continued)*

	Control: liposomal doxorubicin (40 mg/m^2)
Outcomes	Efficacy, safety, tolerability
Starting date	July 2007. Completion date: October 2009
Contact information	
Notes	Sponsor: AbbVie (prior sponsor, Abbott) Trial appears to be completed but no linked publications identified.

NCT02584478

Study name	Phase 1/2a/3 evaluation of adding AL3818 to standard platinum-based chemotherapy in subjects with recurrent or metastatic endometrial, ovarian, fallopian, primary peritoneal or cervical carcinoma (AL3818-US-002) (AL3818)
Methods	An open-label, multi-centre, randomised, phase III trial The trial is evaluating AL3818/anlotinib, a dual-receptor TKI targeting VEGF-R and FGF-R. Participants will be randomised in a 1:1 ratio to intervention or control, stratified by prior angiogenesis inhibitors and number of prior treatments. Note: this trial had multiple phases and started in several gynaecological cancers, but the ongoing trial is a phase III RCT in ovarian cancer.
Participants	• Estimated 270 participants • 18 years or older • Histologically-confirmed platinum-resistant ovarian, fallopian tube or primary peritoneal cancer • Must have measurable disease defined by RECIST 1.1 confirmed by CT or MRI scan within 28 days of enrollment • Life expectancy of at least 3 months • ECOG performance status 0-2
Interventions	**Intervention:** chemotherapy (paclitaxel on days 1, 8 and 15 by default; alternatively pegylated liposomal doxorubicin or topotecan) + AL3818 (taken daily from day 8 to 21) in 21-day cycles **Control:** chemotherapy (paclitaxel on days 1, 8 and 15 by default; alternatively pegylated liposomal doxorubicin or topotecan) in 21-day cycles
Outcomes	**Primary**: PFS **Secondary** • Objective response rate • Duration of response • OS • Toxicity
Starting date	December 2015. Estimated completion date: December 2024
Contact information	
Notes	Sponsor: Advenchen Laboratories, LLC

NCT02839707

Study name	Pegylated liposomal doxorubicin hydrochloride with atezolizumab and/or bevacizumab in treating patients with recurrent ovarian, fallopian tube, or primary peritoneal cancer
Methods	Open-label, randomised, phase II/III trial
Participants	• Estimated 444 participants • 18 years and older • Recurrent platinum-resistant high-grade ovarian, fallopian tube or primary peritoneal cancer • Performance status 0-2
Interventions	3-arm study: Arm 1: pegylated liposomal doxorubicin (day 1) + atezolizumab (days 1 and 15) + bevacizumab (days 1 and 15) Arm 2: pegylated liposomal doxorubicin (day 1) + atezolizumab (days 1 and 15) Arm 3: pegylated liposomal doxorubicin (day 1) + bevacizumab (days 1 and 15)
Outcomes	**Primary** • Dose-limiting toxicities • PFS • OS **Secondary** • Objective response rate • Adverse events • Disease-related symptoms • Patient-reported outcomes • Various biomarker-based outcomes
Starting date	12 May 2017. Estimated completion date: 30 June 2023
Contact information	
Notes	Sponsor: National Cancer Institute (NCI)

NCT03095001

Study name	Intraperitoneal chemotherapy alone or in combination with bevacizumab for ovarian cancer with peritoneal adhesion
Methods	A randomised, phase II, trial with single-masking (investigator)
Participants	• Estimated 70 participants • Age 18 to 70 • Pathologically- and radiologically-confirmed stage IV or postoperative recurrent ovarian cancer • Karnofsky score higher than 80 • Peritoneal adhesions

NCT03095001 *(Continued)*

Interventions	**Intervention:** intraperitoneal carboplatin (AUC = 5) + intraperitoneal bevacizumab (5 mg/kg) + systemic paclitaxel (175 mg/m^2), all given every 3 weeks for 4 to 6 cycles **Control:** intraperitoneal carboplatin (AUC = 5) + systemic paclitaxel (175 mg/m^2), both given every 3 weeks for 4 to 6 cycles
Outcomes	**Primary** • Peritoneal adhesion ORR **Secondary** • Adverse events • Quality of life (assessed by FACT-O) • PFS • OS • Objective response rate
Starting date	Estimated start date: 1 June 2017. Estimated completion date: 1 June 2020
Contact information	
Notes	Sponsor: Chinese PLA General Hospital Estimated study completion date has passed by; published results could not be identified.

NCT03262545

Study name	Efficacy and safety of apatinib as third line therapy in patients with advanced ovarian cancer
Methods	A double-blind, phase II, randomised controlled trial
Participants	• 18 years or older • Histologically- or cytologically-confirmed diagnosis of epithelial ovarian cancer • Unfit for radical surgery and had received second-line chemotherapy; disease progressed or unable to tolerate chemotherapy • ECOG performance status 0-2 • Life expectancy of at least 12 weeks
Interventions	**Intervention:** apatinib 500 mg orally once daily **Control:** placebo orally once daily
Outcomes	**Primary**: PFS at 2 years **Secondary** • OS • Objective response rate • Disease control rate • Quality of life (as measured by EORTC QLQ C30)
Starting date	27 August 2017. Estimated completion date: February 2021
Contact information	

NCT03262545 *(Continued)*

Notes	Sponsor: Sichuan Cancer Hospital and Research Institute

NCT03462212

Study name	Carboplatin-paclitaxel-bevacizumab vs carbo-pacli-beva-rucaparib vs carbo-pacli-ruca, selected according to HRD status, in patients with advanced ovarian, primary peritoneal and fallopian tube cancer, preceded by a phase I dose escalation study on ruca-beva combination (mito25)
Methods	An open-label, multi-centre, randomised, phase I-II trial. Details provided here are for phase II. Participants will be randomised in a 1:1:1 ratio to 3 arms according to a molecular-driven treatment, depending on HRD (homologous recombination deficiency) status. Randomisation will be stratified by residual tumour at primary surgery and neoadjuvant chemotherapy.
Participants	Histologically-confirmed high-grade stage IIIB/IIIC/IV ovarian cancer
Interventions	HRD-positive patients: • Arm B: carboplatin AUC 5 + paclitaxel 175 mg/m^2 IV once every 3 weeks (i.e. on day 1 of a 21 day cycle) for 6 cycles followed by rucaparib 600 mg twice daily for 2 years (i.e. every day of a 28 day cycle for 24 cycles) as maintenance • Arm C: carboplatin AUC 5 + paclitaxel 175 mg/m^2 IV once every 3 weeks + bevacizumab 15 mg/kg IV for 6 cycles followed by bevacizumab 15 mg/kg once every 3 weeks days for 16 cycles (bevacizumab will start from cycle 2) + rucaparib 500 mg twice daily for 2 years as maintenance HRD-negative patients: • Arm A: carboplatin AUC 5 + paclitaxel 175 mg/m^2 once every 3 weeks + bevacizumab 15 mg/kg for 6 cycles followed by bevacizumab 15 mg/kg once every 3 weeks for 16 cycles (bevacizumab will start from cycle 2) • Arm B: carboplatin AUC 5 + paclitaxel 175 mg/m^2 once every 3 weeks for 6 cycles followed by rucaparib 600 mg twice daily for 2 years as maintenance
Outcomes	**Primary:** PFS (time frame: from the date of randomisation to the date of documented progression disease, recurrence or death (whichever occurs first), assessed up to 64 months) **Secondary** • OS • PFS2 (time frame: from randomisation to second objective disease progression or death, assessed up to 64 months) • Time to first subsequent therapy • Time to second subsequent therapy • Overall response rate • Safety and tolerability • Patient-reported outcomes (various)
Starting date	17 March 2021. Estimated completion date: 1 March 2025
Contact information	
Notes	Sponsor: Fondazione Policlinico Universitario Agostino Gemelli IRCCS

NCT03635489

Study name	A study of the efficacy and safety of bevacizumab in Chinese women with newly diagnosed, previously untreated stage III or stage IV epithelial ovarian, fallopian tube, or primary peritoneal cancer
Methods	A randomised, double-blind, phase III trial
Participants	• Estimated 100 participants • Histologically-confirmed epithelial ovarian, fallopian tube or primary peritoneal cancer • ECOG performance status 0-2 • Life expectancy at least 12 weeks
Interventions	**Intervention:** paclitaxel (175 mg/m^2) + carboplatin (AUC = 6) + bevacaziumab (15 mg/kg) **Control:** paclitaxel (175 mg/m^2) + carboplatin (AUC = 6) + placebo (for bevacaziumab infusion) All agents given on day 1 of each 21-day cycle
Outcomes	**Primary**: PFS **Secondary** • OS • Objective response rate • Duration of response • Improvement in abdominal pain • Adverse events
Starting date	15 August 2018. Estimated completion date: 1 July 2023
Contact information	
Notes	

NCT04908787

Study name	A phase III study of BD0801 combined with chemotherapy in recurrent, platinum-resistant epithelial ovarian cancer
Methods	A randomised, double-blind, phase III study Quadruple masking (participant, care provider, investigator, outcomes assessor)
Participants	• 357 participants expected to be randomised by parallel assignment • Age 18 years and older • Platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer • ECOG performance status 0-1 • Exclusion: previous treatment with > 2 chemotherapy regimens
Interventions	**Intervention:** chemotherapy (with one of paclitaxel, topotecan or liposomal doxorubicin) + BD0801 (a humanised rabbit anti-VEGF monoclonal antibody (Xue 2021)) **Control:** chemotherapy (with one of paclitaxel, topotecan or liposomal doxorubicin) + placebo
Outcomes	**Primary**: PFS at 2 years (as assessed by blinded independent review committee) **Secondary**

NCT04908787 *(Continued)*

	• OS • PFS (investigator-assessed) • Objective response rate • Disease control rate • Adverse events • Quality of life • Serum drug concentrations • Rates and duration of immunogenicity
Starting date	First posted: 1 June 2021. Last updated: 26 November 2021
Contact information	
Notes	Sponsor: Jiangsu Simcere Pharmaceutical Co., Ltd.

NCT04919629

Study name	APL-2 and pembrolizumab versus APL-2, pembrolizumab and bevacizumab versus bevacizumab alone for the treatment of recurrent ovarian, fallopian tube, or primary peritoneal cancer and malignant effusion
Methods	An open-label, randomised, phase II trial
Participants	• Estimated 40 participants • 18 years and older • Recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer • No limitations by platinum sensitivity, prior stage or number of lines of prior treatment • Symptomatic ascites or pleural effusion of both requiring ≥ 1 drainage within 4 weeks of study entry • ECOG performance status of 0-2 • Life expectancy of at least 3 months
Interventions	3-arm trial: Arm 1: pegcetacoplan + pembrolizumab Arm 2: pegcetacoplan + pembrolizumab + bevacizumab Arm 3: bevacizumab
Outcomes	**Primary**: accumulation of effusion **Secondary** • OS • PFS • Best response • Overall response rate • Disease control rate • Quality of life
Starting date	Estimated start date: 15 October 2022. Estimated completion date: 15 October 2025
Contact information	

NCT04919629 *(Continued)*

Notes	Sponsor: Roswell Park Cancer Institute

NCT05009082

Study name	AGO-OVAR 28/ ENGOT-ov57 (NCT05009082; EudraCT Number: 2021-001271-16)
Methods	An open-label, international, multi-centre, randomised, phase III trial
Participants	• Estimated 970 participants • Newly-diagnosed, histologically-confirmed, advanced invasive high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer • FIGO stage III/IV except FIGO stage IIIA2 without nodal involvement • Either have undergone upfront primary surgery or plan to undergo chemotherapy with interval debulking surgery
Interventions	**Intervention**: carboplatin (AUC 5) + paclitaxel (175 mg/m^2) + bevacizumab (7.5 mg/kg or 15 mg/kg according to local standard) all given on day 1 every 3 weeks for 6 cycles, followed by bevacizumab (same dose, given on day 1 every 3 weeks) for up to 1 year and niraparib (200 mg or 300 mg) once daily for up to a total of 3 years **Control**: carboplatin (AUC 5) + paclitaxel (175 mg/m^2) both given on day 1 every 3 weeks for 6 cycles, followed by niraparib (200 mg or 300 mg) once daily for up to a total of 3 years
Outcomes	**Primary**: PFS **Secondary** • PFS according to tumour *BRCA* status • OS • Time to first subsequent therapy • Adverse events • Quality of life
Starting date	13 September 2022. Estimated completion date: September 2030
Contact information	
Notes	

NCT05043402

Study name	A study of navicixizumab in patients with platinum resistant ovarian cancer
Methods	An open-label, phase III, 2-stage, randomised trial The trial is investigating navicixizumab - a bispecific antibody designed to inhibit both VEGF and another target (DLL4, 'Delta-like ligand 4') Randomised with sequential assignment
Participants	• Estimated 400 participants • 18 years or older • Platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer

NCT05043402 *(Continued)*

	• Must have received 2 to 5 prior therapies including at least 1 line of therapy containing bevacizumab (or biosimilar) • ECOG performance status 0-1
Interventions	**3-arm trial** **Intervention 1:** paclitaxel (80 mg/m^2 on days 1, 8 and 15 of a 28-day cycle) + navicixizumab (3 mg/kg on days 1 and 15 of a 28-day cycle) **Intervention 2:** navicixizumab (3 mg/kg on days 1 and 15 of a 28-day cycle) **Control:** paclitaxel (80 mg/m^2 on days 1, 8 and 15 of a 28-day cycle)
Outcomes	**Primary** • Overall response rate (assessed at up to 2 years) • PFS (up to 2 years) **Secondary** • OS (up to 2 years) • Time to response • Disease control rate • Duration of response
Starting date	Estimated start date: 30 November 2022. Estimated completion date: 15 August 2024
Contact information	
Notes	Sponsor: OncXerna Theraputics, Inc.

NCT05170594

Study name	A study of bevacizumab combined with fluzoparib/chemotherapy or fluzoparib in the treatment of ovarian cancer
Methods	An open-label, phase II, randomised trial Trial randomises participants to 3 arms, of which 2 arms would give a potentially-relevant comparison for this review
Participants	• Estimated 60 participants • Women aged 18 to 75 years • Histologically- or cytologically-proven recurrent platinum-resistant ovarian, fallopian tube or primary peritoneal cancer • ECOG performance score 0-1 • Life expectancy of at least 12 weeks • No previous treatment with PARP inhibitors or other targeted therapies
Interventions	**Intervention**: fluzoparib (a PARP inhibitor, 150 mg twice daily) + bevacizumab (15 mg/kg every 3 weeks) (Note - this intervention is not entirely clear in the protocol) **Control**: fluzoparib (150 mg twice daily) (3rd arm - other intervention not relevant for this review: bevacizumab (15 mg/kg every 3 weeks) + non-platinum chemotherapy)

NCT05170594 *(Continued)*

Outcomes	**Primary:** PFS (assessed at 2 years) **Secondary** • Objective remission rate • OS • Adverse events
Starting date	24 December 2021. Estimated completion date: 30 June 2024
Contact information	
Notes	

NCT05183984

Study name	Niraparib with bevacizumab after complete cytoreduction in patients with ovarian cancer (NIRVANA-1)
Methods	An open-label, multi-centre, randomised, phase II trial Participants will be randomised in a 1:1 ratio to intervention or control, stratified by *BRCA* status, FIGO state at diagnosis and previous hyperthermic intraperitoneal chemotherapy
Participants	• Estimated 390 participants • Female aged 18 to 99 • Newly-diagnosed, histologically-confirmed ovarian, fallopian tube or primary peritoneal cancer • Stage IIIA/B/C • High-grade serous or grade 2-3 endometrioid morphology, or other non-mucinous or non-clear cell ovarian cancer with a germline deleterious *BRCA*1/2 mutation • No residual disease after frontline cytoreductive surgery
Interventions	**Intervention:** carboplatin (AUC 5-6) + paclitaxel (175 mg/m^2) + bevacizumab 15 mg/kg once every 3 weeks for 5 cycles, followed by bevacizumab (15 mg/kg) once every 3 weeks for 15 months + niraparib (200 or 300 mg/day) for 2 years **Control:** carboplatin (AUC 5-6) + paclitaxel (175 mg/m^2) once every 3 weeks for 5 cycles, followed by niraparib 200 or 300 mg/day for 2 years
Outcomes	**Primary**: PFS up to 24 months (time from randomisation until objective tumour progression or death) **Secondary** • PFS2 (time from randomisaton to objective tumour progression on next-line treatment) • Abnormal physical signs • Time to first and second subsequent treatments • OS • Predictive value of the KELIM (CA-125 ELIMination rate constant K)
Starting date	1 February 2022. Estimated completion date: January 2029
Contact information	
Notes	Sponsor: ARCAGY/GINECO GROUP

NCT05523440	
Study name	Bevacizumab and/or niraparib in patients with recurrent endometrial and/or ovarian cancer with ARID1A mutation (ARID1A)
Methods	An open-label, randomised, phase II trial
Participants	• Estimated 92 participants • 18 years and older • Histologically-confirmed progressive or recurrent endometrial or ovarian cancer with previously identified ARID1A tumour mutations • Measurable disease by RECIST criteria v1.1 • ECOG performance status 0-1 • Life expectancy of at least 12 weeks
Interventions	**Intervention:** niraparib (200 mg or 300 mg depending on body weight and platelet count) once daily + bevacizumab (15 mg/kg on day 1 of each cycle) **Control:** niraparib (200 mg or 300 mg depending on body weight and platelet count) once daily
Outcomes	**Primary** • Objective response rate **Secondary** • Adverse events • Duration of response • PFS
Starting date	Estimated study start date: December 2022. Estimated completion date: December 2026
Contact information	
Notes	Note that this trial includes patients with both endometrial and ovarian cancer, but only results for ovarian cancer would be relevant to this review.

CT: computed tomography; **ECOG:** Eastern Cooperative Oncology Group;**EORTC QLQ C30:** European Organisation for Research and Treatment of Cancer QoL core quality of life questionnaire; **EQ-5D-5L:** EuroQoL 5-dimension questionnaire;**FACT-O:** Functional Assessment of Cancer Therapy - Ovary;**FGF-R:** fibroblast growth factor receptor;**IV**: intravenous; **MRI:** magnetic resonance imaging; **ORR:** objective response rate; **OS:** overall survival; **PARP:** poly(ADP-ribose) polymerase; **PFS:** progression-free survival; **RCT:** randomised controlled trial; **RECIST:** Response Evaluation Criteria in Solid Tumors; **TKI:** tyrosine kinase inhibitor; **VEGF:** vascular endothelial growth factor; **VEGF-R:** vascular endothelial growth factor receptor

DATA AND ANALYSES

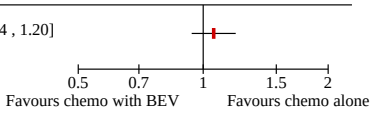
Comparison 1. Newly-diagnosed EOC: chemotherapy with bevacizumab versus chemotherapy alone (placebo for all in the maintenance phase)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Overall survival	1		Hazard Ratio (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Progression-free survival	1		Hazard Ratio (IV, Fixed, 95% CI)	Totals not selected
1.3 Quality of life - Trial Outcome Index score of Functional Assessment of Cancer Therapy—Ovarian Cancer questionnaire	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.4 Hypertension (grade ≥ 2)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
1.5 Proteinuria (grade ≥ 3)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
1.6 Pain (grade ≥ 2)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
1.7 Neutropenia (grade ≥ 4)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
1.8 Febrile neutropenia (any grade)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
1.9 Venous thromboembolic event (any grade)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
1.10 Arterial thromboembolic event (any grade)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.11 Non-central nervous system bleeding (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.12 Gastrointestinal adverse events (grade ≥ 2)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

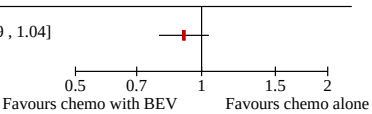
Analysis 1.1. Comparison 1: Newly-diagnosed EOC: chemotherapy with bevacizumab versus chemotherapy alone (placebo for all in the maintenance phase), Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Chemotherapy with BEV Total	Chemotherapy alone Total	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
GOG-0218 2019	0.058269	0.062296	625	625	1.06 [0.94 , 1.20]	



Analysis 1.2. Comparison 1: Newly-diagnosed EOC: chemotherapy with bevacizumab versus chemotherapy alone (placebo for all in the maintenance phase), Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Chemotherapy with BEV Total	Chemotherapy alone Total	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
GOG-0218 2019 (1)	-0.097	0.07	625	625	0.91 [0.79 , 1.04]	

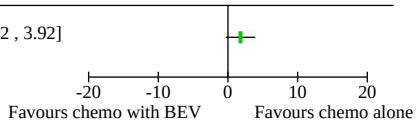


Footnotes

(1) evidence of non-proportionality of hazards visible on Kaplan-Meier curve (Fig 2B, Burger et al. 2011)

Analysis 1.3. Comparison 1: Newly-diagnosed EOC: chemotherapy with bevacizumab versus chemotherapy alone (placebo for all in the maintenance phase), Outcome 3: Quality of life - Trial Outcome Index score of Functional Assessment of Cancer Therapy—Ovarian Cancer questionnaire

Study or Subgroup	Chemotherapy with BEV Mean	SD	Total	Chemotherapy alone Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
GOG-0218 2019 (1)	77.6	13.970952	347	75.8	14.840512	362	1.80 [-0.32 , 3.92]	

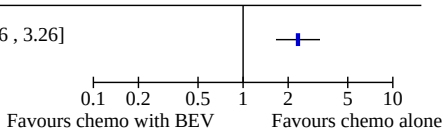


Footnotes

(1) at 6 month of follow-up; Bevacizumab dose: 15 mg/kg

Analysis 1.4. Comparison 1: Newly-diagnosed EOC: chemotherapy with bevacizumab versus chemotherapy alone (placebo for all in the maintenance phase), Outcome 4: Hypertension (grade ≥ 2)

Study or Subgroup	Chemotherapy with BEV Events	Total	Chemotherapy alone Events	Total	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
GOG-0218 2019 (1)	101	607	43	601	2.33 [1.66 , 3.26]	

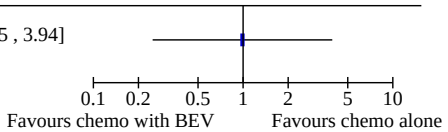


Footnotes

(1) Bevacizumab dose: 15 mg/kg

Analysis 1.5. Comparison 1: Newly-diagnosed EOC: chemotherapy with bevacizumab versus chemotherapy alone (placebo for all in the maintenance phase), Outcome 5: Proteinuria (grade ≥ 3)

Study or Subgroup	Chemotherapy with BEV Events	Total	Chemotherapy alone Events	Total	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
GOG-0218 2019 (1)	4	607	4	601	0.99 [0.25 , 3.94]	

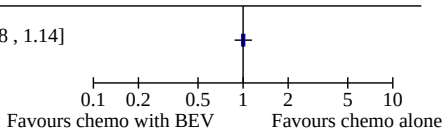


Footnotes

(1) Bevacizumab dose: 15 mg/kg

Analysis 1.6. Comparison 1: Newly-diagnosed EOC: chemotherapy with bevacizumab versus chemotherapy alone (placebo for all in the maintenance phase), Outcome 6: Pain (grade ≥ 2)

Study or Subgroup	Chemotherapy with BEV Events	Total	Chemotherapy alone Events	Total	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
GOG-0218 2019 (1)	254	607	251	601	1.00 [0.88 , 1.14]	

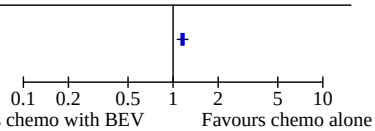


Footnotes

(1) Bevacizumab dose: 15 mg/kg

Analysis 1.7. Comparison 1: Newly-diagnosed EOC: chemotherapy with bevacizumab versus chemotherapy alone (placebo for all in the maintenance phase), Outcome 7: Neutropenia (grade ≥ 4)

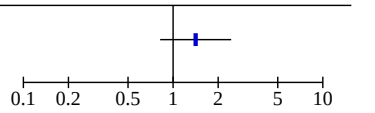
Study or Subgroup	Chemotherapy with BEV Events	Total	Chemotherapy alone Events	Total	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
GOG-0218 2019 (1)	384	575	347	601	1.16 [1.06 , 1.26]	



Footnotes
(1) Bevacizumab dose: 15 mg/kg

Analysis 1.8. Comparison 1: Newly-diagnosed EOC: chemotherapy with bevacizumab versus chemotherapy alone (placebo for all in the maintenance phase), Outcome 8: Febrile neutropenia (any grade)

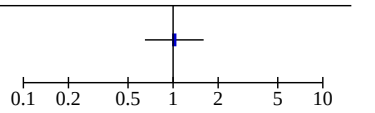
Study or Subgroup	Chemotherapy with BEV Events	Total	Chemotherapy alone Events	Total	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
GOG-0218 2019 (1)	30	607	21	601	1.41 [0.82 , 2.44]	



Footnotes
(1) Bevacizumab dose: 15 mg/kg

Analysis 1.9. Comparison 1: Newly-diagnosed EOC: chemotherapy with bevacizumab versus chemotherapy alone (placebo for all in the maintenance phase), Outcome 9: Venous thromboembolic event (any grade)

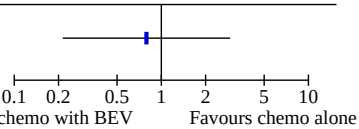
Study or Subgroup	Chemotherapy with BEV Events	Total	Chemotherapy alone Events	Total	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
GOG-0218 2019 (1)	36	607	35	601	1.02 [0.65 , 1.60]	



Footnotes
(1) Bevacizumab dose: 15 mg/kg

Analysis 1.10. Comparison 1: Newly-diagnosed EOC: chemotherapy with bevacizumab versus chemotherapy alone (placebo for all in the maintenance phase), Outcome 10: Arterial thromboembolic event (any grade)

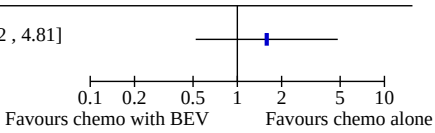
Study or Subgroup	Chemotherapy with BEV Events	Total	Chemotherapy alone Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
GOG-0218 2019 (1)	4	607	5	601	0.79 [0.21 , 2.94]	



Footnotes
(1) Bevacizumab dose: 15 mg/kg

Analysis 1.11. Comparison 1: Newly-diagnosed EOC: chemotherapy with bevacizumab versus chemotherapy alone (placebo for all in the maintenance phase), Outcome 11: Non-central nervous system bleeding (grade ≥ 3)

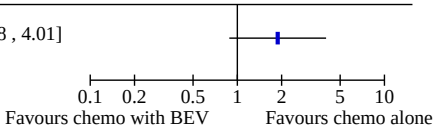
Study or Subgroup	Chemotherapy with BEV Events	Total	Chemotherapy alone Events	Total	Risk Ratio M-H, Fixed, 95% CI
GOG-0218 2019 (1)	8	607	5	601	1.58 [0.52 , 4.81]



Footnotes
(1) Bevacizumab dose: 15 mg/kg

Analysis 1.12. Comparison 1: Newly-diagnosed EOC: chemotherapy with bevacizumab versus chemotherapy alone (placebo for all in the maintenance phase), Outcome 12: Gastrointestinal adverse events (grade ≥ 2)

Study or Subgroup	Chemotherapy with BEV Events	Total	Chemotherapy alone Events	Total	Risk Ratio M-H, Fixed, 95% CI
GOG-0218 2019 (1)	19	607	10	601	1.88 [0.88 , 4.01]



Footnotes
(1) Bevacizumab dose: 15 mg/kg

Comparison 2. Newly-diagnosed EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone

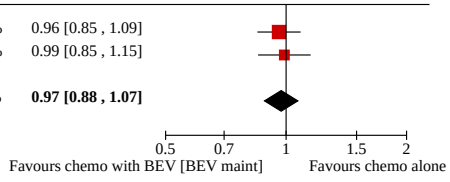
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Overall survival	2	2776	Hazard Ratio (IV, Fixed, 95% CI)	0.97 [0.88, 1.07]
2.2 Overall survival by risk status	2		Hazard Ratio (IV, Fixed, 95% CI)	Subtotals only
2.2.1 Women at high risk for disease progression	2	1316	Hazard Ratio (IV, Fixed, 95% CI)	0.86 [0.76, 0.98]
2.2.2 Women at lower risk for disease progression	2	1460	Hazard Ratio (IV, Fixed, 95% CI)	1.13 [0.97, 1.31]
2.3 Progression-free survival	2	2746	Hazard Ratio (IV, Random, 95% CI)	0.82 [0.64, 1.05]
2.4 Quality of life	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.4.1 Trial Outcome Index score of Functional Assessment of Cancer Therapy—Ovarian Cancer questionnaire	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.4.2 Global Quality of Life European Organization for Research and	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
Treatment of Cancer Questionnaire QLQ-C30				
2.5 Any adverse event (grade ≥ 3)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2.6 Hypertension (grade ≥ 2)	2	2707	Risk Ratio (IV, Fixed, 95% CI)	4.27 [3.25, 5.60]
2.7 Proteinuria (grade ≥ 3)	2	2707	Risk Ratio (M-H, Fixed, 95% CI)	1.97 [1.20, 3.23]
2.8 Pain (grade ≥ 2)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2.9 Neutropenia (grade ≥ 3)	2		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2.9.1 Grade ≥ 3	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2.9.2 Grade ≥ 4	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
2.10 Febrile neutropenia (any grade)	2	2707	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.87, 2.04]
2.11 Venous thromboembolic event (any grade)	2	2707	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [1.03, 1.89]
2.12 Arterial thromboembolic event (any grade)	2	2707	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [1.07, 3.54]
2.13 Non-central nervous system bleeding (grade ≥ 3)	2	2707	Risk Ratio (M-H, Fixed, 95% CI)	2.13 [0.87, 5.20]
2.14 Severe gastrointestinal adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.14.1 Grade ≥ 2 GI events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.14.2 Grade ≥ 3 GI perforation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: Newly-diagnosed EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Chemo with BEV [BEV maint] Total	Chemo alone Total	Weight	Hazard Ratio IV, Fixed, 95% CI
GOG-0218 2019 (1)	-0.040822	0.063444	623	625	59.6%	0.96 [0.85 , 1.09]
ICON7 2015 (2)	-0.01005	0.077114	764	764	40.4%	0.99 [0.85 , 1.15]
Total (95% CI)			**1387**	**1389**	**100.0%**	**0.97 [0.88 , 1.07]**

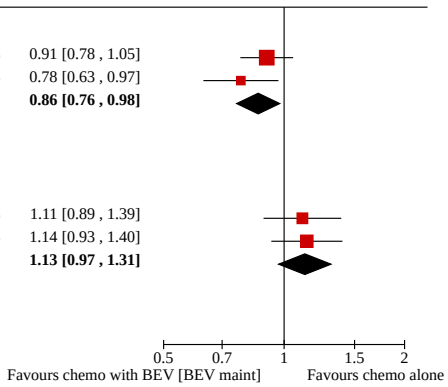
Heterogeneity: Chi² = 0.09, df = 1 (P = 0.76); I² = 0%
Test for overall effect: Z = 0.58 (P = 0.56)
Test for subgroup differences: Not applicable



Footnotes
(1) Bevacizumab dose: 15 mg/kg
(2) evidence of non-proportionality of hazards (p=0.02); Restricted mean survival time difference = 0.9 (95% CI –0.8, 2.6); log-rank test p=0.85

Analysis 2.2. Comparison 2: Newly-diagnosed EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 2: Overall survival by risk status

Study or Subgroup	log[Hazard Ratio]	SE	Chemo with BEV [BEV maint] Total	Chemo alone Total	Weight	Hazard Ratio IV, Fixed, 95% CI
2.2.1 Women at high risk for disease progression						
GOG-0218 2019 (1)	-0.09982	0.07746	407	407	66.9%	0.91 [0.78 , 1.05]
ICON7 2015 (2)	-0.248461	0.110098	248	254	33.1%	0.78 [0.63 , 0.97]
Subtotal (95% CI)			**655**	**661**	**100.0%**	**0.86 [0.76 , 0.98]**
Heterogeneity: Chi² = 1.22, df = 1 (P = 0.27); I² = 18%						
Test for overall effect: Z = 2.35 (P = 0.02)						
2.2.2 Women at lower risk for disease progression						
GOG-0218 2019 (1)	0.105261	0.114018	216	218	45.6%	1.11 [0.89 , 1.39]
ICON7 2015 (3)	0.131028	0.10435	516	510	54.4%	1.14 [0.93 , 1.40]
Subtotal (95% CI)			**732**	**728**	**100.0%**	**1.13 [0.97 , 1.31]**
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² = 0%						
Test for overall effect: Z = 1.55 (P = 0.12)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%						



Footnotes

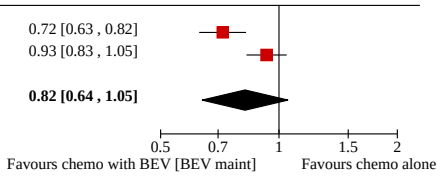
(1) Bevacizumab dose: 15 mg/kg

(2) evidence of non-proportionality of hazards (p=0.01); Restricted mean survival time difference = 4.8 (95% CI 1.5, 8.1); log-rank test p=0.03; Bevacizumab dose: 7.5 mg/kg

(3) Bevacizumab dose: 7.5 mg/kg

Analysis 2.3. Comparison 2: Newly-diagnosed EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 3: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Chemo with BEV [BEV maint] Total	Chemo alone Total	Weight	Hazard Ratio IV, Random, 95% CI
GOG-0218 2019 (1)	-0.33	0.07	623	625	49.0%	0.72 [0.63 , 0.82]
ICON7 2015 (2)	-0.072571	0.059981	745	753	51.0%	0.93 [0.83 , 1.05]
Total (95% CI)			**1368**	**1378**	**100.0%**	**0.82 [0.64 , 1.05]**
Heterogeneity: Tau² = 0.03; Chi² = 7.80, df = 1 (P = 0.005); I² = 87%						
Test for overall effect: Z = 1.54 (P = 0.12)						
Test for subgroup differences: Not applicable						



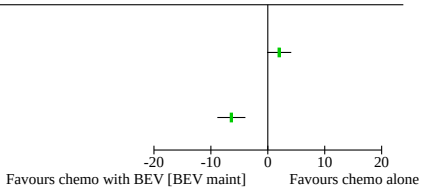
Footnotes

(1) evidence of non-proportionality of hazards visible on Kaplan-Meier curve (Fig 2B, Burger et al. 2011)

(2) evidence of non-proportionality of hazards (p<0·0001); Restricted mean survival time difference = 1.6 (95% CI –0.6, 3.7); log-rank test p=0.25; Bevacizumab dose: 7.5 mg/kg

Analysis 2.4. Comparison 2: Newly-diagnosed EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 4: Quality of life

Study or Subgroup	Chemo with BEV [BEV maint] Mean	SD	Total	Chemo alone Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
2.4.1 Trial Outcome Index score of Functional Assessment of Cancer Therapy—Ovarian Cancer questionnaire							
GOG-0218 2019 (1)	77.8	14.523688	375	75.8	14.840512	362	2.00 [-0.12 , 4.12]
2.4.2 Global Quality of Life European Organization for Research and Treatment of Cancer Questionnaire QLQ-C30							
ICON7 2015 (2)	69.7	19.1	502	76.1	18.2	388	-6.40 [-8.86 , -3.94]



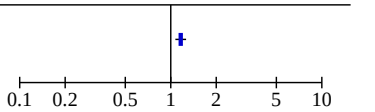
Footnotes

(1) at 6 month of follow-up; Bevacizumab dose: 15 mg/kg

(2) value at week 54 (end of maintenance with bevacizumab); Bevacizumab dose: 7.5 mg/kg

Analysis 2.5. Comparison 2: Newly-diagnosed EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 5: Any adverse event (grade ≥ 3)

Study or Subgroup	Chemo with BEV [BEV maint] Events	Total	Chemo alone Events	Total	Risk Ratio IV, Fixed, 95% CI
ICON7 2015 (1)	491	745	419	740	1.16 [1.07 , 1.26]

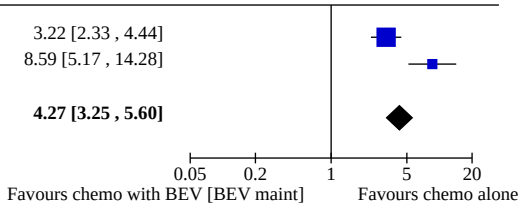


Footnotes
(1) Bevacizumab dose: 7.5 mg/kg

Analysis 2.6. Comparison 2: Newly-diagnosed EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 6: Hypertension (grade ≥ 2)

Study or Subgroup	Chemo with BEV [BEV maint] Events	Total	Chemo alone Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
GOG-0218 2019 (1)	140	608	43	601	71.3%	3.22 [2.33 , 4.44]
ICON7 2015 (2)	136	745	16	753	28.7%	8.59 [5.17 , 14.28]
Total (95% CI)		**1353**		**1354**	**100.0%**	**4.27 [3.25 , 5.60]**
Total events:	276		59			

Heterogeneity: Chi² = 10.23, df = 1 (P = 0.001); I² = 90%
Test for overall effect: Z = 10.44 (P < 0.00001)
Test for subgroup differences: Not applicable

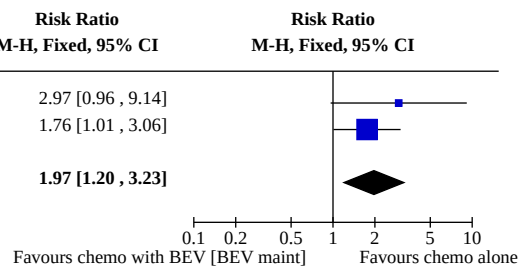


Footnotes
(1) Bevacizumab dose: 15 mg/kg
(2) Bevacizumab dose: 7.5 mg/kg

Analysis 2.7. Comparison 2: Newly-diagnosed EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 7: Proteinuria (grade ≥ 3)

Study or Subgroup	Chemo with BEV [BEV maint] Events	Total	Chemo alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
GOG-0218 2019 (1)	12	608	4	601	17.6%	2.97 [0.96 , 9.14]
ICON7 2015 (2)	33	745	19	753	82.4%	1.76 [1.01 , 3.06]
Total (95% CI)		**1353**		**1354**	**100.0%**	**1.97 [1.20 , 3.23]**
Total events:	45		23			

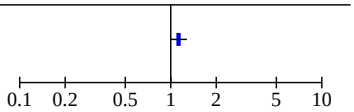
Heterogeneity: Chi² = 0.67, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 2.68 (P = 0.007)
Test for subgroup differences: Not applicable



Footnotes
(1) Bevacizumab dose: 15 mg/kg
(2) Bevacizumab dose: 7.5 mg/kg

Analysis 2.8. Comparison 2: Newly-diagnosed EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 8: Pain (grade ≥ 2)

Study or Subgroup	Chemo with BEV [BEV maint] Events	Total	Chemo alone Events	Total	Risk Ratio IV, Fixed, 95% CI
GOG-0218 2019 (1)	286	608	251	601	1.13 [0.99 , 1.28]

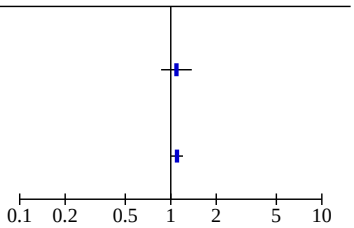


Footnotes

(1) Bevacizumab dose: 15 mg/kg

Analysis 2.9. Comparison 2: Newly-diagnosed EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 9: Neutropenia (grade ≥ 3)

Study or Subgroup	Chemo with BEV [BEV maint] Events	Total	Chemo alone Events	Total	Risk Ratio IV, Fixed, 95% CI
2.9.1 Grade ≥ 3					
ICON7 2015 (1)	123	745	114	753	1.09 [0.86 , 1.38]
2.9.2 Grade ≥ 4					
GOG-0218 2019 (2)	386	608	347	601	1.10 [1.00 , 1.20]



Footnotes

(1) Bevacizumab dose: 7.5 mg/kg

(2) Bevacizumab dose: 15 mg/kg

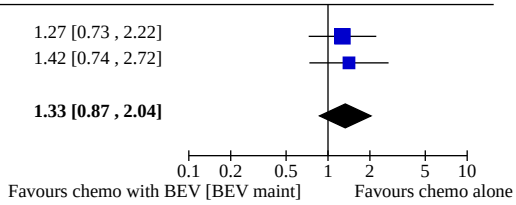
Analysis 2.10. Comparison 2: Newly-diagnosed EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 10: Febrile neutropenia (any grade)

Study or Subgroup	Chemo with BEV [BEV maint] Events	Total	Chemo alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
GOG-0218 2019 (1)	27	608	21	601	58.6%	1.27 [0.73 , 2.22]
ICON7 2015 (2)	21	745	15	753	41.4%	1.42 [0.74 , 2.72]
Total (95% CI)		**1353**		**1354**	**100.0%**	**1.33 [0.87 , 2.04]**
Total events:	48		36			

Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%

Test for overall effect: Z = 1.32 (P = 0.19)

Test for subgroup differences: Not applicable



Footnotes

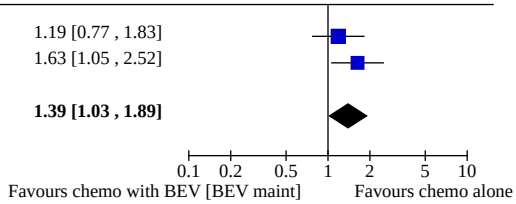
(1) Bevacizumab dose: 15 mg/kg

(2) Bevacizumab dose: 7.5 mg/kg

Analysis 2.11. Comparison 2: Newly-diagnosed EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 11: Venous thromboembolic event (any grade)

Study or Subgroup	Chemo with BEV [BEV maint] Events	Total	Chemo alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
GOG-0218 2019 (1)	42	608	35	601	53.3%	1.19 [0.77 , 1.83]
ICON7 2015 (2)	50	745	31	753	46.7%	1.63 [1.05 , 2.52]
Total (95% CI)		**1353**		**1354**	**100.0%**	**1.39 [1.03 , 1.89]**
Total events:	92		66			

Heterogeneity: Chi² = 1.03, df = 1 (P = 0.31); I² = 2%
Test for overall effect: Z = 2.12 (P = 0.03)
Test for subgroup differences: Not applicable

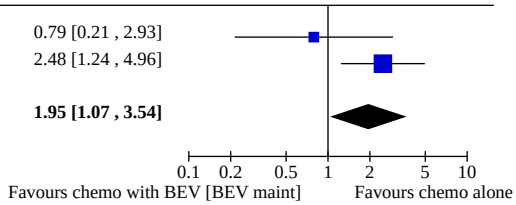


Footnotes
(1) Bevacizumab dose: 15 mg/kg; all grades
(2) Bevacizumab dose: 7.5 mg/kg;

Analysis 2.12. Comparison 2: Newly-diagnosed EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 12: Arterial thromboembolic event (any grade)

Study or Subgroup	Chemo with BEV [BEV maint] Events	Total	Chemo alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
GOG-0218 2019 (1)	4	608	5	601	31.5%	0.79 [0.21 , 2.93]
ICON7 2015 (2)	27	745	11	753	68.5%	2.48 [1.24 , 4.96]
Total (95% CI)		**1353**		**1354**	**100.0%**	**1.95 [1.07 , 3.54]**
Total events:	31		16			

Heterogeneity: Chi² = 2.29, df = 1 (P = 0.13); I² = 56%
Test for overall effect: Z = 2.19 (P = 0.03)
Test for subgroup differences: Not applicable

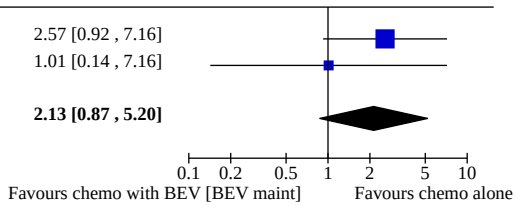


Footnotes
(1) Bevacizumab dose: 15 mg/kg
(2) Bevacizumab dose: 7.5 mg/kg

Analysis 2.13. Comparison 2: Newly-diagnosed EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 13: Non-central nervous system bleeding (grade ≥ 3)

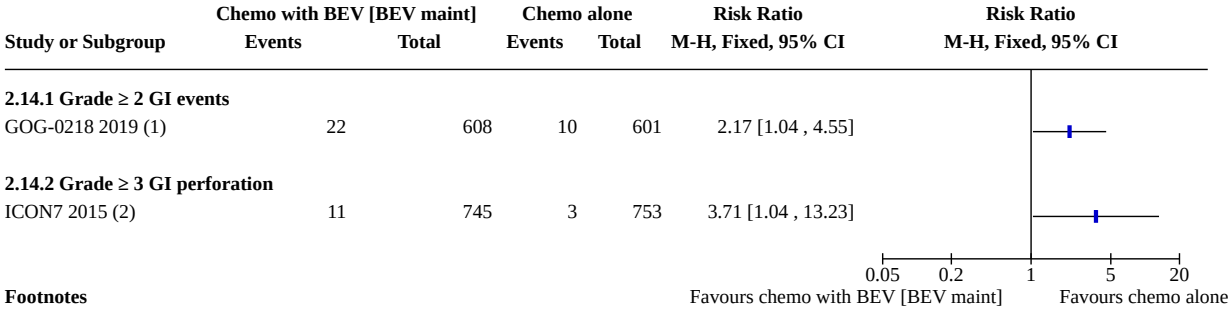
Study or Subgroup	Chemo with BEV [BEV maint] Events	Total	Chemo alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
GOG-0218 2019 (1)	13	608	5	601	71.7%	2.57 [0.92 , 7.16]
ICON7 2015 (2)	2	745	2	753	28.3%	1.01 [0.14 , 7.16]
Total (95% CI)		**1353**		**1354**	**100.0%**	**2.13 [0.87 , 5.20]**
Total events:	15		7			

Heterogeneity: Chi² = 0.69, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 1.66 (P = 0.10)
Test for subgroup differences: Not applicable



Footnotes
(1) Bevacizumab dose: 15 mg/kg;
(2) Bevacizumab dose: 7.5 mg/kg

Analysis 2.14. Comparison 2: Newly-diagnosed EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 14: Severe gastrointestinal adverse events



Footnotes

(1) Bevacizumab dose: 15 mg/kg

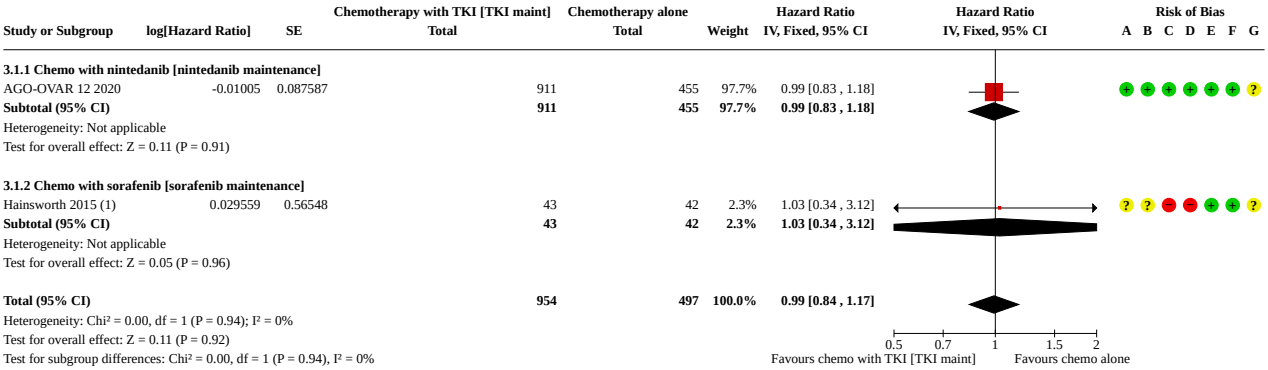
(2) Bevacizumab dose: 7.5 mg/kg

Comparison 3. Newly-diagnosed EOC: chemotherapy with TKI followed by TKI maintenance compared to chemotherapy alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Overall survival	2	1451	Hazard Ratio (IV, Fixed, 95% CI)	0.99 [0.84, 1.17]
3.1.1 Chemo with nintedanib [nintedanib maintenance]	1	1366	Hazard Ratio (IV, Fixed, 95% CI)	0.99 [0.83, 1.18]
3.1.2 Chemo with sorafenib [sorafenib maintenance]	1	85	Hazard Ratio (IV, Fixed, 95% CI)	1.03 [0.34, 3.12]
3.2 Progression-free survival	2	1451	Hazard Ratio (IV, Fixed, 95% CI)	0.88 [0.77, 1.00]
3.2.1 Chemo with nintedanib [nintedanib maintenance]	1	1366	Hazard Ratio (IV, Fixed, 95% CI)	0.86 [0.75, 0.98]
3.2.2 Chemo with sorafenib [sorafenib maintenance]	1	85	Hazard Ratio (IV, Fixed, 95% CI)	1.21 [0.74, 1.97]
3.3 Quality of life - Global Quality of Life European Organization for Research and Treatment of Cancer Questionnaire QLQ-C30	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.4 Any adverse event (grade ≥ 3)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
3.4.1 Chemo with nintedanib [nintedanib maintenance]	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
3.5 Hypertension (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.5.1 Chemo with nintedanib [nintedanib maintenance]	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.6 Abdominal pain (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.6.1 Chemo with nintedanib [nintedanib maintenance]	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.7 Neutropenia (grade ≥ 3)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
3.7.1 Chemo with nintedanib [nintedanib maintenance]	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

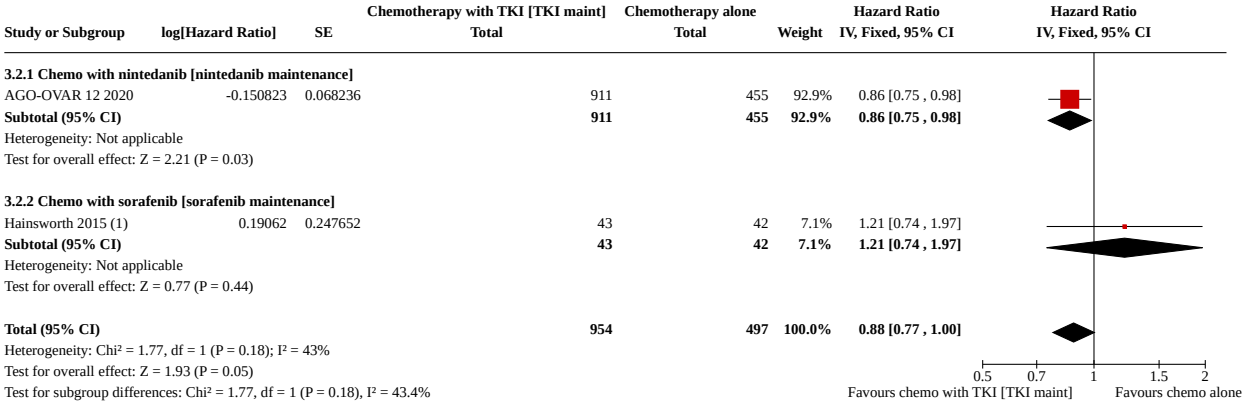
Analysis 3.1. Comparison 3: Newly-diagnosed EOC: chemotherapy with TKI followed by TKI maintenance compared to chemotherapy alone, Outcome 1: Overall survival



Footnotes
(1) HR estimated based on reported Kaplan Meier curve

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

Analysis 3.2. Comparison 3: Newly-diagnosed EOC: chemotherapy with TKI followed by TKI maintenance compared to chemotherapy alone, Outcome 2: Progression-free survival

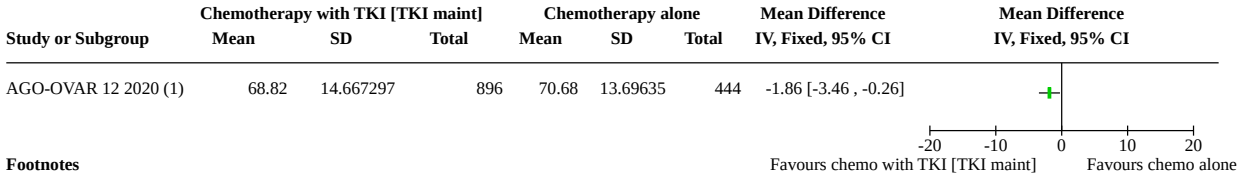


Study or Subgroup	log[Hazard Ratio]	SE	Chemotherapy with TKI [TKI maint] Total	Chemotherapy alone Total	Weight	Hazard Ratio IV, Fixed, 95% CI
3.2.1 Chemo with nintedanib [nintedanib maintenance]						
AGO-OVAR 12 2020	-0.150823	0.068236	911	455	92.9%	0.86 [0.75 , 0.98]
Subtotal (95% CI)			**911**	**455**	**92.9%**	**0.86 [0.75 , 0.98]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.21 (P = 0.03)						
3.2.2 Chemo with sorafenib [sorafenib maintenance]						
Hainsworth 2015 (1)	0.19062	0.247652	43	42	7.1%	1.21 [0.74 , 1.97]
Subtotal (95% CI)			**43**	**42**	**7.1%**	**1.21 [0.74 , 1.97]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.77 (P = 0.44)						
Total (95% CI)			**954**	**497**	**100.0%**	**0.88 [0.77 , 1.00]**
Heterogeneity: Chi² = 1.77, df = 1 (P = 0.18); I² = 43%						
Test for overall effect: Z = 1.93 (P = 0.05)						
Test for subgroup differences: Chi² = 1.77, df = 1 (P = 0.18), I² = 43.4%						

Footnotes

(1) HR estimated based on reported Kaplan Meier curve

Analysis 3.3. Comparison 3: Newly-diagnosed EOC: chemotherapy with TKI followed by TKI maintenance compared to chemotherapy alone, Outcome 3: Quality of life - Global Quality of Life European Organization for Research and Treatment of Cancer Questionnaire QLQ-C30

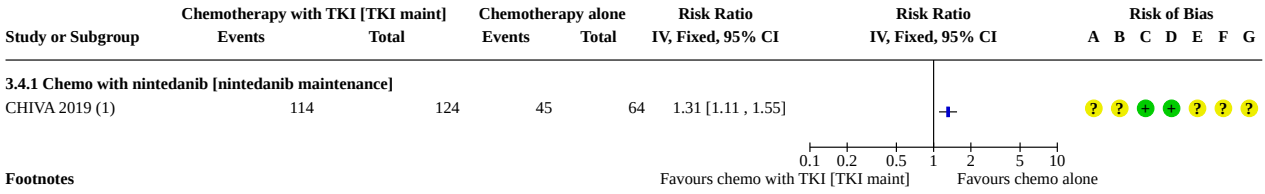


Study or Subgroup	Chemotherapy with TKI [TKI maint] Mean	SD	Total	Chemotherapy alone Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
AGO-OVAR 12 2020 (1)	68.82	14.667297	896	70.68	13.69635	444	-1.86 [-3.46 , -0.26]

Footnotes

(1) adjusted mean global health status and quality-of-life score on the scale normalised to 100

Analysis 3.4. Comparison 3: Newly-diagnosed EOC: chemotherapy with TKI followed by TKI maintenance compared to chemotherapy alone, Outcome 4: Any adverse event (grade ≥ 3)



Study or Subgroup	Chemotherapy with TKI [TKI maint] Events	Total	Chemotherapy alone Events	Total	Risk Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F G
3.4.1 Chemo with nintedanib [nintedanib maintenance]						
CHIVA 2019 (1)	114	124	45	64	1.31 [1.11 , 1.55]	? ? + + ? ? ?

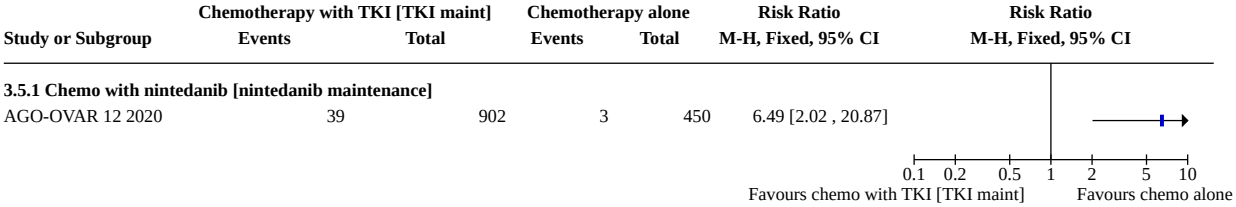
Footnotes

(1) grade 3 or 4

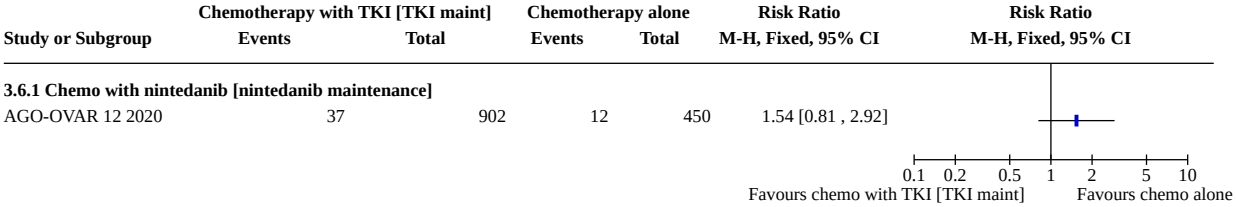
Risk of bias legend

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

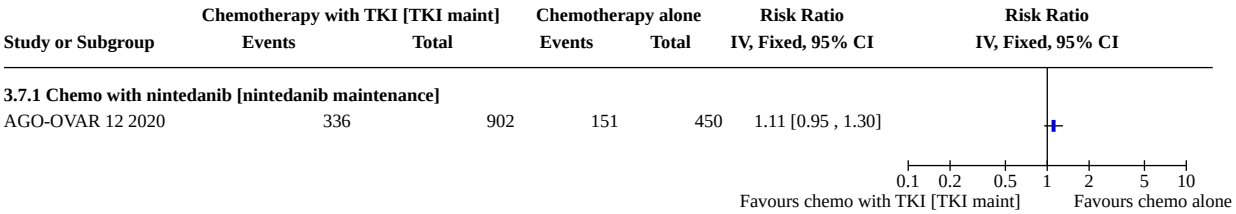
Analysis 3.5. Comparison 3: Newly-diagnosed EOC: chemotherapy with TKI followed by TKI maintenance compared to chemotherapy alone, Outcome 5: Hypertension (grade ≥ 3)



Analysis 3.6. Comparison 3: Newly-diagnosed EOC: chemotherapy with TKI followed by TKI maintenance compared to chemotherapy alone, Outcome 6: Abdominal pain (grade ≥ 3)



Analysis 3.7. Comparison 3: Newly-diagnosed EOC: chemotherapy with TKI followed by TKI maintenance compared to chemotherapy alone, Outcome 7: Neutropenia (grade ≥ 3)

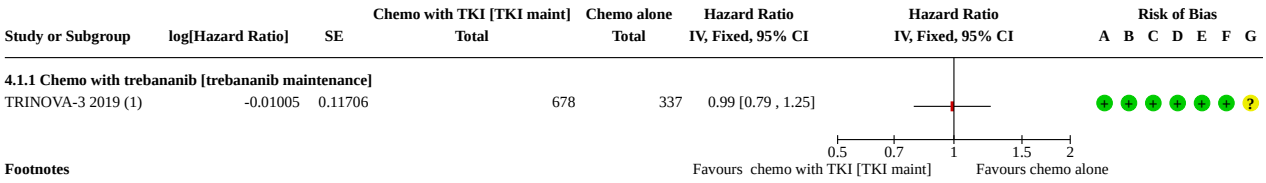


Comparison 4. Newly-diagnosed EOC: chemotherapy with TKI (peptide-Fc fusion protein) followed by TKI maintenance compared to chemotherapy alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Overall survival	1		Hazard Ratio (IV, Fixed, 95% CI)	Totals not selected
4.1.1 Chemo with trebananib [trebananib maintenance]	1		Hazard Ratio (IV, Fixed, 95% CI)	Totals not selected
4.2 Progression-free survival	1		Hazard Ratio (IV, Fixed, 95% CI)	Totals not selected
4.2.1 Chemo with trebananib [trebananib maintenance]	1		Hazard Ratio (IV, Fixed, 95% CI)	Totals not selected
4.3 Any adverse event (grade ≥ 3)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.3.1 Chemo with trebananib [trebananib maintenance]	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
4.4 Pain (grade 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.4.1 Chemo with trebananib [trebananib maintenance]	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.5 Abdominal pain (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.5.1 Chemo with trebananib [trebananib maintenance]	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.6 Neutropenia (grade ≥ 3)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
4.6.1 Chemo with trebananib [trebananib maintenance]	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
4.7 Febrile neutropenia (any grade)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.7.1 Chemo with trebananib [trebananib maintenance]	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4: Newly-diagnosed EOC: chemotherapy with TKI (peptide-Fc fusion protein) followed by TKI maintenance compared to chemotherapy alone, Outcome 1: Overall survival

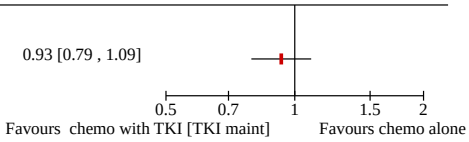


Footnotes
(1) immature OS data

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

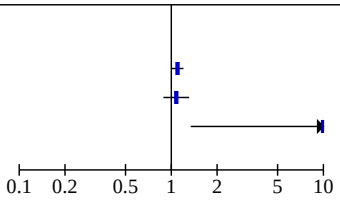
Analysis 4.2. Comparison 4: Newly-diagnosed EOC: chemotherapy with TKI (peptide-Fc fusion protein) followed by TKI maintenance compared to chemotherapy alone, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Chemo with TKI [TKI maint] Total	Chemo alone Total	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
4.2.1 Chemo with trebananib [trebananib maintenance]						
TRINOVA-3 2019	-0.072571	0.082119	678	337	0.93 [0.79 , 1.09]	



Analysis 4.3. Comparison 4: Newly-diagnosed EOC: chemotherapy with TKI (peptide-Fc fusion protein) followed by TKI maintenance compared to chemotherapy alone, Outcome 3: Any adverse event (grade ≥ 3)

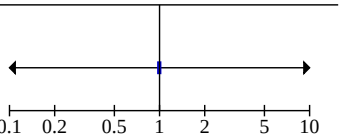
Study or Subgroup	Chemo with TKI [TKI maint] Events	Total	Chemo alone Events	Total	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
4.3.1 Chemo with trebananib [trebananib maintenance]						
TRINOVA-3 2019 (1)	490	675	222	336	1.10 [1.00 , 1.20]	
TRINOVA-3 2019 (2)	221	675	102	336	1.08 [0.89 , 1.31]	
TRINOVA-3 2019 (3)	20	675	1	336	9.96 [1.34 , 73.86]	



Footnotes
(1) grade 3
(2) grade 4
(3) grade 5

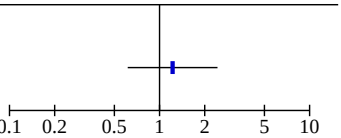
Analysis 4.4. Comparison 4: Newly-diagnosed EOC: chemotherapy with TKI (peptide-Fc fusion protein) followed by TKI maintenance compared to chemotherapy alone, Outcome 4: Pain (grade 3)

Study or Subgroup	Chemo with TKI [TKI maint] Events	Total	Chemo alone Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
4.4.1 Chemo with trebananib [trebananib maintenance]						
TRINOVA-3 2019	2	675	1	336	1.00 [0.09 , 10.94]	



Analysis 4.5. Comparison 4: Newly-diagnosed EOC: chemotherapy with TKI (peptide-Fc fusion protein) followed by TKI maintenance compared to chemotherapy alone, Outcome 5: Abdominal pain (grade ≥ 3)

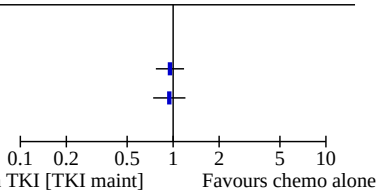
Study or Subgroup	Chemo with TKI [TKI maint] Events	Total	Chemo alone Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
4.5.1 Chemo with trebananib [trebananib maintenance]						
TRINOVA-3 2019 (1)	27	675	11	336	1.22 [0.61 , 2.43]	



Footnotes
(1) grade 3, there were no events of higher grades in both arms

Analysis 4.6. Comparison 4: Newly-diagnosed EOC: chemotherapy with TKI (peptide-Fc fusion protein) followed by TKI maintenance compared to chemotherapy alone, Outcome 6: Neutropenia (grade ≥ 3)

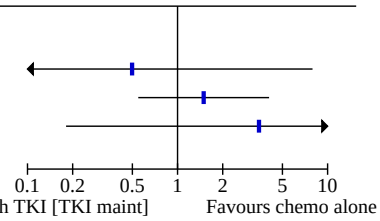
Study or Subgroup	Chemo with TKI [TKI maint] Events	Total	Chemo alone Events	Total	Risk Ratio IV, Fixed, 95% CI
4.6.1 Chemo with trebananib [trebananib maintenance]					
TRINOVA-3 2019 (1)	180	675	94	336	0.95 [0.77 , 1.18]
TRINOVA-3 2019 (2)	146	675	77	336	0.94 [0.74 , 1.20]



Footnotes
(1) grade 3
(2) grade 4

Analysis 4.7. Comparison 4: Newly-diagnosed EOC: chemotherapy with TKI (peptide-Fc fusion protein) followed by TKI maintenance compared to chemotherapy alone, Outcome 7: Febrile neutropenia (any grade)

Study or Subgroup	Chemo with TKI [TKI maint] Events	Total	Chemo alone Events	Total	Risk Ratio M-H, Fixed, 95% CI
4.7.1 Chemo with trebananib [trebananib maintenance]					
TRINOVA-3 2019 (1)	1	675	1	336	0.50 [0.03 , 7.93]
TRINOVA-3 2019 (2)	15	675	5	336	1.49 [0.55 , 4.07]
TRINOVA-3 2019 (3)	3	675	0	336	3.49 [0.18 , 67.36]



Footnotes
(1) grade 1 or 2
(2) grade 3
(3) grade 4

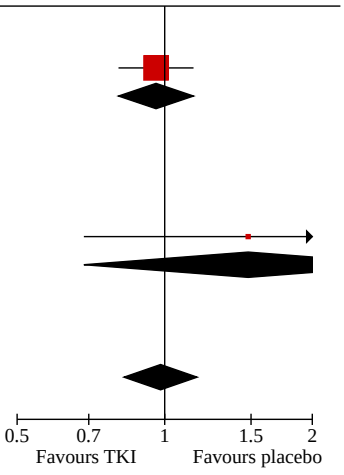
Comparison 5. Newly-diagnosed EOC: maintenance with TKI versus placebo after first-line chemotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Overall survival	2	1186	Hazard Ratio (IV, Fixed, 95% CI)	0.98 [0.83, 1.16]
5.1.1 Pazopanib	1	940	Hazard Ratio (IV, Fixed, 95% CI)	0.96 [0.80, 1.14]
5.1.2 Sorafenib	1	246	Hazard Ratio (IV, Fixed, 95% CI)	1.48 [0.68, 3.20]
5.2 Progression-free survival	2	1186	Hazard Ratio (IV, Fixed, 95% CI)	0.81 [0.69, 0.95]
5.2.1 Pazopanib	1	940	Hazard Ratio (IV, Fixed, 95% CI)	0.77 [0.65, 0.91]
5.2.2 Sorafenib	1	246	Hazard Ratio (IV, Fixed, 95% CI)	1.09 [0.72, 1.64]
5.3 Quality of life - Functional Assessment of Cancer Therapy (FACT)/National Cancer Center Network (NCCN) Ovarian Symptom Index (FOSI) score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.3.1 Sorafenib	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.4 Hypertension (grade ≥3)	2	1184	Risk Ratio (M-H, Fixed, 95% CI)	5.63 [3.81, 8.31]
5.4.1 Pazopanib	1	938	Risk Ratio (M-H, Fixed, 95% CI)	5.46 [3.67, 8.13]
5.4.2 Sorafenib	1	246	Risk Ratio (M-H, Fixed, 95% CI)	10.00 [1.30, 76.94]
5.5 Proteinuria (grade 3 or 4)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.5.1 Pazopanib	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.6 Abdominal pain (grade ≥3)	2	1184	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.52, 4.07]
5.6.1 Pazopanib	1	938	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.51, 4.69]
5.6.2 Sorafenib	1	246	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.06, 15.81]
5.7 Neutropenia (grade 3 or 4)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.7.1 Pazopanib	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

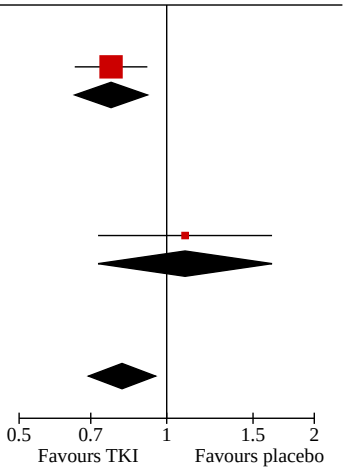
Analysis 5.1. Comparison 5: Newly-diagnosed EOC: maintenance with TKI versus placebo after first-line chemotherapy, Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	TKI Total	Placebo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
5.1.1 Pazopanib						
AGO-OVAR 16 2019	-0.040822	0.089879	472	468	95.0%	0.96 [0.80 , 1.14]
Subtotal (95% CI)			**472**	**468**	**95.0%**	**0.96 [0.80 , 1.14]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.65)						
5.1.2 Sorafenib						
Herzog 2013	0.392042	0.393769	123	123	5.0%	1.48 [0.68 , 3.20]
Subtotal (95% CI)			**123**	**123**	**5.0%**	**1.48 [0.68 , 3.20]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.00 (P = 0.32)						
Total (95% CI)			**595**	**591**	**100.0%**	**0.98 [0.83 , 1.16]**
Heterogeneity: Chi² = 1.15, df = 1 (P = 0.28); I² = 13%						
Test for overall effect: Z = 0.22 (P = 0.82)						
Test for subgroup differences: Chi² = 1.15, df = 1 (P = 0.28), I² = 12.9%						



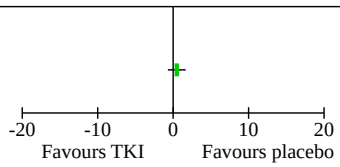
Analysis 5.2. Comparison 5: Newly-diagnosed EOC: maintenance with TKI versus placebo after first-line chemotherapy, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	TKI Total	Placebo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
5.2.1 Pazopanib						
AGO-OVAR 16 2019	-0.261365	0.086973	472	468	85.2%	0.77 [0.65 , 0.91]
Subtotal (95% CI)			**472**	**468**	**85.2%**	**0.77 [0.65 , 0.91]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.01 (P = 0.003)						
5.2.2 Sorafenib						
Herzog 2013	0.086178	0.208444	123	123	14.8%	1.09 [0.72 , 1.64]
Subtotal (95% CI)			**123**	**123**	**14.8%**	**1.09 [0.72 , 1.64]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.41 (P = 0.68)						
Total (95% CI)			**595**	**591**	**100.0%**	**0.81 [0.69 , 0.95]**
Heterogeneity: Chi² = 2.37, df = 1 (P = 0.12); I² = 58%						
Test for overall effect: Z = 2.61 (P = 0.009)						
Test for subgroup differences: Chi² = 2.37, df = 1 (P = 0.12), I² = 57.8%						



Analysis 5.3. Comparison 5: Newly-diagnosed EOC: maintenance with TKI versus placebo after first-line chemotherapy, Outcome 3: Quality of life - Functional Assessment of Cancer Therapy (FACT)/National Cancer Center Network (NCCN) Ovarian Symptom Index (FOSI) score

Study or Subgroup	TKI Mean	TKI SD	TKI Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI
5.3.1 Sorafenib							
Herzog 2013 (1)	25.01	3.83	76	24.53	3.58	76	0.48 [-0.70 , 1.66]

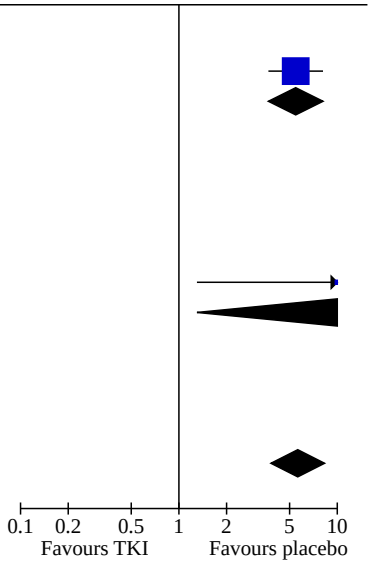


Footnotes

(1) at the end of maintenance phase; TKI: sorafenib

Analysis 5.4. Comparison 5: Newly-diagnosed EOC: maintenance with TKI versus placebo after first-line chemotherapy, Outcome 4: Hypertension (grade ≥3)

Study or Subgroup	TKI Events	TKI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.4.1 Pazopanib						
AGO-OVAR 16 2019 (1)	147	477	26	461	96.4%	5.46 [3.67 , 8.13]
Subtotal (95% CI)		**477**		**461**	**96.4%**	**5.46 [3.67 , 8.13]**
Total events:	147		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 8.39 (P < 0.00001)						
5.4.2 Sorafenib						
Herzog 2013 (2)	10	123	1	123	3.6%	10.00 [1.30 , 76.94]
Subtotal (95% CI)		**123**		**123**	**3.6%**	**10.00 [1.30 , 76.94]**
Total events:	10		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.21 (P = 0.03)						
Total (95% CI)		**600**		**584**	**100.0%**	**5.63 [3.81 , 8.31]**
Total events:	157		27			
Heterogeneity: Chi² = 0.33, df = 1 (P = 0.57); I² = 0%						
Test for overall effect: Z = 8.69 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.32, df = 1 (P = 0.57), I² = 0%						



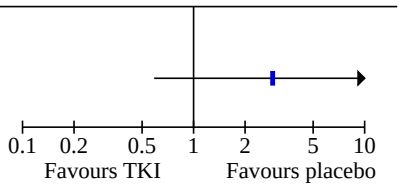
Footnotes

(1) grade 3 or 4

(2) grade 3 or higher

Analysis 5.5. Comparison 5: Newly-diagnosed EOC: maintenance with TKI versus placebo after first-line chemotherapy, Outcome 5: Proteinuria (grade 3 or 4)

Study or Subgroup	TKI Events	TKI Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
5.5.1 Pazopanib					
AGO-OVAR 16 2019 (1)	6	477	2	461	2.90 [0.59 , 14.29]

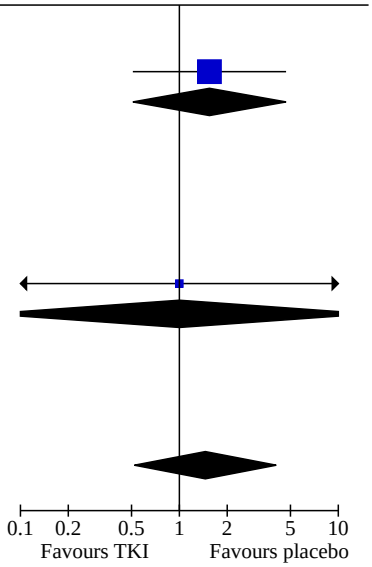


Footnotes

(1) grade 3 or 4

Analysis 5.6. Comparison 5: Newly-diagnosed EOC: maintenance with TKI versus placebo after first-line chemotherapy, Outcome 6: Abdominal pain (grade ≥3)

Study or Subgroup	TKI Events	TKI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.6.1 Pazopanib						
AGO-OVAR 16 2019 (1)	8	477	5	461	83.6%	1.55 [0.51 , 4.69]
Subtotal (95% CI)		**477**		**461**	**83.6%**	**1.55 [0.51 , 4.69]**
Total events:	8		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.77 (P = 0.44)						
5.6.2 Sorafenib						
Herzog 2013 (2)	1	123	1	123	16.4%	1.00 [0.06 , 15.81]
Subtotal (95% CI)		**123**		**123**	**16.4%**	**1.00 [0.06 , 15.81]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**600**		**584**	**100.0%**	**1.46 [0.52 , 4.07]**
Total events:	9		6			
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.77); I² = 0%						
Test for overall effect: Z = 0.72 (P = 0.47)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.77), I² = 0%						



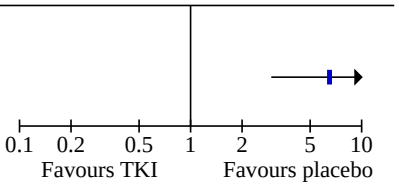
Footnotes

(1) grade 3 or 4

(2) grade 3 or higher

Analysis 5.7. Comparison 5: Newly-diagnosed EOC: maintenance with TKI versus placebo after first-line chemotherapy, Outcome 7: Neutropenia (grade 3 or 4)

Study or Subgroup	TKI Events	TKI Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
5.7.1 Pazopanib					
AGO-OVAR 16 2019 (1)	47	477	7	461	6.49 [2.96 , 14.21]



Footnotes

(1) grade 3 or 4

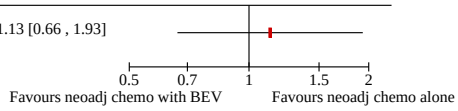
Comparison 6. Newly-diagnosed EOC: neoadjuvant chemotherapy with bevacizumab versus chemotherapy alone followed by adjuvant chemotherapy with bevacizumab and bevacizumab maintenance for all

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Progression-free survival	1		Hazard Ratio (IV, Fixed, 95% CI)	Totals not selected
6.2 Any adverse event (grade ≥ 3)	2	163	Risk Ratio (IV, Fixed, 95% CI)	0.84 [0.66, 1.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.3 Hypertension (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.4 Abdominal pain (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.5 Neutropenia (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.6 Gastrointestinal disorders	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Analysis 6.1. Comparison 6: Newly-diagnosed EOC: neoadjuvant chemotherapy with bevacizumab versus chemotherapy alone followed by adjuvant chemotherapy with bevacizumab and bevacizumab maintenance for all, Outcome 1: Progression-free survival

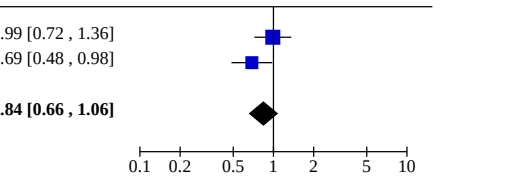
Study or Subgroup	log[Hazard Ratio]	SE	Neoadj chemo with BEV Total	Neoadj chemo alone Total	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
GEICO-1205 2019	0.122218	0.273739	35	33	1.13 [0.66 , 1.93]	



Analysis 6.2. Comparison 6: Newly-diagnosed EOC: neoadjuvant chemotherapy with bevacizumab versus chemotherapy alone followed by adjuvant chemotherapy with bevacizumab and bevacizumab maintenance for all, Outcome 2: Any adverse event (grade ≥ 3)

Study or Subgroup	Neoadj chemo with BEV Events	Total	Neoadj chemo alone Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
ANTHALYA 2017 (1)	34	55	25	40	55.1%	0.99 [0.72 , 1.36]	
GEICO-1205 2019 (2)	19	35	26	33	44.9%	0.69 [0.48 , 0.98]	
Total (95% CI)		**90**		**73**	**100.0%**	**0.84 [0.66 , 1.06]**	
Total events:	53		51				

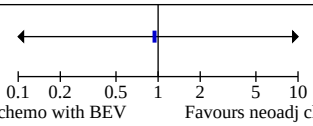
Heterogeneity: Chi² = 2.24, df = 1 (P = 0.13); I² = 55%
Test for overall effect: Z = 1.44 (P = 0.15)
Test for subgroup differences: Not applicable



Footnotes
(1) neoadjuvant and IDS periods combined
(2) entire study period

Analysis 6.3. Comparison 6: Newly-diagnosed EOC: neoadjuvant chemotherapy with bevacizumab versus chemotherapy alone followed by adjuvant chemotherapy with bevacizumab and bevacizumab maintenance for all, Outcome 3: Hypertension (grade ≥ 3)

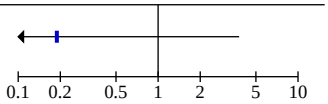
Study or Subgroup	Neoadj chemo with BEV Events	Total	Neoadj chemo alone Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
GEICO-1205 2019 (1)	1	35	1	33	0.94 [0.06 , 14.47]	



Footnotes
(1) only neoadjuvante phase

Analysis 6.4. Comparison 6: Newly-diagnosed EOC: neoadjuvant chemotherapy with bevacizumab versus chemotherapy alone followed by adjuvant chemotherapy with bevacizumab and bevacizumab maintenance for all, Outcome 4: Abdominal pain (grade ≥ 3)

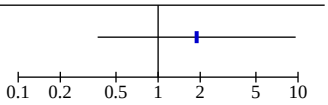
Study or Subgroup	Neoadj chemo with BEV Events	Total	Neoadj chemo alone Events	Total	Risk Ratio M-H, Fixed, 95% CI
GEICO-1205 2019 (1)	0	35	2	33	0.19 [0.01 , 3.79]



Footnotes
(1) only neoadjuvante phase

Analysis 6.5. Comparison 6: Newly-diagnosed EOC: neoadjuvant chemotherapy with bevacizumab versus chemotherapy alone followed by adjuvant chemotherapy with bevacizumab and bevacizumab maintenance for all, Outcome 5: Neutropenia (grade ≥ 3)

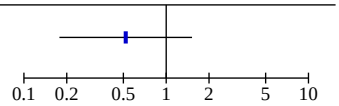
Study or Subgroup	Neoadj chemo with BEV Events	Total	Neoadj chemo alone Events	Total	Risk Ratio M-H, Fixed, 95% CI
GEICO-1205 2019 (1)	4	35	2	33	1.89 [0.37 , 9.62]



Footnotes
(1) only neoadjuvante phase

Analysis 6.6. Comparison 6: Newly-diagnosed EOC: neoadjuvant chemotherapy with bevacizumab versus chemotherapy alone followed by adjuvant chemotherapy with bevacizumab and bevacizumab maintenance for all, Outcome 6: Gastrointestinal disorders

Study or Subgroup	Neoadj chemo with BEV Events	Total	Neoadj chemo alone Events	Total	Risk Ratio IV, Fixed, 95% CI
ANTHALYA 2017 (1)	5	55	7	40	0.52 [0.18 , 1.52]



Footnotes
(1) neoadjuvant and IDS periods combined; grade unclear, AE listed under serious AEs

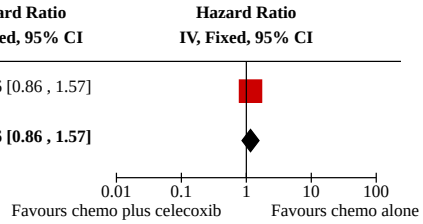
Comparison 7. Newly-diagnosed EOC: chemotherapy with celecoxib versus chemotherapy alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Overall survival	1	196	Hazard Ratio (IV, Fixed, 95% CI)	1.16 [0.86, 1.57]
7.2 Progression-free survival	1	196	Hazard Ratio (IV, Fixed, 95% CI)	1.07 [0.85, 1.34]
7.3 Febrile neutropenia (grade ≥ 3)	1	196	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.45, 1.96]
7.4 Gastrointestinal adverse events (grade ≥ 3)	1	196	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.46, 2.85]

Analysis 7.1. Comparison 7: Newly-diagnosed EOC: chemotherapy with celecoxib versus chemotherapy alone, Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Chemo plus celecoxib Total	Chemo Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Reyners 2012	0.14842	0.153548	97	99	100.0%	1.16 [0.86 , 1.57]
Total (95% CI)			**97**	**99**	**100.0%**	**1.16 [0.86 , 1.57]**

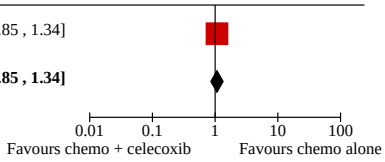
Heterogeneity: Not applicable
Test for overall effect: Z = 0.97 (P = 0.33)
Test for subgroup differences: Not applicable



Analysis 7.2. Comparison 7: Newly-diagnosed EOC: chemotherapy with celecoxib versus chemotherapy alone, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Chemo plus celecoxib Total	Chemo alone Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Reyners 2012	0.067659	0.115035	97	99	100.0%	1.07 [0.85 , 1.34]
Total (95% CI)			**97**	**99**	**100.0%**	**1.07 [0.85 , 1.34]**

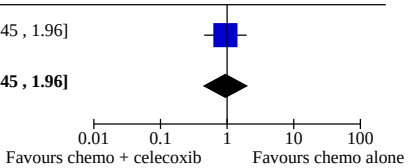
Heterogeneity: Not applicable
Test for overall effect: Z = 0.59 (P = 0.56)
Test for subgroup differences: Not applicable



Analysis 7.3. Comparison 7: Newly-diagnosed EOC: chemotherapy with celecoxib versus chemotherapy alone, Outcome 3: Febrile neutropenia (grade ≥ 3)

Study or Subgroup	Chemotherapy with celecoxib Events	Total	Chemotherapy alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Reyners 2012	12	97	13	99	100.0%	0.94 [0.45 , 1.96]
Total (95% CI)		**97**		**99**	**100.0%**	**0.94 [0.45 , 1.96]**
Total events:	12		13			

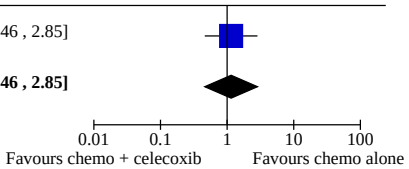
Heterogeneity: Not applicable
Test for overall effect: Z = 0.16 (P = 0.87)
Test for subgroup differences: Not applicable



Analysis 7.4. Comparison 7: Newly-diagnosed EOC: chemotherapy with celecoxib versus chemotherapy alone, Outcome 4: Gastrointestinal adverse events (grade ≥ 3)

Study or Subgroup	Chemotherapy with celecoxib Events	Total	Chemotherapy alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Reyners 2012	9	97	8	99	100.0%	1.15 [0.46 , 2.85]
Total (95% CI)		**97**		**99**	**100.0%**	**1.15 [0.46 , 2.85]**
Total events:	9		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.30 (P = 0.77)
Test for subgroup differences: Not applicable



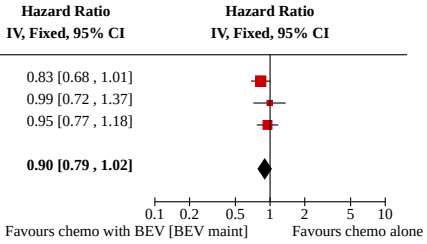
Comparison 8. Recurrent platinum-sensitive EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Overall survival	3	1564	Hazard Ratio (IV, Fixed, 95% CI)	0.90 [0.79, 1.02]
8.2 Progression-free survival	3	1564	Hazard Ratio (IV, Fixed, 95% CI)	0.56 [0.50, 0.63]
8.3 Quality of life - Trial Outcome Index score of Functional Assessment of Cancer Therapy—Ovarian Cancer questionnaire	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.4 Any adverse event (grade ≥ 3)	3	1538	Risk Ratio (IV, Fixed, 95% CI)	1.11 [1.07, 1.16]
8.5 Hypertension (grade ≥ 3)	3	1538	Risk Ratio (M-H, Fixed, 95% CI)	5.82 [3.84, 8.83]
8.6 Proteinuria (grade ≥ 3)	3	1538	Risk Ratio (M-H, Fixed, 95% CI)	20.27 [6.42, 64.00]
8.7 Pain (grade ≥ 3)	2	1058	Risk Ratio (M-H, Fixed, 95% CI)	3.09 [1.81, 5.28]
8.8 Abdominal pain (grade ≥ 3)	2	1058	Risk Ratio (M-H, Fixed, 95% CI)	16.88 [4.72, 60.34]
8.9 Neutropenia (grade ≥ 3)	2	1058	Risk Ratio (IV, Fixed, 95% CI)	1.04 [0.83, 1.31]
8.10 Febrile neutropenia (any grade)	3	1538	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.70, 2.06]
8.11 Venous thromboembolic event (grade ≥ 3)	2	1137	Risk Ratio (M-H, Fixed, 95% CI)	1.73 [0.65, 4.60]
8.12 Arterial thromboembolic event (any grade)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.13 Non-central nervous system bleeding (any grade)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
8.14 Gastrointestinal perforations (any grade)	2	1058	Risk Ratio (M-H, Fixed, 95% CI)	4.96 [0.86, 28.51]

Analysis 8.1. Comparison 8: Recurrent platinum-sensitive EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Chemotherapy with BEV [BEV maint] Total	Chemo alone Total	Weight	Hazard Ratio IV, Fixed, 95% CI
GOG-0213 2017	-0.187535	0.098534	337	337	45.9%	0.83 [0.68 , 1.01]
MITO-16b 2021	-0.01005	0.164292	203	203	16.5%	0.99 [0.72 , 1.37]
OCEANS 2015	-0.051293	0.1089	242	242	37.6%	0.95 [0.77 , 1.18]
Total (95% CI)			**782**	**782**	**100.0%**	**0.90 [0.79 , 1.02]**

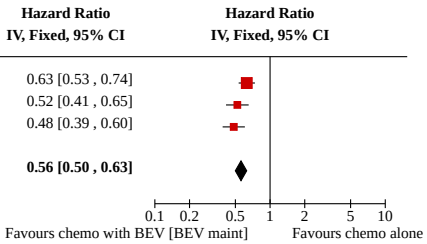
Heterogeneity: Chi² = 1.28, df = 2 (P = 0.53); I² = 0%
Test for overall effect: Z = 1.60 (P = 0.11)
Test for subgroup differences: Not applicable



Analysis 8.2. Comparison 8: Recurrent platinum-sensitive EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Chemotherapy with BEV [BEV maint] Total	Chemo alone Total	Weight	Hazard Ratio IV, Fixed, 95% CI
GOG-0213 2017	-0.465215	0.082885	337	337	48.7%	0.63 [0.53 , 0.74]
MITO-16b 2021 (1)	-0.653926	0.115304	203	203	25.2%	0.52 [0.41 , 0.65]
OCEANS 2015	-0.72567	0.113324	242	242	26.1%	0.48 [0.39 , 0.60]
Total (95% CI)			**782**	**782**	**100.0%**	**0.56 [0.50 , 0.63]**

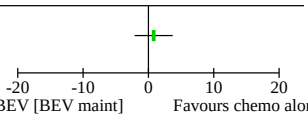
Heterogeneity: Chi² = 3.98, df = 2 (P = 0.14); I² = 50%
Test for overall effect: Z = 10.03 (P < 0.00001)
Test for subgroup differences: Not applicable



Footnotes
(1) as assessed by central review

Analysis 8.3. Comparison 8: Recurrent platinum-sensitive EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 3: Quality of life - Trial Outcome Index score of Functional Assessment of Cancer Therapy—Ovarian Cancer questionnaire

Study or Subgroup	Chemotherapy with BEV [BEV maint] Mean	SD	Total	Chemo alone Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
GOG-0213 2017 (1)	77.8	16.03122	257	77	16.646021	229	0.80 [-2.11 , 3.71]

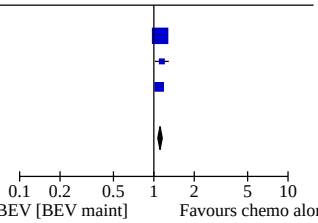


Footnotes
(1) at 12 months after cycle 1

Analysis 8.4. Comparison 8: Recurrent platinum-sensitive EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 4: Any adverse event (grade ≥ 3)

Study or Subgroup	Chemotherapy with BEV [BEV maint] Events	Total	Chemo alone Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
GOG-0213 2017	317	330	282	327	61.7%	1.11 [1.06 , 1.17]
MITO-16b 2021	158	201	137	200	10.3%	1.15 [1.02 , 1.29]
OCEANS 2015	223	247	192	233	27.9%	1.10 [1.02 , 1.18]
Total (95% CI)		**778**		**760**	**100.0%**	**1.11 [1.07 , 1.16]**
Total events:	698		611			

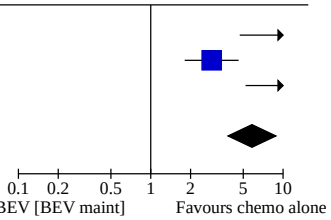
Heterogeneity: Chi² = 0.44, df = 2 (P = 0.80); I² = 0%
Test for overall effect: Z = 5.47 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 8.5. Comparison 8: Recurrent platinum-sensitive EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 5: Hypertension (grade ≥ 3)

Study or Subgroup	Chemotherapy with BEV [BEV maint] Events	Total	Chemo alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
GOG-0213 2017 (1)	39	330	2	327	8.3%	19.32 [4.70 , 79.36]
MITO-16b 2021	58	201	20	200	83.1%	2.89 [1.81 , 4.61]
OCEANS 2015	45	247	2	233	8.5%	21.22 [5.21 , 86.50]
Total (95% CI)		**778**		**760**	**100.0%**	**5.82 [3.84 , 8.83]**
Total events:	142		24			

Heterogeneity: Chi² = 14.62, df = 2 (P = 0.0007); I² = 86%
Test for overall effect: Z = 8.28 (P < 0.00001)
Test for subgroup differences: Not applicable

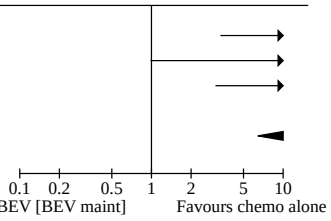


Footnotes
(1) no grade 4 hypertension

Analysis 8.6. Comparison 8: Recurrent platinum-sensitive EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 6: Proteinuria (grade ≥ 3)

Study or Subgroup	Chemotherapy with BEV [BEV maint] Events	Total	Chemo alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
GOG-0213 2017	27	330	0	327	16.4%	54.50 [3.34 , 889.76]
MITO-16b 2021	8	201	0	200	16.4%	16.92 [0.98 , 291.12]
OCEANS 2015	27	247	2	233	67.2%	12.73 [3.06 , 52.96]
Total (95% CI)		**778**		**760**	**100.0%**	**20.27 [6.42 , 64.00]**
Total events:	62		2			

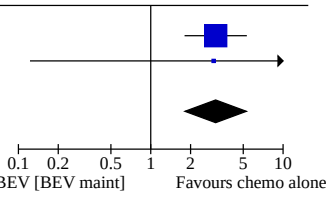
Heterogeneity: Chi² = 0.91, df = 2 (P = 0.64); I² = 0%
Test for overall effect: Z = 5.13 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 8.7. Comparison 8: Recurrent platinum-sensitive EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 7: Pain (grade ≥ 3)

Study or Subgroup	Chemotherapy with BEV [BEV maint] Events	Total	Chemo alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
GOG-0213 2017	50	330	16	327	97.0%	3.10 [1.80 , 5.32]
MITO-16b 2021	1	201	0	200	3.0%	2.99 [0.12 , 72.84]
Total (95% CI)		**531**		**527**	**100.0%**	**3.09 [1.81 , 5.28]**
Total events:	51		16			

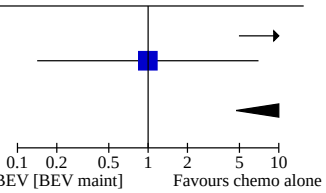
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%
Test for overall effect: Z = 4.14 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 8.8. Comparison 8: Recurrent platinum-sensitive EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 8: Abdominal pain (grade ≥ 3)

Study or Subgroup	Chemotherapy with BEV [BEV maint] Events	Total	Chemo alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
GOG-0213 2017	40	330	0	327	20.0%	80.27 [4.96 , 1299.88]
MITO-16b 2021	2	201	2	200	80.0%	1.00 [0.14 , 6.99]
Total (95% CI)		**531**		**527**	**100.0%**	**16.88 [4.72 , 60.34]**
Total events:	42		2			

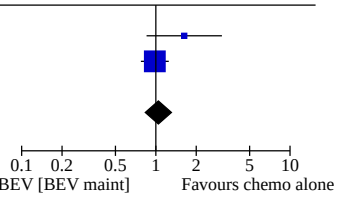
Heterogeneity: Chi² = 9.30, df = 1 (P = 0.002); I² = 89%
Test for overall effect: Z = 4.35 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 8.9. Comparison 8: Recurrent platinum-sensitive EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 9: Neutropenia (grade ≥ 3)

Study or Subgroup	Chemotherapy with BEV [BEV maint] Events	Total	Chemo alone Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
GOG-0213 2017	23	330	14	327	12.0%	1.63 [0.85 , 3.11]
MITO-16b 2021	80	201	81	200	88.0%	0.98 [0.77 , 1.25]
Total (95% CI)		**531**		**527**	**100.0%**	**1.04 [0.83 , 1.31]**
Total events:	103		95			

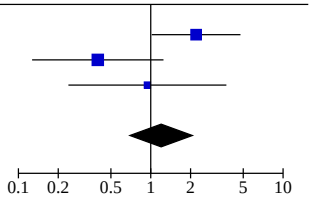
Heterogeneity: Chi² = 2.06, df = 1 (P = 0.15); I² = 51%
Test for overall effect: Z = 0.38 (P = 0.71)
Test for subgroup differences: Not applicable



Analysis 8.10. Comparison 8: Recurrent platinum-sensitive EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 10: Febrile neutropenia (any grade)

Study or Subgroup	Chemotherapy with BEV [BEV maint] Events	Total	Chemo alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
GOG-0213 2017	20	330	9	327	39.0%	2.20 [1.02 , 4.76]
MITO-16b 2021	4	201	10	200	43.2%	0.40 [0.13 , 1.25]
OCEANS 2015	4	247	4	233	17.8%	0.94 [0.24 , 3.73]
Total (95% CI)		**778**		**760**	**100.0%**	**1.20 [0.70 , 2.06]**
Total events:	28		23			

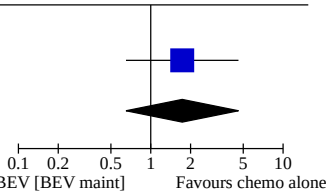
Heterogeneity: Chi² = 6.08, df = 2 (P = 0.05); I² = 67%
Test for overall effect: Z = 0.65 (P = 0.51)
Test for subgroup differences: Not applicable



Analysis 8.11. Comparison 8: Recurrent platinum-sensitive EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 11: Venous thromboembolic event (grade ≥ 3)

Study or Subgroup	Chemotherapy with BEV [BEV maint] Events	Total	Chemo alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
GOG-0213 2017 (1)	0	330	0	327		Not estimable
OCEANS 2015	11	247	6	233	100.0%	1.73 [0.65 , 4.60]
Total (95% CI)		**577**		**560**	**100.0%**	**1.73 [0.65 , 4.60]**
Total events:	11		6			

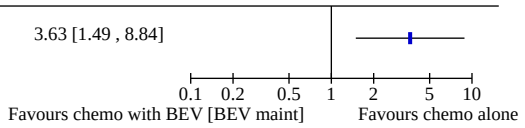
Heterogeneity: Not applicable
Test for overall effect: Z = 1.10 (P = 0.27)
Test for subgroup differences: Not applicable



Footnotes
(1) any venous thromboembolism events

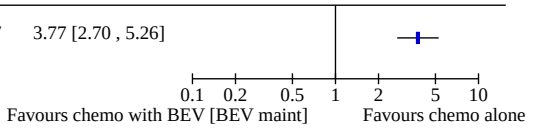
Analysis 8.12. Comparison 8: Recurrent platinum-sensitive EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 12: Arterial thromboembolic event (any grade)

Study or Subgroup	Chemotherapy with BEV [BEV maint] Events	Total	Chemo alone Events	Total	Risk Ratio M-H, Fixed, 95% CI
GOG-0213 2017	22	330	6	327	3.63 [1.49 , 8.84]

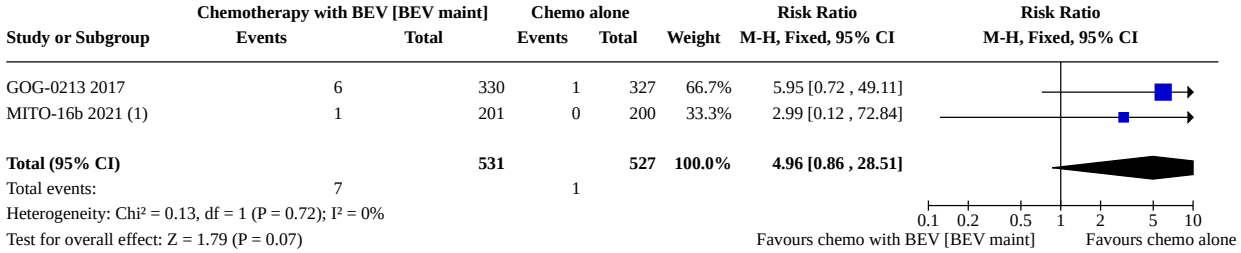


Analysis 8.13. Comparison 8: Recurrent platinum-sensitive EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 13: Non-central nervous system bleeding (any grade)

Study or Subgroup	Chemotherapy with BEV [BEV maint] Events	Total	Chemo alone Events	Total	Risk Ratio IV, Fixed, 95% CI
GOG-0213 2017	137	330	36	327	3.77 [2.70 , 5.26]



Analysis 8.14. Comparison 8: Recurrent platinum-sensitive EOC: chemotherapy with bevacizumab followed by bevacizumab maintenance compared to chemotherapy alone, Outcome 14: Gastrointestinal perforations (any grade)



Footnotes

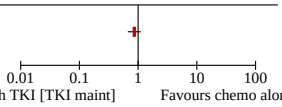
(1) Colonic perforation grade 4

Comparison 9. Recurrent platinum-sensitive EOC: chemotherapy with TKI followed by TKI maintenance compared to chemotherapy alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Overall survival	1		Hazard Ratio (IV, Fixed, 95% CI)	Totals not selected
9.2 Progression-free survival	1		Hazard Ratio (IV, Fixed, 95% CI)	Totals not selected
9.3 Quality of life - Global Quality of Life European Organization for Research and Treatment of Cancer Questionnaire QLQ-C30	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.4 Hypertension (grade 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.5 Proteinuria (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.6 Neutropenia (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.7 Febrile neutropenia (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 9.1. Comparison 9: Recurrent platinum-sensitive EOC: chemotherapy with TKI followed by TKI maintenance compared to chemotherapy alone, Outcome 1: Overall survival

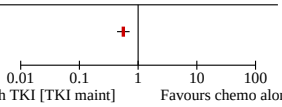
Study or Subgroup	log[Hazard Ratio]	SE	Chemotherapy with TKI [TKI maint] Total	Chemotherapy alone Total	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
ICON6 2021 (1)	-0.150823	0.128787	164	118	0.86 [0.67 , 1.11]	



Footnotes
(1) TKI: cediranib; evidence of non-proportionality of hazards (p=0.0031); Restricted mean survival time difference = 4.8 (95% CI –0.09, 9.74); log-rank test p=0.24

Analysis 9.2. Comparison 9: Recurrent platinum-sensitive EOC: chemotherapy with TKI followed by TKI maintenance compared to chemotherapy alone, Outcome 2: Progression-free survival

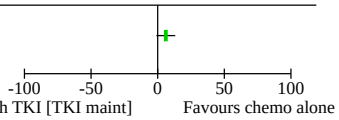
Study or Subgroup	log[Hazard Ratio]	SE	Chemotherapy with TKI [TKI maint] Total	Chemotherapy alone Total	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
ICON6 2021 (1)	-0.579818	0.125634	164	118	0.56 [0.44 , 0.72]	



Footnotes
(1) TKI: cediranib; evidence of non-proportional hazards (p=0·06); Restricted mean survival time over 2 years in chemo with TKI arm 12.5 months (95% CI 11.7, 13.4) and chemo alone 9.4 months (95%

Analysis 9.3. Comparison 9: Recurrent platinum-sensitive EOC: chemotherapy with TKI followed by TKI maintenance compared to chemotherapy alone, Outcome 3: Quality of life - Global Quality of Life European Organization for Research and Treatment of Cancer Questionnaire QLQ-C30

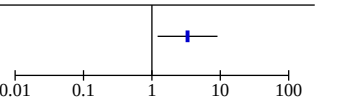
Study or Subgroup	Chemotherapy with TKI [TKI maint] Mean	SD	Total	Chemotherapy alone Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
ICON6 2021 (1)	68.7	19.7	91	62.6	21.9	55	6.10 [-0.96 , 13.16]	



Footnotes
(1) TKI: cediranib; measured at 12 months

Analysis 9.4. Comparison 9: Recurrent platinum-sensitive EOC: chemotherapy with TKI followed by TKI maintenance compared to chemotherapy alone, Outcome 4: Hypertension (grade 3)

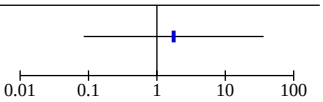
Study or Subgroup	Chemotherapy with TKI [TKI maint] Events	Total	Chemotherapy alone Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
ICON6 2021 (1)	38	329	4	115	3.32 [1.21 , 9.10]	



Footnotes
(1) TKI: cediranib; no events of grade 4 or 5

Analysis 9.5. Comparison 9: Recurrent platinum-sensitive EOC: chemotherapy with TKI followed by TKI maintenance compared to chemotherapy alone, Outcome 5: Proteinuria (grade ≥ 3)

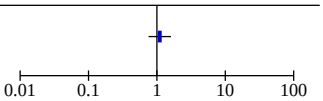
Study or Subgroup	Chemotherapy with TKI [TKI maint] Events	Total	Chemotherapy alone Events	Total	Risk Ratio M-H, Fixed, 95% CI
ICON6 2021 (1)	2	329	0	115	1.76 [0.09 , 36.34]



Footnotes
(1) TKI: cediranib

Analysis 9.6. Comparison 9: Recurrent platinum-sensitive EOC: chemotherapy with TKI followed by TKI maintenance compared to chemotherapy alone, Outcome 6: Neutropenia (grade ≥ 3)

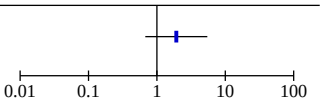
Study or Subgroup	Chemotherapy with TKI [TKI maint] Events	Total	Chemotherapy alone Events	Total	Risk Ratio M-H, Fixed, 95% CI
ICON6 2021 (1)	85	329	27	115	1.10 [0.75 , 1.60]



Footnotes
(1) TKI: cediranib

Analysis 9.7. Comparison 9: Recurrent platinum-sensitive EOC: chemotherapy with TKI followed by TKI maintenance compared to chemotherapy alone, Outcome 7: Febrile neutropenia (grade ≥ 3)

Study or Subgroup	Chemotherapy with TKI [TKI maint] Events	Total	Chemotherapy alone Events	Total	Risk Ratio M-H, Fixed, 95% CI
ICON6 2021 (1)	22	329	4	115	1.92 [0.68 , 5.46]



Footnotes
(1) TKI: cediranib

Comparison 10. Recurrent platinum-resistant EOC: chemotherapy with bevacizumab compared to chemotherapy alone

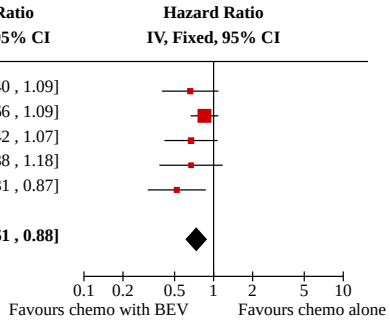
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Overall survival	5	778	Hazard Ratio (IV, Fixed, 95% CI)	0.73 [0.61, 0.88]
10.2 Progression-free survival	5	778	Hazard Ratio (IV, Fixed, 95% CI)	0.49 [0.42, 0.58]
10.3 Any adverse event (grade ≥ 3)	1	101	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.88, 1.87]
10.4 Hypertension (grade ≥ 2 & grade ≥ 3)	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.4.1 Grade ≥ 2	2	436	Risk Ratio (M-H, Fixed, 95% CI)	3.11 [1.83, 5.27]
10.4.2 Grade ≥ 3	5	769	Risk Ratio (M-H, Fixed, 95% CI)	3.83 [1.79, 8.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.5 Proteinuria (grade ≥ 3)	4	683	Risk Ratio (M-H, Fixed, 95% CI)	6.26 [1.13, 34.70]
10.6 Neutropenia (grade ≥ 3)	3	308	Risk Ratio (IV, Fixed, 95% CI)	1.35 [1.01, 1.80]
10.7 Febrile neutropenia (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.8 Venous thromboembolic event (grade ≥ 3)	2	436	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.21, 1.63]
10.9 Arterial thromboembolic event (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.10 Gastrointestinal perforations (grade ≥ 2)	2	436	Risk Ratio (M-H, Fixed, 95% CI)	6.89 [0.86, 55.09]

Analysis 10.1. Comparison 10: Recurrent platinum-resistant EOC: chemotherapy with bevacizumab compared to chemotherapy alone, Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Chemo with BEV Total	Chemo alone Total	Weight	Hazard Ratio IV, Fixed, 95% CI
APPROVE 2022 (1)	-0.415515	0.255736	78	74	12.5%	0.66 [0.40 , 1.09]
AURELIA 2014 (2)	-0.162519	0.125634	179	182	51.7%	0.85 [0.66 , 1.09]
Liu 2019a (3)	-0.400478	0.240939	43	43	14.1%	0.67 [0.42 , 1.07]
Nishikawa 2020	-0.400478	0.28689	52	51	9.9%	0.67 [0.38 , 1.18]
Roque 2022	-0.653926	0.26325	39	37	11.8%	0.52 [0.31 , 0.87]
Total (95% CI)			**391**	**387**	**100.0%**	**0.73 [0.61 , 0.88]**

Heterogeneity: Chi² = 3.50, df = 4 (P = 0.48); I² = 0%
Test for overall effect: Z = 3.42 (P = 0.0006)
Test for subgroup differences: Not applicable

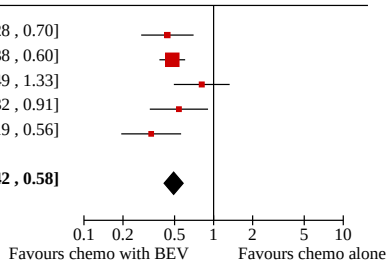


Footnotes
(1) OS data immature
(2) Unstratified HR with 95%CIs
(3) HR estimated based on KM curve

Analysis 10.2. Comparison 10: Recurrent platinum-resistant EOC: chemotherapy with bevacizumab compared to chemotherapy alone, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Chemo with BEV Total	Chemo alone Total	Weight	Hazard Ratio IV, Fixed, 95% CI
APPROVE 2022	-0.820981	0.237371	78	74	13.1%	0.44 [0.28 , 0.70]
AURELIA 2014 (1)	-0.733969	0.116522	179	182	54.5%	0.48 [0.38 , 0.60]
Liu 2019a (2)	-0.210721	0.252806	43	43	11.6%	0.81 [0.49 , 1.33]
Nishikawa 2020	-0.616186	0.263799	52	51	10.6%	0.54 [0.32 , 0.91]
Roque 2022	-1.108663	0.271151	39	37	10.1%	0.33 [0.19 , 0.56]
Total (95% CI)			**391**	**387**	**100.0%**	**0.49 [0.42 , 0.58]**

Heterogeneity: Chi² = 6.45, df = 4 (P = 0.17); I² = 38%
Test for overall effect: Z = 8.25 (P < 0.00001)
Test for subgroup differences: Not applicable

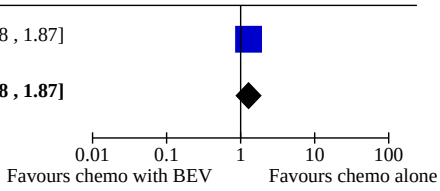


Footnotes
(1) Unstratified HR with 95%CIs
(2) HR estimated based on KM curve

Analysis 10.3. Comparison 10: Recurrent platinum-resistant EOC: chemotherapy with bevacizumab compared to chemotherapy alone, Outcome 3: Any adverse event (grade ≥ 3)

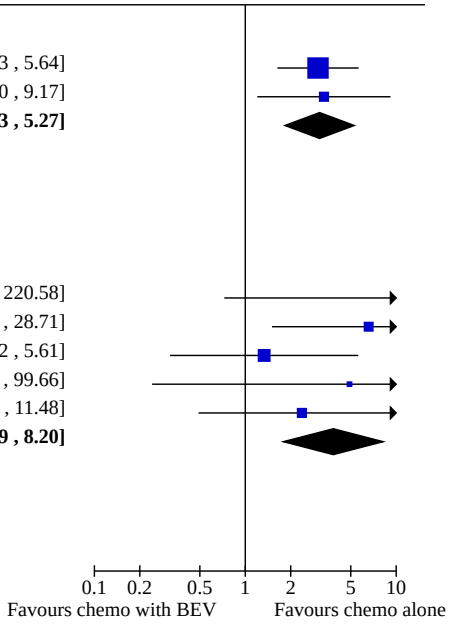
Study or Subgroup	Chemo with BEV Events	Chemo with BEV Total	Chemo alone Events	Chemo alone Total	Weight	Risk Ratio M-H, Random, 95% CI
Nishikawa 2020	30	51	23	50	100.0%	1.28 [0.88 , 1.87]
Total (95% CI)		**51**		**50**	**100.0%**	**1.28 [0.88 , 1.87]**
Total events:	30		23			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.27 (P = 0.20)
Test for subgroup differences: Not applicable



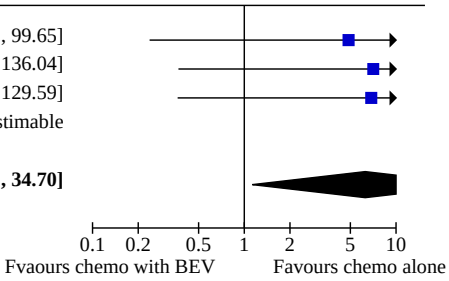
Analysis 10.4. Comparison 10: Recurrent platinum-resistant EOC: chemotherapy with bevacizumab compared to chemotherapy alone, Outcome 4: Hypertension (grade ≥ 2 & grade ≥ 3)

Study or Subgroup	Chemo with BEV Events	Total	Chemo alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.4.1 Grade ≥ 2						
AURELIA 2014	36	179	12	181	74.4%	3.03 [1.63 , 5.64]
Roque 2022	14	39	4	37	25.6%	3.32 [1.20 , 9.17]
Subtotal (95% CI)		**218**		**218**	**100.0%**	**3.11 [1.83 , 5.27]**
Total events:	50		16			
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%						
Test for overall effect: Z = 4.20 (P < 0.0001)						
10.4.2 Grade ≥ 3						
APPROVE 2022	6	74	0	72	6.3%	12.65 [0.73 , 220.58]
AURELIA 2014	13	179	2	181	24.7%	6.57 [1.50 , 28.71]
Liu 2019a	4	43	3	43	37.3%	1.33 [0.32 , 5.61]
Nishikawa 2020	2	51	0	50	6.3%	4.90 [0.24 , 99.66]
Roque 2022	5	39	2	37	25.5%	2.37 [0.49 , 11.48]
Subtotal (95% CI)		**386**		**383**	**100.0%**	**3.83 [1.79 , 8.20]**
Total events:	30		7			
Heterogeneity: Chi² = 3.64, df = 4 (P = 0.46); I² = 0%						
Test for overall effect: Z = 3.45 (P = 0.0006)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%						



Analysis 10.5. Comparison 10: Recurrent platinum-resistant EOC: chemotherapy with bevacizumab compared to chemotherapy alone, Outcome 5: Proteinuria (grade ≥ 3)

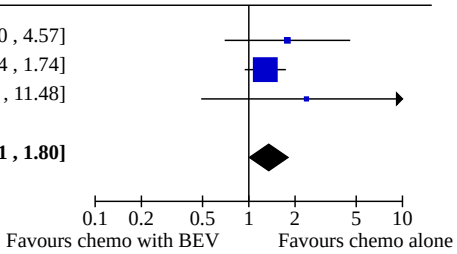
Study or Subgroup	Chemo with BEV Events	Total	Chemo alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
APPROVE 2022	2	74	0	72	33.6%	4.87 [0.24 , 99.65]
AURELIA 2014	3	179	0	181	33.0%	7.08 [0.37 , 136.04]
Nishikawa 2020	3	51	0	50	33.5%	6.87 [0.36 , 129.59]
Roque 2022	0	39	0	37		Not estimable
Total (95% CI)		**343**		**340**	**100.0%**	**6.26 [1.13 , 34.70]**
Total events:	8		0			
Heterogeneity: Chi² = 0.04, df = 2 (P = 0.98); I² = 0%						
Test for overall effect: Z = 2.10 (P = 0.04)						
Test for subgroup differences: Not applicable						



Analysis 10.6. Comparison 10: Recurrent platinum-resistant EOC: chemotherapy with bevacizumab compared to chemotherapy alone, Outcome 6: Neutropenia (grade ≥ 3)

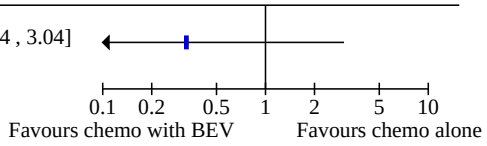
Study or Subgroup	Chemo with BEV Events	Chemo with BEV Total	Chemo alone Events	Chemo alone Total	Weight	Risk Ratio IV, Fixed, 95% CI
APPROVE 2022	11	74	6	72	9.4%	1.78 [0.70 , 4.57]
Liu 2019a	32	43	25	43	87.3%	1.28 [0.94 , 1.74]
Roque 2022	5	39	2	37	3.3%	2.37 [0.49 , 11.48]
Total (95% CI)		**156**		**152**	**100.0%**	**1.35 [1.01 , 1.80]**
Total events:	48		33			

Heterogeneity: Chi² = 0.94, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 2.03 (P = 0.04)
Test for subgroup differences: Not applicable



Analysis 10.7. Comparison 10: Recurrent platinum-resistant EOC: chemotherapy with bevacizumab compared to chemotherapy alone, Outcome 7: Febrile neutropenia (grade ≥ 3)

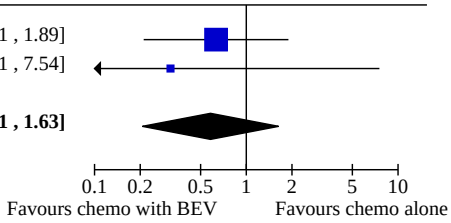
Study or Subgroup	Chemo with BEV Events	Chemo with BEV Total	Chemo alone Events	Chemo alone Total	Risk Ratio M-H, Fixed, 95% CI
Nishikawa 2020	1	51	3	50	0.33 [0.04 , 3.04]



Analysis 10.8. Comparison 10: Recurrent platinum-resistant EOC: chemotherapy with bevacizumab compared to chemotherapy alone, Outcome 8: Venous thromboembolic event (grade ≥ 3)

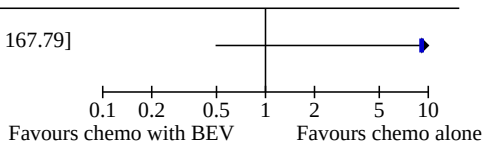
Study or Subgroup	Chemo with BEV Events	Chemo with BEV Total	Chemo alone Events	Chemo alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AURELIA 2014	5	179	8	181	83.8%	0.63 [0.21 , 1.89]
Roque 2022	0	39	1	37	16.2%	0.32 [0.01 , 7.54]
Total (95% CI)		**218**		**218**	**100.0%**	**0.58 [0.21 , 1.63]**
Total events:	5		9			

Heterogeneity: Chi² = 0.16, df = 1 (P = 0.69); I² = 0%
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Not applicable

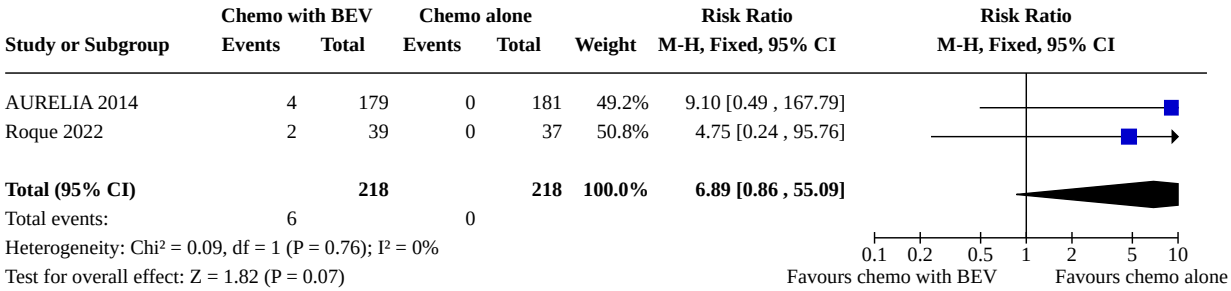


Analysis 10.9. Comparison 10: Recurrent platinum-resistant EOC: chemotherapy with bevacizumab compared to chemotherapy alone, Outcome 9: Arterial thromboembolic event (grade ≥ 3)

Study or Subgroup	Chemo with BEV Events	Chemo with BEV Total	Chemo alone Events	Chemo alone Total	Risk Ratio M-H, Fixed, 95% CI
AURELIA 2014	4	179	0	181	9.10 [0.49 , 167.79]



Analysis 10.10. Comparison 10: Recurrent platinum-resistant EOC: chemotherapy with bevacizumab compared to chemotherapy alone, Outcome 10: Gastrointestinal perforations (grade ≥ 2)



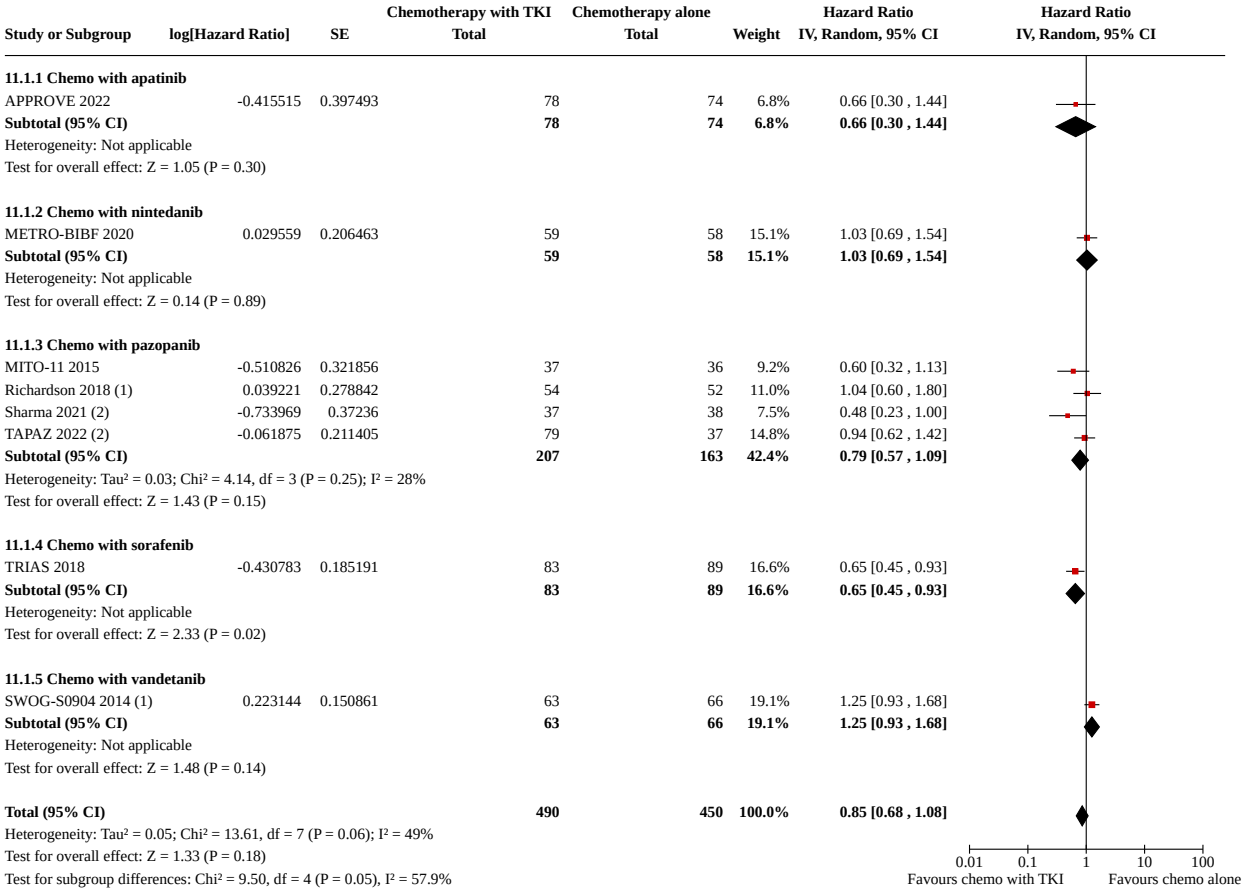
Comparison 11. Recurrent platinum-resistant EOC: chemotherapy with TKI compared to chemotherapy alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Overall survival	8	940	Hazard Ratio (IV, Random, 95% CI)	0.85 [0.68, 1.08]
11.1.1 Chemo with apatinib	1	152	Hazard Ratio (IV, Random, 95% CI)	0.66 [0.30, 1.44]
11.1.2 Chemo with nintedanib	1	117	Hazard Ratio (IV, Random, 95% CI)	1.03 [0.69, 1.54]
11.1.3 Chemo with pazopanib	4	370	Hazard Ratio (IV, Random, 95% CI)	0.79 [0.57, 1.09]
11.1.4 Chemo with sorafenib	1	172	Hazard Ratio (IV, Random, 95% CI)	0.65 [0.45, 0.93]
11.1.5 Chemo with vandetanib	1	129	Hazard Ratio (IV, Random, 95% CI)	1.25 [0.93, 1.68]
11.2 Progression-free survival	8	940	Hazard Ratio (IV, Random, 95% CI)	0.70 [0.55, 0.89]
11.2.1 Chemo with apatinib	1	152	Hazard Ratio (IV, Random, 95% CI)	0.44 [0.28, 0.70]
11.2.2 Chemo with nintedanib	1	117	Hazard Ratio (IV, Random, 95% CI)	0.91 [0.62, 1.33]
11.2.3 Chemo with pazopanib	4	370	Hazard Ratio (IV, Random, 95% CI)	0.68 [0.47, 0.98]
11.2.4 Chemo with sorafenib	1	172	Hazard Ratio (IV, Random, 95% CI)	0.60 [0.43, 0.83]
11.2.5 Chemo with vandetanib	1	129	Hazard Ratio (IV, Random, 95% CI)	0.99 [0.78, 1.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.3 Quality of life - Global Quality of Life European Organization for Research and Treatment of Cancer Questionnaire QLQ-C30	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11.4 Any adverse event (grade ≥ 3)	4	548	Risk Ratio (IV, Random, 95% CI)	1.23 [1.02, 1.49]
11.4.1 Chemo with apatinib	1	146	Risk Ratio (IV, Random, 95% CI)	2.22 [1.30, 3.81]
11.4.2 Chemo with nintedanib	1	114	Risk Ratio (IV, Random, 95% CI)	1.18 [0.87, 1.60]
11.4.3 Chemo with pazopanib	1	116	Risk Ratio (IV, Random, 95% CI)	1.24 [0.99, 1.56]
11.4.4 Chemo with sorafenib	1	172	Risk Ratio (IV, Random, 95% CI)	1.09 [0.98, 1.20]
11.5 Hypertension (grade ≥ 3)	9	1075	Risk Ratio (M-H, Random, 95% CI)	4.20 [1.58, 11.14]
11.5.1 Chemo with apatinib	1	146	Risk Ratio (M-H, Random, 95% CI)	12.65 [0.73, 220.58]
11.5.2 Chemo with nintedanib	1	114	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.29, 5.30]
11.5.3 Chemo with pazopanib	5	518	Risk Ratio (M-H, Random, 95% CI)	7.64 [3.17, 18.41]
11.5.4 Chemo with sorafenib	1	172	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.22, 5.16]
11.5.5 Chemo with vandetanib	1	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
11.6 Proteinuria (grade ≥ 2)	3	387	Risk Ratio (M-H, Random, 95% CI)	4.00 [0.49, 32.86]
11.6.1 Chemo with apatinib	1	146	Risk Ratio (M-H, Random, 95% CI)	4.87 [0.24, 99.65]
11.6.2 Chemo with pazopanib	1	116	Risk Ratio (M-H, Random, 95% CI)	3.32 [0.18, 62.76]
11.6.3 Chemo with vandetanib	1	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
11.7 Pain (grade ≥ 2)	3	361	Risk Ratio (IV, Random, 95% CI)	0.97 [0.44, 2.15]
11.7.1 Chemo with pazopanib	2	189	Risk Ratio (IV, Random, 95% CI)	0.98 [0.20, 4.88]
11.7.2 Chemo with sorafenib	1	172	Risk Ratio (IV, Random, 95% CI)	1.07 [0.45, 2.57]
11.8 Abdominal pain (grade ≥ 2)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.8.1 Chemo with pazopanib	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
11.9 Neutropenia (grade ≥ 3)	9	1069	Risk Ratio (IV, Random, 95% CI)	1.73 [1.15, 2.61]
11.9.1 Chemo with apatinib	1	146	Risk Ratio (IV, Random, 95% CI)	1.78 [0.70, 4.57]
11.9.2 Chemo with nintedanib	1	114	Risk Ratio (IV, Random, 95% CI)	14.00 [0.82, 239.49]
11.9.3 Chemo with pazopanib	5	512	Risk Ratio (IV, Random, 95% CI)	2.35 [1.42, 3.90]
11.9.4 Chemo with sorafenib	1	172	Risk Ratio (IV, Random, 95% CI)	1.03 [0.78, 1.35]
11.9.5 Chemo with vandetanib	1	125	Risk Ratio (IV, Random, 95% CI)	0.92 [0.64, 1.32]
11.10 Febrile neutropenia (any grade)	6	748	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.68, 3.30]
11.10.1 Chemo with nintedanib	1	114	Risk Ratio (M-H, Random, 95% CI)	2.80 [0.12, 67.32]
11.10.2 Chemo with pazopanib	3	337	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.41, 5.06]
11.10.3 Chemo with sorafenib	1	172	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.41, 4.06]
11.10.4 Chemo with vandetanib	1	125	Risk Ratio (M-H, Random, 95% CI)	3.15 [0.13, 75.76]
11.11 Non-central nervous system bleeding (grade ≥ 3)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
11.11.1 Chemo with sorafenib	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
11.12 Gastrointestinal adverse events (grade ≥ 3)	3	386	Risk Ratio (IV, Random, 95% CI)	1.08 [0.46, 2.53]
11.12.1 Chemo with nintedanib	1	114	Risk Ratio (IV, Random, 95% CI)	0.93 [0.06, 14.54]
11.12.2 Chemo with pazopanib	1	100	Risk Ratio (IV, Random, 95% CI)	2.00 [0.88, 4.53]
11.12.3 Chemo with sorafenib	1	172	Risk Ratio (IV, Random, 95% CI)	0.69 [0.43, 1.11]
11.13 Bowel fistula or perforation (grade ≥ 3)	5	557	Risk Ratio (M-H, Random, 95% CI)	2.74 [0.77, 9.75]
11.13.1 Chemo with nintedanib	1	114	Risk Ratio (M-H, Random, 95% CI)	2.80 [0.12, 67.32]
11.13.2 Chemo with pazopanib	4	443	Risk Ratio (M-H, Random, 95% CI)	2.73 [0.68, 10.90]

Analysis 11.1. Comparison 11: Recurrent platinum-resistant EOC: chemotherapy with TKI compared to chemotherapy alone, Outcome 1: Overall survival



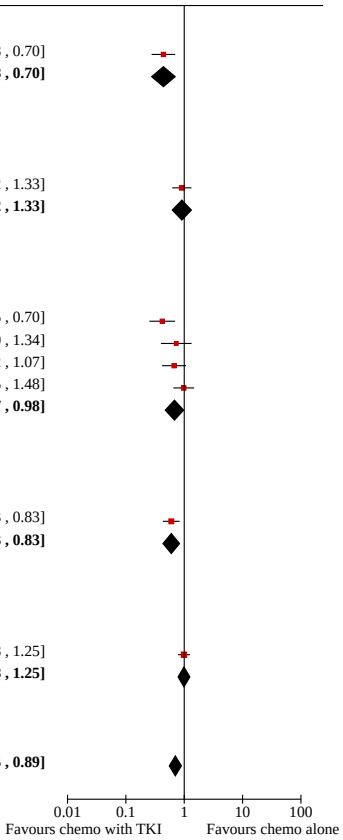
Footnotes

(1) population with recurrent EOC regardless of platinum-sensitivity status

(2) HR est from KM curve

Analysis 11.2. Comparison 11: Recurrent platinum-resistant EOC: chemotherapy with TKI compared to chemotherapy alone, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Chemotherapy with TKI Total	Chemotherapy alone Total	Weight	Hazard Ratio IV, Random, 95% CI
11.2.1 Chemo with apatinib						
APPROVE 2022	-0.820981	0.237371	78	74	11.5%	0.44 [0.28 , 0.70]
Subtotal (95% CI)			**78**	**74**	**11.5%**	**0.44 [0.28 , 0.70]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.46 (P = 0.0005)						
11.2.2 Chemo with nintedanib						
METRO-BIBF 2020	-0.094311	0.192776	59	58	13.5%	0.91 [0.62 , 1.33]
Subtotal (95% CI)			**59**	**58**	**13.5%**	**0.91 [0.62 , 1.33]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.49 (P = 0.62)						
11.2.3 Chemo with pazopanib						
MITO-11 2015	-0.867501	0.258992	37	36	10.6%	0.42 [0.25 , 0.70]
Richardson 2018	-0.314711	0.308414	54	52	8.8%	0.73 [0.40 , 1.34]
Sharma 2021 (1)	-0.400478	0.240939	37	38	11.3%	0.67 [0.42 , 1.07]
TAPAZ 2022 (1)	-0.020203	0.209908	79	37	12.7%	0.98 [0.65 , 1.48]
Subtotal (95% CI)			**207**	**163**	**43.4%**	**0.68 [0.47 , 0.98]**
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 6.51$, df = 3 (P = 0.09); $I^2 = 54\%$						
Test for overall effect: Z = 2.09 (P = 0.04)						
11.2.4 Chemo with sorafenib						
TRIAS 2018	-0.510826	0.167769	83	89	14.6%	0.60 [0.43 , 0.83]
Subtotal (95% CI)			**83**	**89**	**14.6%**	**0.60 [0.43 , 0.83]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.04 (P = 0.002)						
11.2.5 Chemo with vandetanib						
SWOG-S0904 2014 (2)	-0.01005	0.119093	63	66	17.0%	0.99 [0.78 , 1.25]
Subtotal (95% CI)			**63**	**66**	**17.0%**	**0.99 [0.78 , 1.25]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.08 (P = 0.93)						
Total (95% CI)			**490**	**450**	**100.0%**	**0.70 [0.55 , 0.89]**
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 20.09$, df = 7 (P = 0.005); $I^2 = 65\%$						
Test for overall effect: Z = 2.87 (P = 0.004)						
Test for subgroup differences: $Chi^2 = 13.43$, df = 4 (P = 0.009), $I^2 = 70.2\%$						



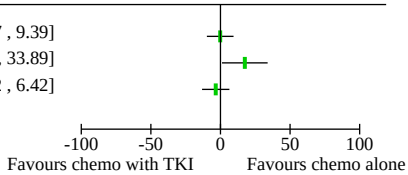
Footnotes

(1) HR est from KM curve

(2) population with recurrent EOC regardless of platinum-sensitivity status

Analysis 11.3. Comparison 11: Recurrent platinum-resistant EOC: chemotherapy with TKI compared to chemotherapy alone, Outcome 3: Quality of life - Global Quality of Life European Organization for Research and Treatment of Cancer Questionnaire QLQ-C30

Study or Subgroup	Chemotherapy with TKI Mean	SD	Total	Chemotherapy alone Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
METRO-BIBF 2020 (1)	55.09	19.24	39	55.28	24.28	41	-0.19 [-9.77 , 9.39]
Sharma 2021 (2)	21.6	25	10	4.1	7.7	8	17.50 [1.11 , 33.89]
TAPAZ 2022 (3)	-7.9	18.91822	40	-4.5	20.488012	26	-3.40 [-13.22 , 6.42]



Footnotes

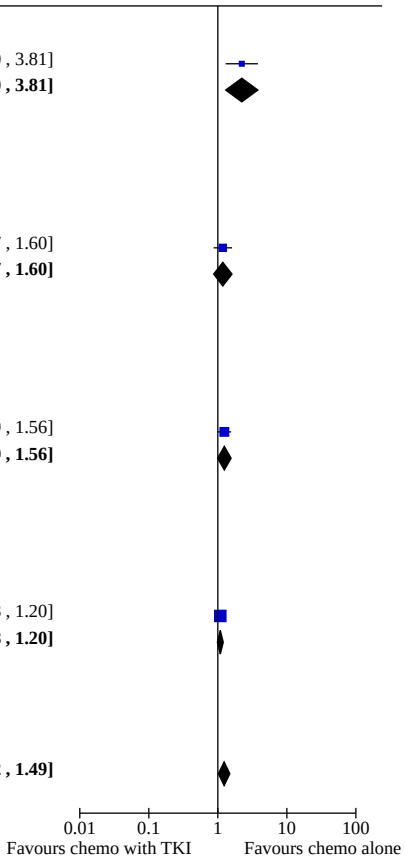
(1) measure after 6 weeks

(2) measure after 6 cycles

(3) mean change from baseline to 4 months

Analysis 11.4. Comparison 11: Recurrent platinum-resistant EOC: chemotherapy with TKI compared to chemotherapy alone, Outcome 4: Any adverse event (grade ≥ 3)

Study or Subgroup	Chemotherapy with TKI Events	Total	Chemotherapy alone Events	Total	Weight	Risk Ratio IV, Random, 95% CI
11.4.1 Chemo with apatinib						
APPROVE 2022 (1)	32	74	14	72	10.0%	2.22 [1.30 , 3.81]
Subtotal (95% CI)		**74**		**72**	**10.0%**	**2.22 [1.30 , 3.81]**
Total events:	32		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.91 (P = 0.004)						
11.4.2 Chemo with nintedanib						
METRO-BIBF 2020	38	59	30	55	21.1%	1.18 [0.87 , 1.60]
Subtotal (95% CI)		**59**		**55**	**21.1%**	**1.18 [0.87 , 1.60]**
Total events:	38		30			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
11.4.3 Chemo with pazopanib						
TAPAZ 2022 (2)	69	79	26	37	28.0%	1.24 [0.99 , 1.56]
Subtotal (95% CI)		**79**		**37**	**28.0%**	**1.24 [0.99 , 1.56]**
Total events:	69		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.89 (P = 0.06)						
11.4.4 Chemo with sorafenib						
TRIAS 2018	78	83	77	89	40.9%	1.09 [0.98 , 1.20]
Subtotal (95% CI)		**83**		**89**	**40.9%**	**1.09 [0.98 , 1.20]**
Total events:	78		77			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.65 (P = 0.10)						
Total (95% CI)		**295**		**253**	**100.0%**	**1.23 [1.02 , 1.49]**
Total events:	217		147			
Heterogeneity: Tau² = 0.02; Chi² = 7.46, df = 3 (P = 0.06); I² = 60%						
Test for overall effect: Z = 2.14 (P = 0.03)						
Test for subgroup differences: Chi² = 7.46, df = 3 (P = 0.06), I² = 59.8%						

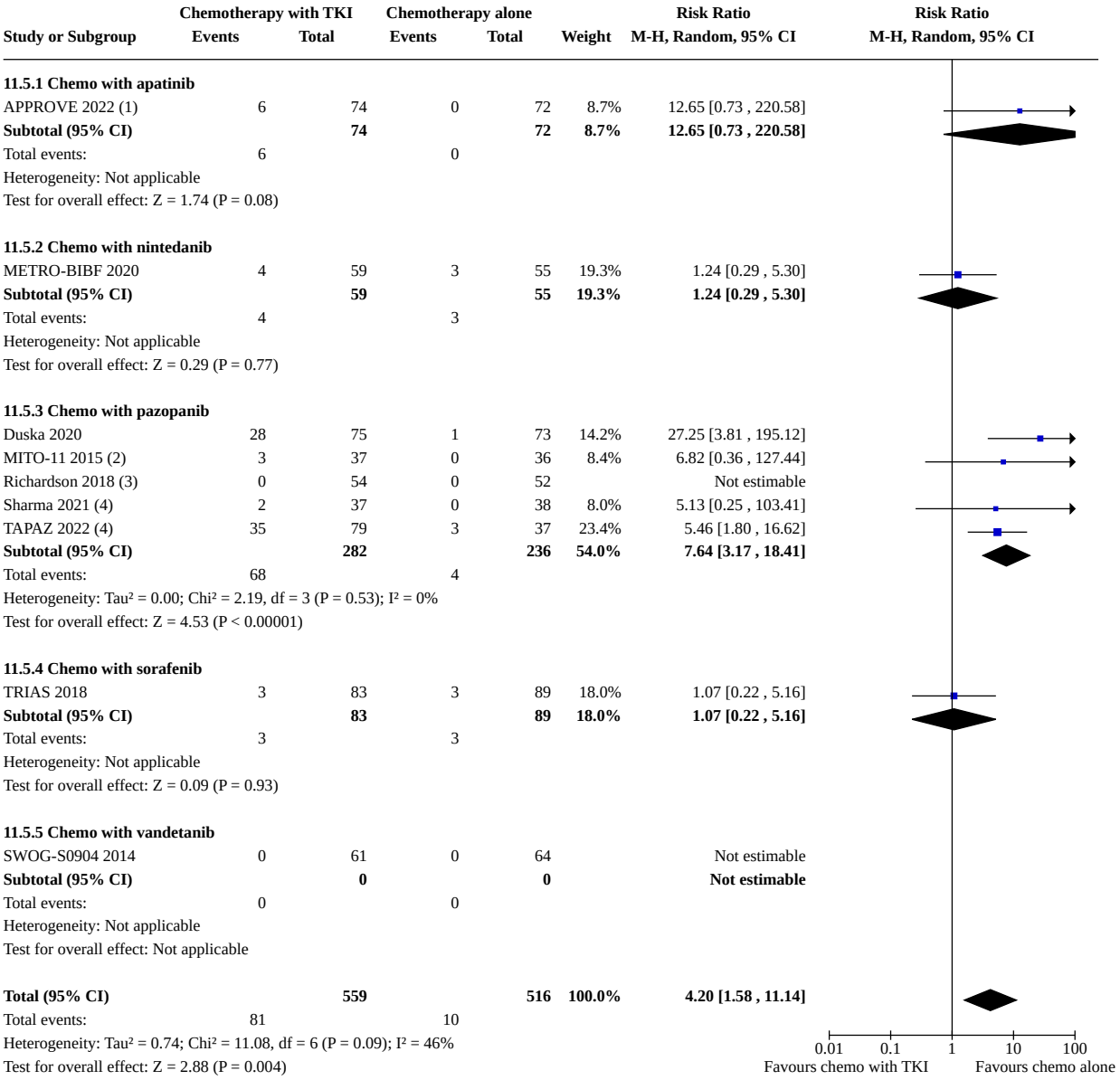


Footnotes

(1) treatment-emergent AE

(2) data from conference abstract

Analysis 11.5. Comparison 11: Recurrent platinum-resistant EOC: chemotherapy with TKI compared to chemotherapy alone, Outcome 5: Hypertension (grade ≥ 3)

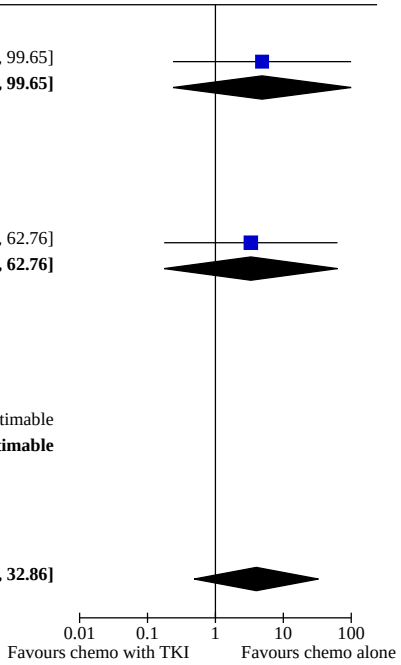


Footnotes

(1) treatment-emergent AE; grade 3&4
(2) grade 3&4; grade 2: 7 events in chemo with pazopanib arm
(3) severe hypertension Risk Ratio, 12.0; 95% CI, 1.6-88.8
(4) grade 3&4

Analysis 11.6. Comparison 11: Recurrent platinum-resistant EOC: chemotherapy with TKI compared to chemotherapy alone, Outcome 6: Proteinuria (grade ≥ 2)

Study or Subgroup	Chemotherapy with TKI Events	Total	Chemotherapy alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
11.6.1 Chemo with apatinib						
APPROVE 2022 (1)	2	74	0	72	48.6%	4.87 [0.24 , 99.65]
Subtotal (95% CI)		**74**		**72**	**48.6%**	**4.87 [0.24 , 99.65]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.03 (P = 0.30)						
11.6.2 Chemo with pazopanib						
TAPAZ 2022 (2)	3	79	0	37	51.4%	3.33 [0.18 , 62.76]
Subtotal (95% CI)		**79**		**37**	**51.4%**	**3.33 [0.18 , 62.76]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.80 (P = 0.42)						
11.6.3 Chemo with vandetanib						
SWOG-S0904 2014	0	61	0	64		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**214**		**173**	**100.0%**	**4.00 [0.49 , 32.86]**
Total events:	5		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%						
Test for overall effect: Z = 1.29 (P = 0.20)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%						



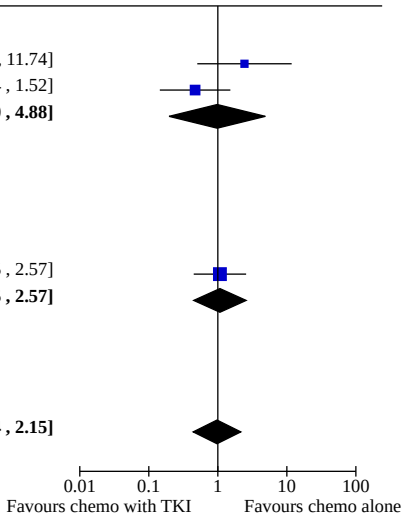
Footnotes

(1) treatment-emergent AE; grade 3&4

(2) grade 3&4

Analysis 11.7. Comparison 11: Recurrent platinum-resistant EOC: chemotherapy with TKI compared to chemotherapy alone, Outcome 7: Pain (grade ≥ 2)

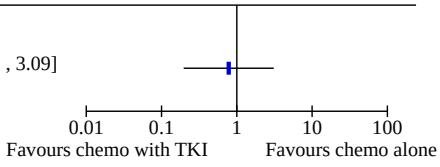
Study or Subgroup	Chemotherapy with TKI Events	Total	Chemotherapy alone Events	Total	Weight	Risk Ratio IV, Random, 95% CI
11.7.1 Chemo with pazopanib						
MITO-11 2015	5	37	2	36	20.7%	2.43 [0.50 , 11.74]
TAPAZ 2022 (1)	5	79	5	37	32.2%	0.47 [0.14 , 1.52]
Subtotal (95% CI)		**116**		**73**	**52.9%**	**0.98 [0.20 , 4.88]**
Total events:	10		7			
Heterogeneity: Tau² = 0.85; Chi² = 2.70, df = 1 (P = 0.10); I² = 63%						
Test for overall effect: Z = 0.03 (P = 0.98)						
11.7.2 Chemo with sorafenib						
TRIAS 2018	9	83	9	89	47.1%	1.07 [0.45 , 2.57]
Subtotal (95% CI)		**83**		**89**	**47.1%**	**1.07 [0.45 , 2.57]**
Total events:	9		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.16 (P = 0.88)						
Total (95% CI)		**199**		**162**	**100.0%**	**0.97 [0.44 , 2.15]**
Total events:	19		16			
Heterogeneity: Tau² = 0.15; Chi² = 2.83, df = 2 (P = 0.24); I² = 29%						
Test for overall effect: Z = 0.07 (P = 0.95)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.92), I² = 0%						



Footnotes
(1) grade 3&4

Analysis 11.8. Comparison 11: Recurrent platinum-resistant EOC: chemotherapy with TKI compared to chemotherapy alone, Outcome 8: Abdominal pain (grade ≥ 2)

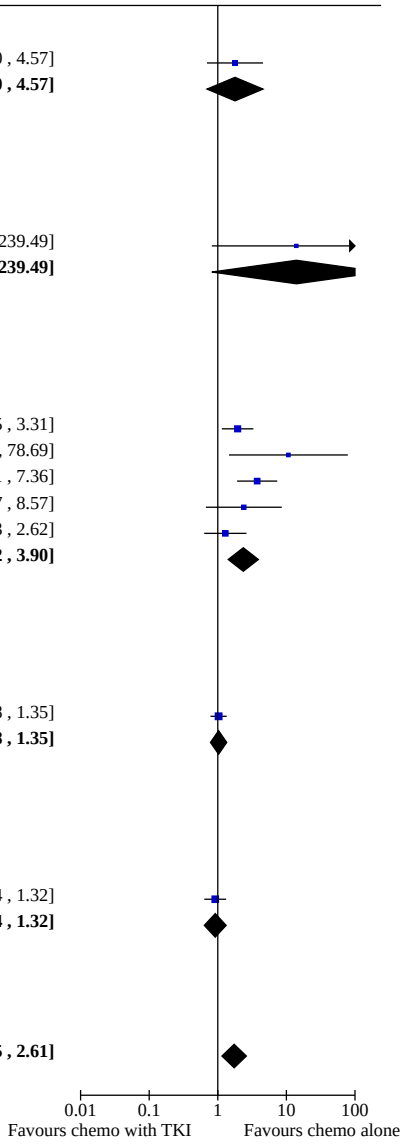
Study or Subgroup	Chemotherapy with TKI Events	Total	Chemotherapy alone Events	Total	Risk Ratio IV, Fixed, 95% CI
11.8.1 Chemo with pazopanib					
TAPAZ 2022 (1)	5	79	3	37	0.78 [0.20 , 3.09]



Footnotes
(1) grade 3&4

Analysis 11.9. Comparison 11: Recurrent platinum-resistant EOC: chemotherapy with TKI compared to chemotherapy alone, Outcome 9: Neutropenia (grade ≥ 3)

Study or Subgroup	Chemotherapy with TKI Events	Total	Chemotherapy alone Events	Total	Weight	Risk Ratio IV, Random, 95% CI
11.9.1 Chemo with apatinib						
APPROVE 2022 (1)	11	74	6	72	9.9%	1.78 [0.70 , 4.57]
Subtotal (95% CI)		**74**		**72**	**9.9%**	**1.78 [0.70 , 4.57]**
Total events:	11		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.21 (P = 0.23)						
11.9.2 Chemo with nintedanib						
METRO-BIBF 2020	7	59	0	55	1.9%	14.00 [0.82 , 239.49]
Subtotal (95% CI)		**59**		**55**	**1.9%**	**14.00 [0.82 , 239.49]**
Total events:	7		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.82 (P = 0.07)						
11.9.3 Chemo with pazopanib						
Duska 2020	30	75	15	73	15.3%	1.95 [1.15 , 3.31]
MITO-11 2015	11	37	1	36	3.5%	10.70 [1.46 , 78.69]
Richardson 2018	30	50	8	50	13.2%	3.75 [1.91 , 7.36]
Sharma 2021	7	37	3	38	6.9%	2.40 [0.67 , 8.57]
TAPAZ 2022	22	79	8	37	12.7%	1.29 [0.63 , 2.62]
Subtotal (95% CI)		**278**		**234**	**51.7%**	**2.35 [1.42 , 3.90]**
Total events:	100		35			
Heterogeneity: Tau² = 0.14; Chi² = 7.23, df = 4 (P = 0.12); I² = 45%						
Test for overall effect: Z = 3.31 (P = 0.0009)						
11.9.4 Chemo with sorafenib						
TRIAS 2018	46	83	48	89	18.9%	1.03 [0.78 , 1.35]
Subtotal (95% CI)		**83**		**89**	**18.9%**	**1.03 [0.78 , 1.35]**
Total events:	46		48			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.20 (P = 0.84)						
11.9.5 Chemo with vandetanib						
SWOG-S0904 2014	28	61	32	64	17.7%	0.92 [0.64 , 1.32]
Subtotal (95% CI)		**61**		**64**	**17.7%**	**0.92 [0.64 , 1.32]**
Total events:	28		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
Total (95% CI)		**555**		**514**	**100.0%**	**1.73 [1.15 , 2.61]**
Total events:	192		121			
Heterogeneity: Tau² = 0.21; Chi² = 26.32, df = 8 (P = 0.0009); I² = 70%						
Test for overall effect: Z = 2.63 (P = 0.009)						
Test for subgroup differences: Chi² = 13.58, df = 4 (P = 0.009), I² = 70.5%						

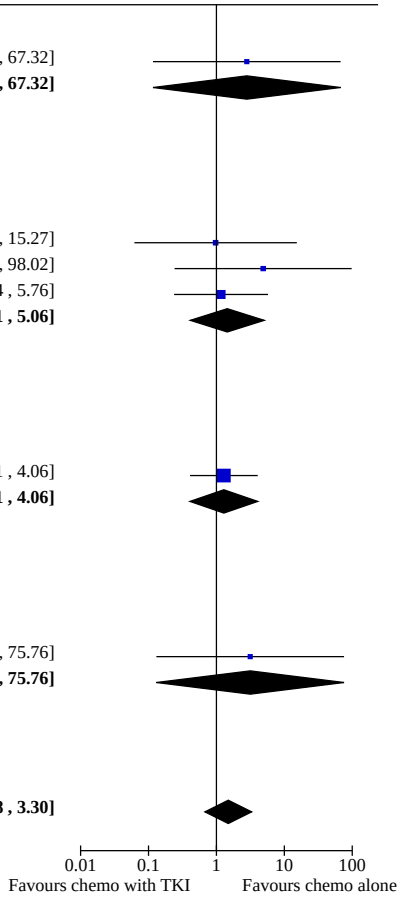


Footnotes

(1) treatment-emergent AE;

Analysis 11.10. Comparison 11: Recurrent platinum-resistant EOC: chemotherapy with TKI compared to chemotherapy alone, Outcome 10: Febrile neutropenia (any grade)

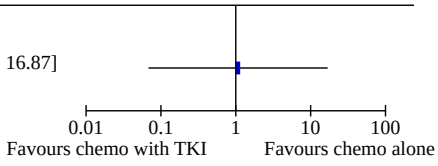
Study or Subgroup	Chemotherapy with TKI Events	Total	Chemotherapy alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
11.10.1 Chemo with nintedanib						
METRO-BIBF 2020 (1)	1	59	0	55	6.2%	2.80 [0.12 , 67.32]
Subtotal (95% CI)		**59**		**55**	**6.2%**	**2.80 [0.12 , 67.32]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
11.10.2 Chemo with pazopanib						
Duska 2020	1	75	1	73	8.3%	0.97 [0.06 , 15.27]
MITO-11 2015	2	37	0	36	7.0%	4.87 [0.24 , 98.02]
TAPAZ 2022	5	79	2	37	24.7%	1.17 [0.24 , 5.76]
Subtotal (95% CI)		**191**		**146**	**40.0%**	**1.44 [0.41 , 5.06]**
Total events:	8		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.79, df = 2 (P = 0.67); I² = 0%						
Test for overall effect: Z = 0.58 (P = 0.57)						
11.10.3 Chemo with sorafenib						
TRIAS 2018	6	83	5	89	47.6%	1.29 [0.41 , 4.06]
Subtotal (95% CI)		**83**		**89**	**47.6%**	**1.29 [0.41 , 4.06]**
Total events:	6		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.43 (P = 0.67)						
11.10.4 Chemo with vandetanib						
SWOG-S0904 2014	1	61	0	64	6.2%	3.15 [0.13 , 75.76]
Subtotal (95% CI)		**61**		**64**	**6.2%**	**3.15 [0.13 , 75.76]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
Total (95% CI)		**394**		**354**	**100.0%**	**1.49 [0.68 , 3.30]**
Total events:	16		8			
Heterogeneity: Tau² = 0.00; Chi² = 1.22, df = 5 (P = 0.94); I² = 0%						
Test for overall effect: Z = 0.99 (P = 0.32)						
Test for subgroup differences: Chi² = 0.43, df = 3 (P = 0.93), I² = 0%						



Footnotes
(1) grade 3 & 4 only

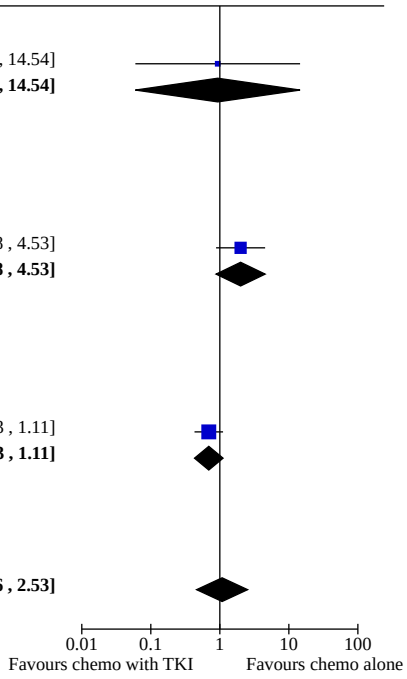
Analysis 11.11. Comparison 11: Recurrent platinum-resistant EOC: chemotherapy with TKI compared to chemotherapy alone, Outcome 11: Non-central nervous system bleeding (grade ≥ 3)

Study or Subgroup	Chemotherapy with TKI Events	Total	Chemotherapy alone Events	Total	Risk Ratio IV, Fixed, 95% CI
11.11.1 Chemo with sorafenib					
TRIAS 2018	1	83	1	89	1.07 [0.07 , 16.87]



Analysis 11.12. Comparison 11: Recurrent platinum-resistant EOC: chemotherapy with TKI compared to chemotherapy alone, Outcome 12: Gastrointestinal adverse events (grade ≥ 3)

Study or Subgroup	Chemotherapy with TKI Events	Total	Chemotherapy alone Events	Total	Weight	Risk Ratio IV, Random, 95% CI
11.12.1 Chemo with nintedanib						
METRO-BIBF 2020 (1)	1	59	1	55	8.3%	0.93 [0.06 , 14.54]
Subtotal (95% CI)		**59**		**55**	**8.3%**	**0.93 [0.06 , 14.54]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
11.12.2 Chemo with pazopanib						
Richardson 2018 (2)	14	50	7	50	39.5%	2.00 [0.88 , 4.53]
Subtotal (95% CI)		**50**		**50**	**39.5%**	**2.00 [0.88 , 4.53]**
Total events:	14		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.66 (P = 0.10)						
11.12.3 Chemo with sorafenib						
TRIAS 2018 (1)	20	83	31	89	52.2%	0.69 [0.43 , 1.11]
Subtotal (95% CI)		**83**		**89**	**52.2%**	**0.69 [0.43 , 1.11]**
Total events:	20		31			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.52 (P = 0.13)						
Total (95% CI)		**192**		**194**	**100.0%**	**1.08 [0.46 , 2.53]**
Total events:	35		39			
Heterogeneity: Tau² = 0.30; Chi² = 4.83, df = 2 (P = 0.09); I² = 59%						
Test for overall effect: Z = 0.18 (P = 0.86)						
Test for subgroup differences: Chi² = 4.83, df = 2 (P = 0.09), I² = 58.6%						

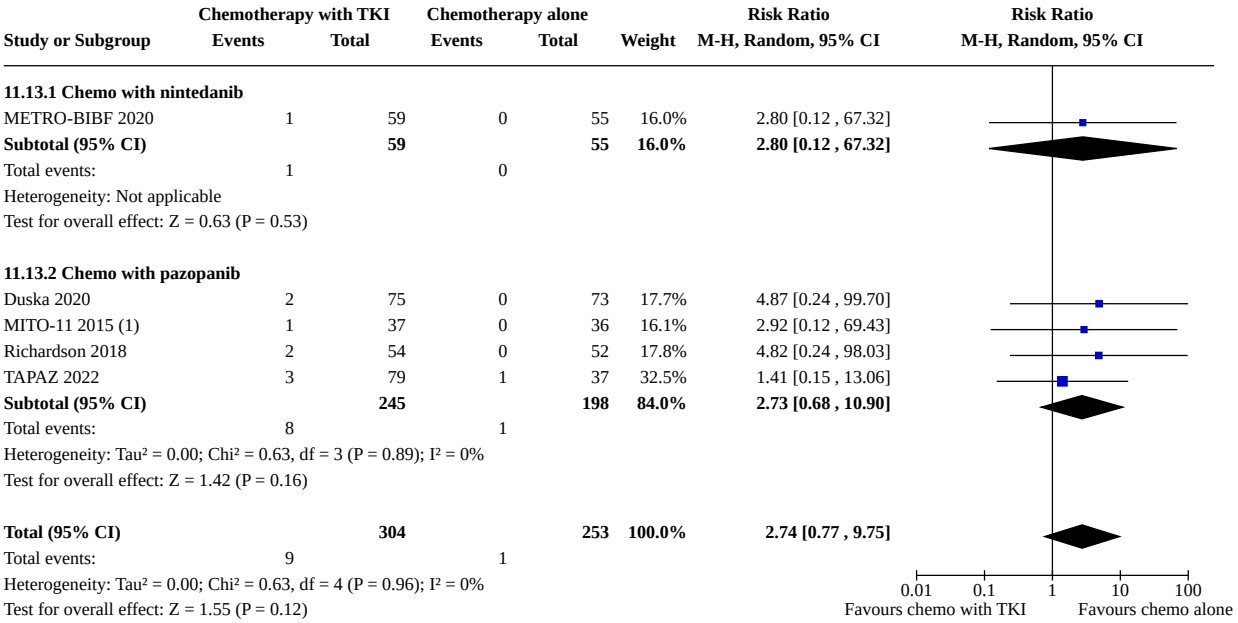


Footnotes

(1) grade 3&4

(2) grade 3 (no grade 4 events)

Analysis 11.13. Comparison 11: Recurrent platinum-resistant EOC: chemotherapy with TKI compared to chemotherapy alone, Outcome 13: Bowel fistula or perforation (grade ≥ 3)



Footnotes
(1) Ileal perforation

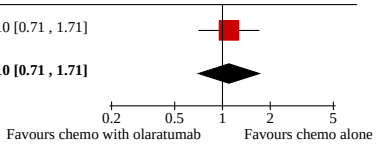
Comparison 12. Recurrent platinum-resistant EOC: chemotherapy with olaratumab compared to chemotherapy alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Overall survival	1	123	Hazard Ratio (IV, Fixed, 95% CI)	1.10 [0.71, 1.71]
12.2 Progression-free survival	1	123	Hazard Ratio (IV, Fixed, 95% CI)	1.04 [0.70, 1.56]
12.3 Proteinuria (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
12.4 Pain (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
12.5 Abdominal pain (grade ≥ 3)	1	123	Risk Ratio (IV, Fixed, 95% CI)	0.25 [0.05, 1.11]
12.6 Neutropenia (grade ≥ 3)	1	123	Risk Ratio (IV, Fixed, 95% CI)	1.57 [0.55, 4.54]

Analysis 12.1. Comparison 12: Recurrent platinum-resistant EOC: chemotherapy with olaratumab compared to chemotherapy alone, Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Chemotherapy with olaratumab Total	Chemotherapy alone Total	Weight	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
McGuire 2018	0.09349	0.225527	62	61	100.0%	1.10 [0.71 , 1.71]	
Total (95% CI)			**62**	**61**	**100.0%**	**1.10 [0.71 , 1.71]**	

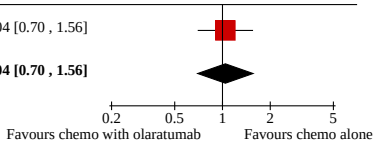
Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)
Test for subgroup differences: Not applicable



Analysis 12.2. Comparison 12: Recurrent platinum-resistant EOC: chemotherapy with olaratumab compared to chemotherapy alone, Outcome 2: Progression-free survival

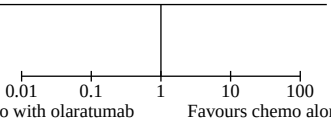
Study or Subgroup	log[Hazard Ratio]	SE	Chemotherapy with olaratumab Total	Chemotherapy alone Total	Weight	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
McGuire 2018	0.042101	0.204835	62	61	100.0%	1.04 [0.70 , 1.56]	
Total (95% CI)			**62**	**61**	**100.0%**	**1.04 [0.70 , 1.56]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.21 (P = 0.84)
Test for subgroup differences: Not applicable



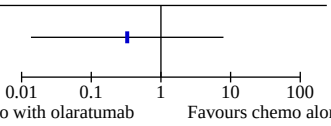
Analysis 12.3. Comparison 12: Recurrent platinum-resistant EOC: chemotherapy with olaratumab compared to chemotherapy alone, Outcome 3: Proteinuria (grade ≥ 3)

Study or Subgroup	Chemotherapy with olaratumab Events	Total	Chemotherapy alone Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
McGuire 2018	0	62	0	61	Not estimable	



Analysis 12.4. Comparison 12: Recurrent platinum-resistant EOC: chemotherapy with olaratumab compared to chemotherapy alone, Outcome 4: Pain (grade ≥ 3)

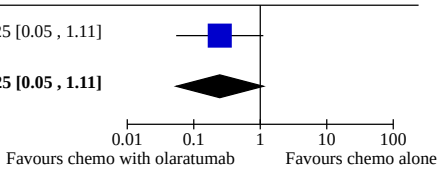
Study or Subgroup	Chemotherapy with olaratumab Events	Total	Chemotherapy alone Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
McGuire 2018	0	62	1	61	0.33 [0.01 , 7.90]	



Analysis 12.5. Comparison 12: Recurrent platinum-resistant EOC: chemotherapy with olaratumab compared to chemotherapy alone, Outcome 5: Abdominal pain (grade ≥ 3)

Study or Subgroup	Chemotherapy with olaratumab Events	Total	Chemotherapy alone Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
McGuire 2018	2	62	8	61	100.0%	0.25 [0.05 , 1.11]
Total (95% CI)		**62**		**61**	**100.0%**	**0.25 [0.05 , 1.11]**
Total events:	2		8			

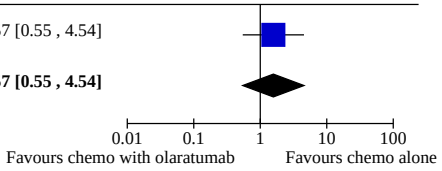
Heterogeneity: Not applicable
Test for overall effect: Z = 1.82 (P = 0.07)
Test for subgroup differences: Not applicable



Analysis 12.6. Comparison 12: Recurrent platinum-resistant EOC: chemotherapy with olaratumab compared to chemotherapy alone, Outcome 6: Neutropenia (grade ≥ 3)

Study or Subgroup	Chemotherapy with olaratumab Events	Total	Chemotherapy alone Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
McGuire 2018	8	62	5	61	100.0%	1.57 [0.55 , 4.54]
Total (95% CI)		**62**		**61**	**100.0%**	**1.57 [0.55 , 4.54]**
Total events:	8		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.84 (P = 0.40)
Test for subgroup differences: Not applicable



Comparison 13. Recurrent EOC: chemotherapy with TKI (peptide-Fc fusion protein) compared to chemotherapy alone

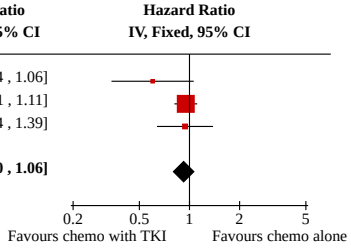
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Overall survival	3	1250	Hazard Ratio (IV, Fixed, 95% CI)	0.92 [0.80, 1.06]
13.2 Progression-free survival	3	1250	Hazard Ratio (IV, Fixed, 95% CI)	0.73 [0.65, 0.82]
13.3 Quality of life - Functional Assessment of Cancer Therapy—Ovarian Cancer questionnaire	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13.4 Hypertension (grade ≥ 3)	3	1242	Risk Ratio (M-H, Fixed, 95% CI)	2.92 [0.70, 12.18]
13.5 Proteinuria (grade ≥ 3)	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
13.6 Pain (grade ≥ 3)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
13.7 Abdominal pain (grade ≥ 3)	3	1242	Risk Ratio (IV, Fixed, 95% CI)	0.99 [0.60, 1.65]
13.8 Neutropenia (grade ≥ 3)	2	1134	Risk Ratio (IV, Fixed, 95% CI)	0.60 [0.40, 0.89]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.9 Febrile neutropenia (any grade)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
13.10 Venous thromboembolic event (any grade)	2	1021	Risk Ratio (IV, Fixed, 95% CI)	0.68 [0.25, 1.85]
13.11 Arterial thromboembolic event (any grade)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
13.12 Non-central nervous system bleeding (grade ≥ 3)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected
13.13 Gastrointestinal perforation (grade ≥ 3)	1		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Analysis 13.1. Comparison 13: Recurrent EOC: chemotherapy with TKI (peptide-Fc fusion protein) compared to chemotherapy alone, Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Chemotherapy with TKI Total	Chemotherapy alone Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Karlan 2012	-0.51	0.29	53	55	6.2%	0.60 [0.34 , 1.06]
TRINOVA-1 2016	-0.051293	0.080379	458	461	80.5%	0.95 [0.81 , 1.11]
TRINOVA-2 2017 (1)	-0.061875	0.197858	114	109	13.3%	0.94 [0.64 , 1.39]
Total (95% CI)			**625**	**625**	**100.0%**	**0.92 [0.80 , 1.06]**

Heterogeneity: Chi² = 2.33, df = 2 (P = 0.31); I² = 14%
Test for overall effect: Z = 1.12 (P = 0.26)
Test for subgroup differences: Not applicable

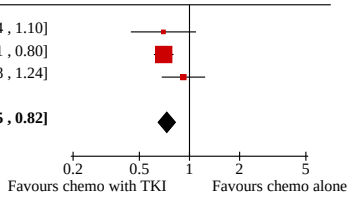


Footnotes
(1) evidence of non-proportionality of hazards

Analysis 13.2. Comparison 13: Recurrent EOC: chemotherapy with TKI (peptide-Fc fusion protein) compared to chemotherapy alone, Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Chemotherapy with TKI Total	Chemotherapy alone Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Karlan 2012	-0.36	0.23	53	55	7.0%	0.70 [0.44 , 1.10]
TRINOVA-1 2016	-0.356675	0.069173	458	461	77.3%	0.70 [0.61 , 0.80]
TRINOVA-2 2017 (1)	-0.083382	0.153261	114	109	15.7%	0.92 [0.68 , 1.24]
Total (95% CI)			**625**	**625**	**100.0%**	**0.73 [0.65 , 0.82]**

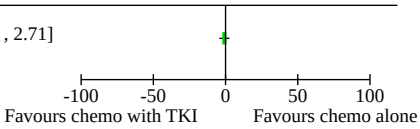
Heterogeneity: Chi² = 2.68, df = 2 (P = 0.26); I² = 26%
Test for overall effect: Z = 5.16 (P < 0.00001)
Test for subgroup differences: Not applicable



Footnotes
(1) evidence of non-proportionality of hazards

Analysis 13.3. Comparison 13: Recurrent EOC: chemotherapy with TKI (peptide-Fc fusion protein) compared to chemotherapy alone, Outcome 3: Quality of life - Functional Assessment of Cancer Therapy—Ovarian Cancer questionnaire

Study or Subgroup	Chemotherapy with TKI Mean	SD	Total	Chemotherapy alone Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
TRINOVA-1 2016 (1)	-2.4	16.6	169	-1.6	15.2	146	-0.80 [-4.31 , 2.71]



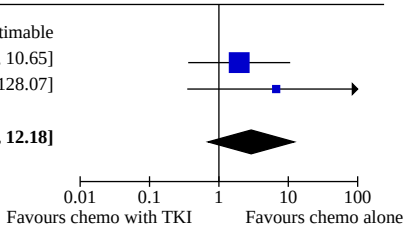
Footnotes

(1) mean change from baseline to 25 weeks (approximate median progression-free survival in the trial)

Analysis 13.4. Comparison 13: Recurrent EOC: chemotherapy with TKI (peptide-Fc fusion protein) compared to chemotherapy alone, Outcome 4: Hypertension (grade ≥ 3)

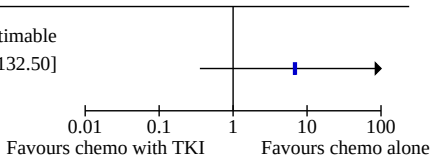
Study or Subgroup	Chemotherapy with TKI Events	Total	Chemotherapy alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Karlan 2012	0	53	0	55		Not estimable
TRINOVA-1 2016	4	461	2	452	79.8%	1.96 [0.36 , 10.65]
TRINOVA-2 2017	3	113	0	108	20.2%	6.69 [0.35 , 128.07]
Total (95% CI)		**627**		**615**	**100.0%**	**2.92 [0.70 , 12.18]**
Total events:	7		2			

Heterogeneity: Chi² = 0.52, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 1.47 (P = 0.14)
Test for subgroup differences: Not applicable



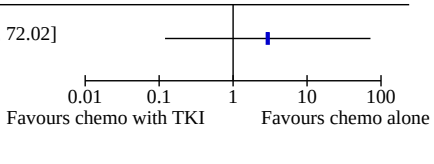
Analysis 13.5. Comparison 13: Recurrent EOC: chemotherapy with TKI (peptide-Fc fusion protein) compared to chemotherapy alone, Outcome 5: Proteinuria (grade ≥ 3)

Study or Subgroup	Chemotherapy with TKI Events	Total	Chemotherapy alone Events	Total	Risk Ratio M-H, Fixed, 95% CI
Karlan 2012	0	53	0	55	Not estimable
TRINOVA-1 2016	3	461	0	452	6.86 [0.36 , 132.50]



Analysis 13.6. Comparison 13: Recurrent EOC: chemotherapy with TKI (peptide-Fc fusion protein) compared to chemotherapy alone, Outcome 6: Pain (grade ≥ 3)

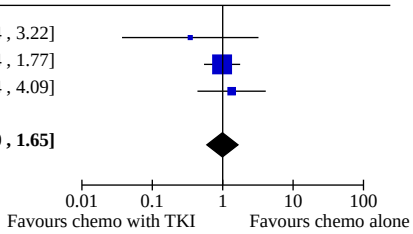
Study or Subgroup	Chemotherapy with TKI Events	Total	Chemotherapy alone Events	Total	Risk Ratio M-H, Fixed, 95% CI
TRINOVA-1 2016	1	461	0	452	2.94 [0.12 , 72.02]



Analysis 13.7. Comparison 13: Recurrent EOC: chemotherapy with TKI (peptide-Fc fusion protein) compared to chemotherapy alone, Outcome 7: Abdominal pain (grade ≥ 3)

Study or Subgroup	Chemotherapy with TKI Events	Total	Chemotherapy alone Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Karlan 2012	1	53	3	55	5.2%	0.35 [0.04 , 3.22]
TRINOVA-1 2016	21	461	21	452	74.1%	0.98 [0.54 , 1.77]
TRINOVA-2 2017	7	113	5	108	20.7%	1.34 [0.44 , 4.09]
Total (95% CI)		**627**		**615**	**100.0%**	**0.99 [0.60 , 1.65]**
Total events:	29		29			

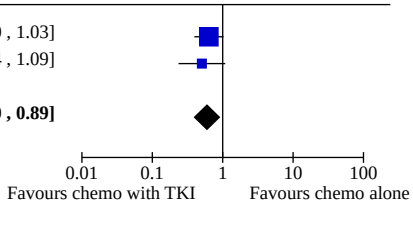
Heterogeneity: Chi² = 1.13, df = 2 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.04 (P = 0.97)
Test for subgroup differences: Not applicable



Analysis 13.8. Comparison 13: Recurrent EOC: chemotherapy with TKI (peptide-Fc fusion protein) compared to chemotherapy alone, Outcome 8: Neutropenia (grade ≥ 3)

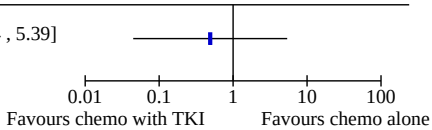
Study or Subgroup	Chemotherapy with TKI Events	Total	Chemotherapy alone Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
TRINOVA-1 2016	26	461	40	452	72.0%	0.64 [0.40 , 1.03]
TRINOVA-2 2017	9	113	17	108	28.0%	0.51 [0.24 , 1.09]
Total (95% CI)		**574**		**560**	**100.0%**	**0.60 [0.40 , 0.89]**
Total events:	35		57			

Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 2.50 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 13.9. Comparison 13: Recurrent EOC: chemotherapy with TKI (peptide-Fc fusion protein) compared to chemotherapy alone, Outcome 9: Febrile neutropenia (any grade)

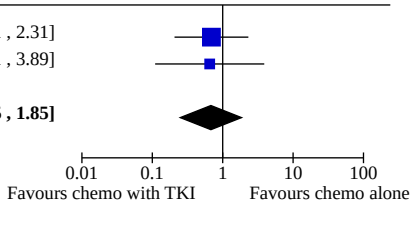
Study or Subgroup	Chemotherapy with TKI Events	Total	Chemotherapy alone Events	Total	Risk Ratio M-H, Fixed, 95% CI
TRINOVA-1 2016	1	461	2	452	0.49 [0.04 , 5.39]



Analysis 13.10. Comparison 13: Recurrent EOC: chemotherapy with TKI (peptide-Fc fusion protein) compared to chemotherapy alone, Outcome 10: Venous thromboembolic event (any grade)

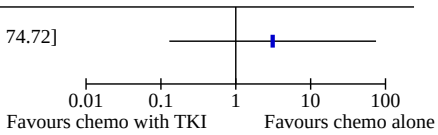
Study or Subgroup	Chemotherapy with TKI Events	Total	Chemotherapy alone Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
Karlan 2012	4	53	6	55	68.6%	0.69 [0.21 , 2.31]
TRINOVA-1 2016	2	461	3	452	31.4%	0.65 [0.11 , 3.89]
Total (95% CI)		**514**		**507**	**100.0%**	**0.68 [0.25 , 1.85]**
Total events:	6		9			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.76 (P = 0.45)
Test for subgroup differences: Not applicable



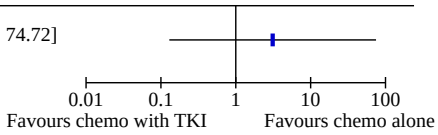
Analysis 13.11. Comparison 13: Recurrent EOC: chemotherapy with TKI (peptide-Fc fusion protein) compared to chemotherapy alone, Outcome 11: Arterial thromboembolic event (any grade)

Study or Subgroup	Chemotherapy with TKI Events	Total	Chemotherapy alone Events	Total	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Karlan 2012	1	53	0	55	3.11 [0.13 , 74.72]	



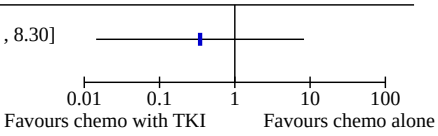
Analysis 13.12. Comparison 13: Recurrent EOC: chemotherapy with TKI (peptide-Fc fusion protein) compared to chemotherapy alone, Outcome 12: Non-central nervous system bleeding (grade ≥ 3)

Study or Subgroup	Chemotherapy with TKI Events	Total	Chemotherapy alone Events	Total	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Karlan 2012	1	53	0	55	3.11 [0.13 , 74.72]	



Analysis 13.13. Comparison 13: Recurrent EOC: chemotherapy with TKI (peptide-Fc fusion protein) compared to chemotherapy alone, Outcome 13: Gastrointestinal perforation (grade ≥ 3)

Study or Subgroup	Chemotherapy with TKI Events	Total	Chemotherapy alone Events	Total	Risk Ratio IV, Fixed, 95% CI	Risk Ratio IV, Fixed, 95% CI
Karlan 2012	0	53	1	55	0.35 [0.01 , 8.30]	



ADDITIONAL TABLES

Table 1. Overview of included studies

Study ID	Number of references	Intervention/s (N)	Control (N)	Number randomised	Randomisation ratio	Type of anti-angiogenesis agent	Newly-diagnosed or relapsed/recurrent EOC	Population in relation to platinum-sensitivity*	Percentage (%) stage IV (newly-diagnosed EOC only)	Prior treatment
Newly-diagnosed EOC										
AGO-OVAR 12 2020	6	Chemotherapy + nintedanib (911)	Chemotherapy (455)	1366	2:1	Nintedanib: TKI targeting VEGF-R, PDGF-R and FGF-R	Newly-diagnosed	PS 100%	24% in intervention arm; 24% in control arm); overall 24%	N/A
AGO-OVAR 16 2019	13	Pazopanib (472)	Placebo (468)	940	1:1	Pazopanib: TKI targeting VEGF-R, PDGF-R and c-kit	Newly-diagnosed	PS 100%	16.3% in intervention group; 16.9% in control group; overall 16.6%	N/A
ANTHALYA 2017	6	Chemotherapy + bevacizumab (58)	Chemotherapy (37)	95	2:1	Bevacizumab: antibody against VEGF	Newly-diagnosed	PS 100%	26% in intervention group; 35% in control group; overall 30%	N/A
CHIVA 2019	6	Chemotherapy + nintedanib (124)	Chemotherapy (64)	188	2:1	Nintedanib: TKI targeting VEGF-R, PDGF-R and FGF-R	Newly-diagnosed	PS 100%	N/A	N/A

Table 1. Overview of included studies *(Continued)*

GEICO-1205 2019	3	Chemotherapy + bevacizumab (35)	Chemotherapy (33)	68	1:1	Bevacizumab: antibody against VEGF	Newly-diagnosed	PS 100%	34% in intervention arm and 33% in control arm; 33.8% overall	N/A
GOG-0218 2019	20	Chemotherapy + bevacizumab (625) Chemotherapy + bevacizumab with bevacizumab maintenance (623)	Chemotherapy (625)	1873	1:1:1	Bevacizumab: antibody against VEGF	Newly-diagnosed	PS 100%	26.2% intervention in initiation only arm; 26.5% in initiation and maintenance arm; 24.5% in control arm; 25.7% overall	N/A
Hainsworth 2015	4	Chemotherapy + sorafenib (43)	Chemotherapy (42)	85	1:1	Sorafenib: TKI targeting VEGF-R, PDGF-R, and RAF kinases	Newly-diagnosed	PS 100%	33% in control arm; 19% in intervention arm; 25.9% overall	N/A
Herzog 2013	3	Sorafenib (123)	Placebo (123)	246	1:1	Sorafenib: TKI targeting VEGF-R, PDGF-R, and RAF kinases	Newly-diagnosed	PS 100%	Stage at diagnosis not provided but all stage III/V; 8.1% suboptimally debulked at primary	N/A

Table 1. Overview of included studies *(Continued)*

									surgery in each arm	
ICON7 2015	16	Chemotherapy + bevacizumab (764)	Chemotherapy (764)	1528	1:1	Bevacizumab: antibody against VEGF	Newly-diagnosed	PS 100%	12% in control arm; 13% in intervention arm; 13.2% overall	N/A
Reyners 2012	2	Chemotherapy + celecoxib (97)	Chemotherapy (99)	196	1:1	Celecoxib: COX-2 inhibitor	Newly-diagnosed	PS 100%	25.3% in control arm; 22.7% in intervention arm; 23.7% overall	N/A
TRINOVA-3 2019	2	Chemotherapy + trebananib (678)	Chemotherapy (337)	1015	2:1	Trebananib: TKI targeting Ang1 and Ang2 (angiopoietins)	Newly-diagnosed	PS 100%	24% in control arm; 27% in intervention arm; 26.2% overall	N/A
Platinum-sensitive recurrence										
AVANOVA2 2019	5	Niraparib + bevacizumab (48)	Niraparib (49)	97	1:1	Bevacizumab: antibody against VEGF	Recurrent	PS (66%) PPS (34%)	N/A	Platinum-based chemotherapy. Overall previous lines of treatment: one = 49.5%; two = 44.3%; three or more = 6%
Cong 2019	1	Chemotherapy + bevacizumab (82)	Chemotherapy (82)	164	1:1	Bevacizumab: antibody against VEGF	Recurrent	PS	N/A	Platinum-based chemotherapy

Table 1. Overview of included studies *(Continued)*

GOG-0213 2017	3	Chemotherapy + bevacizumab (377)	Chemotherapy (337)	674	1:1	Bevacizumab: antibody against VEGF	Recurrent	PS	N/A	Platinum-based chemotherapy
ICON6 2021	8	Chemotherapy + cediranib + placebo maintenance (174) Chemotherapy + cediranib + cediranib maintenance (164)	Chemotherapy placebo maintenance (118)	486+ (456)	2:3:3	Cediranib: TKI targeting VEGF-R, PDGF-R, and c-kit	Recurrent	PS 67% PPS 33%	N/A	Platinum-based chemotherapy, 89% with paclitaxel. Overall 5% had had previous bevacizumab treatment.
Li 2019	1	Chemotherapy with paclitaxel and carboplatin + bevacizumab (34)	Chemotherapy with paclitaxel and carboplatin (34)	68	1:1	Bevacizumab: antibody against VEGF	Recurrent	PS 100%	N/A	Platinum-based chemotherapy at least (presumed)
Liu 2019b	5	Olaparib + cediranib (44)	Olaparib (46)	90	1:1	Cediranib: TKI targeting VEGF-R, PDGF-R, and c-kit	Recurrent	PS 100%	N/A	Platinum-based chemotherapy and max 1 non-platinum therapy in recurrent setting
Liu 2022	4	Cediranib + olaparib (189) Olaparib (189)	Chemotherapy (carboplatin and paclitaxel, carboplatin and gemcitabine, or carboplatin and pegylated liposomal doxorubicin) (187)	565	1:1:1	TKI with PARPi	Recurrent	PS	N/A	Platinum and non-platinum based chemotherapy (65% only 1 prior line of chemotherapy)

Table 1. Overview of included studies *(Continued)*

MITO-16b 2021	2	Chemotherapy + bevacizumab (203)	Chemotherapy (203)	406	1:1	Bevacizumab: antibody against VEGF	Recurrent	PS 100%	N/A	First-line platinum-based treatment, including bevacizumab
OCEANS 2015	12	Chemotherapy + bevacizumab (242)	Chemotherapy + placebo (242)	484	1:1	Bevacizumab: antibody against VEGF	Recurrent	PS	N/A	Platinum-based front-line chemotherapy
Platinum-resistant recurrence										
AMBITION 2022	5	Olaparib + cediranib (16)	Olaparib + durvalumab (14)	30 for relevant comparison [3 other arms, N = 70 in total]	1:1	Cediranib: TKI targeting VEGF-R, PDGF-R, and c-kit	Recurrent	PR	N/A	At least 2 prior lines of anticancer therapy
APPROVE 2022	3	Chemotherapy + apatinib (78)	Chemotherapy (74)	150	1:1	Apatinib: TKI targeting VEGF-R2	Recurrent	PR 100%	N/A	Platinum-based chemotherapy
AURELIA 2014	16	Chemotherapy + bevacizumab (179)	Chemotherapy (182)	361	1:1	Bevacizumab: antibody against VEGF	Recurrent	PR 100%	N/A	Platinum-based chemotherapy (max 2)
BAROCCO 2022	2	Cediranib-olaparib combination (continuous n= 41) (intermittent n= 41)	Weekly paclitaxel (n= 41)	123	1:1:1	Cediranib: TKI targeting VEGF-R, PDGF-R, and c-kit	Recurrent	PR (100%)	N/A	39.8% up to 2 previous lines of chemotherapy; 60.2% ≥3 previous lines of chemotherapy. 53.7% prior anti-angiogenic treatment
EORTC-1508 2021	2	Bevacizumab (33) atezolizumab + cevacizumab + placebo (32) Atezolizumab + bevacizumab +	Atezolizumab + placebo (11) Atezolizumab + acetylsalicylic acid (13)	122	1:1	Bevacizumab: antibody against VEGF	Recurrent	PR 100%	N/A	Platinum-based chemotherapy (max of 2 non-platinum regimens)

Table 1. Overview of included studies *(Continued)*

		acetylsalicylic acid (33)								
Gotlieb 2012	5	Aflibercept (29)	Placebo (26)	55	1:1	Aflibercept: fusion protein targeting VEGF-A and VEGF-B	Recurrent	PR	N/A	At least 2 lines of previous chemotherapy, one platinum-based
Li 2021	1	Bevacizimab + albumin-binding paclitaxel	Albumin-binding paclitaxel	70	1:1	Bevacizumab: antibody against VEGF	Recurrent	PR	N/A	Unclear as English language abstract only
Liu 2019a	1	Chemotherapy + bevacizumab (43)	Chemotherapy (43)	86	1:1	Bevacizumab: antibody against VEGF	Recurrent	PR 100%	N/A	Platinum-based chemotherapy
Liu 2021a	1	Chemotherapy + bevacizumab (38)	Chemotherapy (38)	76	1:1	Bevacizumab: antibody against VEGF	Recurrent	PR	N/A	Platinum-based chemotherapy; platinum-free interval 4.3 months ±0.6 months control group and 4.8 ±0.8 months in bevacizumab group (P=0.06)
McGuire 2018	3	Chemotherapy + olaratumab (62)	Chemotherapy (61)	123	1:1	Olaratumab: monoclonal antibody targeting PDGFR-α	Recurrent	PR	N/A	Platinum-based chemotherapy
METRO-BIBF 2020	3	Cyclophosphamide + nintedanib (59)	Cyclophosphamide (58)	117	1:1	Nintedanib: TKI targeting VEGF-R, PDGF-R and FGF-R	Recurrent	PR or intolerant 100%	N/A	Two or more lines of chemotherapy
MITO-11 2015	3	Chemotherapy + pazopanib (37)	Chemotherapy (37)	74	1:1	Pazopanib: TKI targeting VEGF-R, PDGF-R and c-kit	Recurrent	PR	N/A	Prevous chemotherapy lines: one = 43.8%; two = 47.9% three or more = 8.2%
NICCC 2020	2	Nintedanib (47)	Chemotherapy	91	1:1	Nintedanib: TKI targeting VEGF-	Recurrent	PR 100%	N/A	Platinum-based chemotherapy.

Table 1. Overview of included studies *(Continued)*

			(44)			R, PDGF-R and FGF-R				participants had clear cell carcinoma of EOC or endometrial origin. 91 participants with EOC.
Nishikawa 2020	1	Chemotherapy + bevacizumab (52)	Chemotherapy (single-agent no more details) (51)	103	1:1	Bevacizumab: antibody against VEGF	Recurrent	PR 100%	N/A	previously treated with ≥3 cycles of bevacizumab + platinum chemotherapy; progression occurred <6 months after completion of platinum treatment
OCTOVA 2021	3	Olaparib + cediranib (47)	Olaparib (46) Chemotherapy (46)	139	1:1:1	Cediranib: TKI targeting VEGF-R, PDGF-R, and c-kit	Recurrent	PR 100%	N/A	Prior PARPi therapy (22%) Prior antiangiogenic therapy, 47 (34%) Platinum and non-platinum based chemotherapy
Roque 2022	3	Ixabepilone + bevacizumab (39)	Ixabepilone (37)	76	1:1	Bevacizumab: antibody against VEGF	Recurrent	PR or refractory 100%	N/A	Not reported
Sharma 2021	2	Etoposide + cyclophosphamide + pazopanib (37)	Etoposide + cyclophosphamide (38)	75	1:1	Pazopanib: TKI targeting VEGF-R, PDGF-R, c-kit, and FGF-R	Recurrent	PR 51%; Platinum refractory 49%	N/A	Prior treatment with at least 2 chemotherapy regimens in advanced tumor
SWOG-S0904 2014	3	Chemotherapy + vandetanib (63)	Chemotherapy (66)	129	1:1	Vandetanib: TKI targeting VEGF-R, EGF-R, and RET	Recurrent	All patients were considered platinum resistant	N/A	Platinum-based front-line chemotherapy +/- up to 3 chemotherapy regimens in current setting +/-

Table 1. Overview of included studies *(Continued)*

								or refractory		primary anti-angiogenic therapy
TRIAS 2018	3	Topotecan + sorafenib (85) (83 included in analyses) [maintenance: sorafenib]	Topotecan + placebo (89) [maintenance: placebo]	174 (172)	1:1	Sorafenib: TKI targeting VEGF-R, PDGF-R, and RAF kinases	Recurrent	PR or refractory 100%	N/A	No more than two prior treatment regimens for recurrent EOC
Mixed platinum-sensitive and platinum-resistant recurrence										
Duska 2020	3	Chemotherapy + pazopanib (75)	Chemotherapy (76)	148	1:1	Pazopanib: TKI targeting VEGF-R, PDGF-R and c-kit	Recurrent	PS (40%) PR (60%)	N/A	Chemotherapy (max 3)
Gupta 2019	2	Cyclophosphamide + celecoxib (26)	Cyclophosphamide (26)	52	1:1	Celecoxib: COX-2 inhibitor	Recurrent	PS 38.5% PR 57.7% P refractory 3.8%	N/A	No limit on prior lines of therapy
Karlan 2012	9	Chemotherapy + lower-dose trebananib (AMG386) (53) Chemotherapy + higher-dose trebananib (AMG386) (53)	Chemotherapy + placebo (55)	161	1:1:1	Trebananib: TKI targeting Ang1 and Ang2 (angiopoietins)	Recurrent	PS (52%) PR (47%)	N/A	Platinum and non-platinum based chemotherapy (max 3 in total)
Ledermann 2011	3	Nintedanib (BIBF 1120) (43)	Placebo (41)	84	1:1	Nintedanib: TKI targeting VEGF-R, PDGF-R and FGF-R	Recurrent	PS (59%) PR (41%)	N/A	Chemotherapy (2 or more rounds)
Matulonis 2019	2	Cabozantinib (57)	Chemotherapy (54)	111	1:1	Cabozantinib: TKI targeting VEGF-R2, c-MET, c-kit, Tie2, FLT-3, and RET	Recurrent	PR (50%) PS (50%)	N/A	Platinum-based chemotherapy +/- non-platinum based regimens (max 3 in total)

Table 1. Overview of included studies *(Continued)*

Richardson 2018	3	Chemotherapy + pazopanib (54)	Chemotherapy + placebo (52)	106	1:1	Pazopanib: TKI targeting VEGF-R, PDGF-R and c-kit	Recurrent	PR (51%) PS (49%)	N/A	Platinum-based chemotherapy +/- non-platinum based chemotherapy (max 3 in total)
TAPAZ 2022	3	Paclitaxel + pazopanib (79)	Paclitaxel (37)	116	2:1	Pazopanib: TKI targeting VEGF-R, PDGF-R and c-kit	Recurrent	PPS 70.7%; PR 29.3%	N/A	Not reported
TRINOVA-1 2016	8	Chemotherapy + trebananib (461)	Chemotherapy + placebo (458)	919	1:1	Trebananib: TKI targeting Ang1 and Ang2 (angiopoietins)	Recurrent	PR (53%) PS (47%)	N/A	Platinum-based chemotherapy +/- up to 2 other chemotherapy regimens +/- anti-angiogenic therapy
TRINOVA-2 2017	3	Chemotherapy + trebananib (114)	Chemotherapy + placebo (109)	223	1:1	Trebananib: TKI targeting Ang1 and Ang2 (angiopoietins)	Recurrent	PR (59%) PS (41%)	N/A	Platinum-based chemotherapy +/- up to 2 other chemotherapy regimens +/- anti-angiogenic therapy
Other										
GOG-0241 2019	3	Chemotherapy (two different regimes) + bevacizumab	Chemotherapy (two different regimes)	50	1:1:1:1	Bevacizumab: antibody against VEGF	Newly-diagnosed & recurrent. Mucinous EOC only	N/A	N/A	No previous chemotherapy
Zhao 2015	3	Intraperitoneal chemotherapy + bevacizumab (31)	Intraperitoneal chemotherapy (27)	58	1:1	Bevacizumab: antibody against VEGF	Unclear	Unclear	77.4% in intervention group; 77.8% in control group; overall 77.6%	Unclear

PPS: partially-platinum sensitive; **ALT:** alanine transaminase; **AMG386:** trebananib; **Ang1:** angiopoietin 1; **Ang2:** angiopoietin 2; **AST:** aspartate aminotransferase; **AUC:** area under the curve;**BIBF** : BIBF 1120 = nintedanib; ***BRCA*:** breast cancer gene; **CA125:** cancer antigen 125; **COX-2:** cyclo-oxygenase-2; **CT:**computed tomography; **CTCAE:** Common Terminology Criteria for Adverse Events; **ECOG:** Eastern Cooperative Oncology Group; **EOC:** epithelial ovarian cancer; **EORTC:** European Organisation for Research and Treatment of Cancer; **FACT/GOG NTX**: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity; **FACT-O (TOI):** Functional Assessment of Cancer Therapy-Ovarian (Trial Outcome Index); **FGF-R** : fibroblast growth factor receptor; **FIGO:** International Federation of Gynecology and Obstetrics; **FLT-3:** Fms-like receptor tyrosine kinase-3; **FOSI:** Functional Assessment of Cancer Therapy (FACT)/National Comprehensive Cancer Network (NCCN) Ovarian Symptom Index; **GCIG:** Gynecological Cancer InterGroup; **GFR**: glomerular filtration rate; **GOG:** Gynecologic Oncology Group; **HRD:** homologous recombination deficiency; **ICON**: International Collaborative Ovarian Neoplasm study; **IDS:** interval debulking surgery; **IQR:** interquartile range; **ITT:** intention-to-treat; **IV:** intravenous(ly); **IVRS/IWRS:** Interactive Voice Response System/ Interactive Web Response System; **KGOG**: Korean Gynecologic Oncology Group; **KPS:** Karnofsky Performance Status; **MET:** mesenchymal epithelial transition;**MRI:** magnetic resonance imaging; **NCI:** National Cancer Institute; **ORR:** objective response rate; **OS:** overall survival; **PARP:** poly(ADP-ribose) polymerase; **PARPi:** poly(ADP-ribose) polymerase inhibitor; **PDGF-R:** platelet-derived growth factor receptor; **PDGFR-α:** alpha subunit of PDGF-R; **PD-L1**: Programmed death-ligand 1; **PLB**: placebo; **PLD:** pegylated liposomal doxorubicin; **PFS:** progression-free survival; **PPS:** partially-platinum sensitive; **PR:** platinum-resistant; **PS:** platinum-sensitive; **QoL:** quality of life; **RAF:** Rapidly Accelerated Fibrosarcoma; **RECIST:** Response Evaluation Criteria in Solid Tumors; **RET:**REarranged during Transfection; **SWOG**: Southwest Oncology Group; **Tie2:** angiopoetin-1 receptor; **TKI:** tyrosine kinase inhibitor; **TNM:** tumour nodes metastases; **ULN:** upper limit of normal; **USS:** ultrasound scan; **VEGF:** vascular endothelial growth factor; **VEGF-R:** vascular endothelial growth factor receptor; **WHO:** World Health Organization

[+]ICON6 2021 486 randomised overall, of which 30 randomised to initial 30 mg dose of cediranib and excluded because of increased toxic effects, leaving 456.

APPENDICES

Appendix 1. MEDLINE search strategy

MEDLINE Ovid 1990 to October week 3, 2010

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. (animals not (humans and animals)).sh.
11. 9 not 10
12. ovar*.mp.
13. (cancer* or carcinoma* or neoplasm* or tumor* or tumour* or malignan*).mp.
14. 12 and 13
15. exp Ovarian Neoplasms/
16. 14 or 15
17. exp Angiogenesis Inhibitors/
18. exp Vascular Endothelial Growth Factors/
19. vascular endothelial growth factor*.mp.
20. (angiogenesis adj5 inhibit*).mp.
21. VEGF.mp.
22. (VEGFR or VEGF-R).mp.
23. exp Antibodies, Monoclonal/
24. monoclonal antibodies.mp.
25. (bevacizumab or avastin).mp.
26. (VEGF-Trap or aflibercept or AVE0005).mp.
27. exp Protein-Tyrosine Kinases/
28. (tyrosine kinase adj5 inhibit*).mp.
29. (sorafenib or nexavar or BAY 43-0006 or NSC724772).mp.
30. (cediranib or AZD2171 or recentin).mp.
31. (sunitinib or SU11248).mp.
32. (pazopanib or GW-786034).mp.
33. BIBF 1120.mp.
34. (imatinib mesylate or ST 1571 or gleevec).mp.
35. AEE788.mp.
36. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
37. 11 and 16 and 36

key: pt=publication type, ab=abstract, fs=floating subheading, mp=title, original title, abstract, name of substance word, subject heading word, sh=medical subject heading

Appendix 2. Embase search strategy

EMBASE Ovid 1990 to 2010, week 43

1. exp Controlled Clinical Trial/
2. randomized.ab.
3. placebo.ab.
4. dt.fs.

5. randomly.ab.
6. trial.ab.
7. groups.ab.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. (animal not (human and animal)).sh.
10. 8 not 9
11. (ovar* and (cancer* or carcinoma* or neoplas* or tumor* or tumour* or malignan*)).mp.
12. exp Ovary Tumor/
13. 11 or 12
14. exp Angiogenesis Inhibitor/
15. exp Vasculotropin/
16. vascular endothelial growth factor*.mp.
17. (angiogenesis adj5 inhibit*).mp.
18. VEGF.mp.
19. (VEGFR or VEGF-R).mp.
20. exp Monoclonal Antibody/
21. monoclonal antibodies.mp.
22. (bevacizumab or avastin).mp.
23. (VEGF-Trap or aflibercept or AVE0005).mp.
24. exp Protein Tyrosine Kinase/
25. (tyrosine kinase adj5 inhibit*).mp.
26. (sorafenib or nexavar or Bay 43-0006 or NSC724772).mp.
27. (cediranib or AZD2171 or recentin).mp.
28. (sunitinib or SU11248).mp.
29. (pazopanib or GW-786034).mp.
30. BIBF 1120.mp.
31. (imatinib mesylate or ST 1571 or gleevec).mp.
32. AEE788.mp.
33. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34. 10 and 13 and 33

key: mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name, ab=abstract, sh=subject heading, fs=floating subheading

Appendix 3. CENTRAL search strategy

CENTRAL Issue 10, November 2010

1. ovar* and (cancer* or carcinoma* or neoplasm* or tumor* or tumour* or malignan*)
2. MeSH descriptor Ovarian Neoplasms explode all trees
3. (#1 OR #2)
4. MeSH descriptor Angiogenesis Inhibitors explode all trees
5. MeSH descriptor Vascular Endothelial Growth Factors explode all trees
6. vascular endothelial growth factor*
7. angiogenesis near/5 inhibit*
8. VEGF
9. VEGFR or VEGF-R
10. MeSH descriptor Antibodies, Monoclonal explode all trees
11. monoclonal antibodies
12. bevacizumab or avastin
13. VEGF-Trap or aflibercept or AVE0005
14. MeSH descriptor Protein-Tyrosine Kinases explode all trees
15. tyrosine kinase near/5 inhibit*
16. sorafenib or nexavar or BAY 43-0006 or NSC724772

17.cediranib or AZD2171 or recentin
18.sunitinib or SU11248
19.pazopanib or GW-786034
20.BIBF 1120
21.imatinib mesylate or ST 1571 or gleevec
22.AEE788
23.(#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 ORhttp://www3.interscience.wiley.com/cochrane/searchHistory?mode=runquery&qnum=23#21 OR #22)
24.#3 and #23

Appendix 4. Search strategy for recent systematic reviews of angiogenesis inhibitors (Ovid MEDLINE and Embase)

1. All fields: Ovar*
2. All fields: (cancer* or carcinoma* or neoplasm* or tumor* or tumour* or malignan*)
3. 1 AND 2
4. Subject heading: Ovarian neoplasms
5. 3 OR 4
6. Subject heading: angiogenesis inhibitors
7. Subject heading: vascular endothelial growth factors
8. All fields: (angiogenesis adj5 inhibit*)
9. All fields: VEGF
10. All fields: VEGFR OR VEGF-R
11. Subject heading: Antibodies, monoclonal
12. All fields: monoclonal antibodies
13. All fields: bevacizumab OR Avastin
14. All fields: VEGF-Trap OR aflibercept OR AVE0005
15. Subject heading: Protein-Tyrosine Kinases
16. All fields: (tyrosine kinase adj5 inhibit*)
17. All fields: (sorafenib OR nexavar OR BAY 43-0006 OR NSC724772)
18. All fields: (cediranib OR AZD2171 OR recentin)
19. All fields: (sunitinib OR SU11248)
20. All fields: (pazopanib OR GW-786034)
21. All fields: (nintedanib OR BIBF 1120)
22. All fields: (imatinib OR ST 1571 OR Gleevec)
23. All fields: AEE788
24. All fields: brivanib
25. All fields: Cabozantinib
26. All fields: (vandetanib OR ZD6474)
27. All fields: (trebananib OR AMG386)
28. All fields: apatinib
29. All fields: celecoxib
30. 6 OR…29 [fields 6 to 29 combined with OR]
31. 5 AND 30
32. Year of Publication: 2020 OR 2021 OR 2022
33. 31 and 32
34. Publication type: systematic review
35. 33 and 34

WHAT'S NEW

Date	Event	Description
16 December 2022	Amended	2 additional studies included following further search

Date	Event	Description
15 November 2022	New citation required and conclusions have changed	Review updated; conclusions changed
10 October 2022	New search has been performed	43 new studies included

HISTORY

Protocol first published: Issue 3, 2009
Review first published: Issue 9, 2011

CONTRIBUTIONS OF AUTHORS

The original protocol was written by JM and KG, with significant input from Heather Dickinson, Andy Bryant (AB) and Shibani Nicum (SN). Sean Kehoe (SK) and JM had the initial concept for the title and approved the final version of the protocol. KG, SP, YC and JM analysed the results of the searches and contacted regulatory bodies, pharmaceutical companies and authors/investigators of relevant completed and ongoing trials for further information. KG, Igor Martinek (IM), JM and AB wrote the previous version of the review.

For this update, the contributions were as follows:

Search sift and full-text review: KG, SP, YC, MAEA and JM

Data extraction: KG, SP, YC, MAEA, ER, AT, JM

Data analysis: ER, KG, JM

Writing of final version of the review: KG, ER, JM

Approval of final version of the review: KG, SP, ER, YC, MAEA, AT, JM

DECLARATIONS OF INTEREST

Kezia Gaitskell: none known
Ewelina Rogozińska: none known
Sarah Platt: none known
Yifan Chen: none known
Abigail Tattersall: none known
Mohamed Abd El Aziz: none known
Jo Morrison: none known

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Internal sources

- National Institute for Health and Care Research (NIHR) Cochrane Review Group (CRG) Infrastructure funding, UK

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External sources

- External sources of support, Other

  No external sources of support

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The following methodological changes were made a priori for this update of the review, compared to the original protocol and previous review. Since the original protocol was written, there have been a number of developments in this field, and angiogenesis inhibitors are now used as standard of care for selected patients in some settings. We therefore planned to include studies that contained the following comparisons in this update of the review as a pre-planned analysis.

- Angiogenesis inhibitors plus conventional chemotherapy versus conventional chemotherapy (including those where the angiogenesis inhibitor is continued as maintenance after chemotherapy).
- Angiogenesis inhibitors versus no treatment (e.g. in a maintenance setting).
- Angiogenesis inhibitor 1 versus angiogenesis inhibitor 2, with either chemotherapy in each arm or no other treatment.
- Chemotherapy plus angiogenesis inhibitor 1 versus chemotherapy plus angiogenesis inhibitor 1 plus angiogenesis inhibitor 2.
- Angiogenesis inhibitor versus alternative chemotherapy.

In the original version of the review, we did not specify a minimum number of participants. In this version of the review, we specified a minimum of 10 participants for a study to be included, as studies smaller than this were unlikely to be of high quality, in line with other review methodology.

In the original version of the review, as we expected to find few trials, we did not plan any subgroup analyses. However, in this update, due to the significant number of clinical trials in this area and importance of different clinical scenarios, we considered setting of treatment; namely, newly-diagnosed EOC and recurrent disease, subdivided by platinum-sensitivity, as pre-planned analyses.

In comparison to the previous version of the review, our main approach to meta-analysis was by fitting a fixed-effect rather than random-effects model. This was based on an assumption that the drugs within the individual comparisons are estimating a common treatment effect. We applied a random-effects model only in comparisons where we incorporated trials with individuals with recurrent EOC regardless of platinum-sensitivity status. Further changes in our methodological approach are as follows.

- In case of non-proportionality of hazards (reported or visible on Kaplan Meier curve), we decided to still use hazard ratio as a measure of effect if reported, but acknowledge its limitations.
- For toxicity, we focused on twelve outcomes of a specific grade level (for details, see Methods), rather than a previously specified approach. Where possible, adverse events are 'any reported' side effects rather than treatment-related.

We had originally planned that grades of toxicity would be extracted and grouped as follows (CTEP 2006):

- haematological (leucopenia, anaemia, thrombocytopenia, neutropenia, haemorrhage);
- gastrointestinal (nausea, vomiting, anorexia, diarrhoea, liver, proctitis);
- genitourinary;
- skin (stomatitis, mucositis, alopecia, allergy);
- neurological (peripheral and central); and
- other side effects not categorised above.

As another a priori change, we adapted the adverse events for this update, based on the outcomes that were reported by the studies identified in the original version of this review, as follows:

- any severe adverse event (G3+);
- hypertension (G2+);
- proteinuria (G2+);
- pain (G2+);
- abdominal pain (G2+);
- neutropenia (G3+);
- febrile neutropenia (any grade);
- venous thromboembolic event (any grade);
- arterial thromboembolic event (any grade);
- non-central nervous system bleeding (G3+);
- gastrointestinal adverse events (G2+);
- bowel fistula or perforation (G3+).

For definitions of the grading, please see academy.myeloma.org.uk/wp-content/uploads/2015/04/CTCAE_v5.pdf. Other differences between the original protocol and previous version of the review are detailed in the previous version of the review (Gaitskell 2011).

INDEX TERMS

Medical Subject Headings (MeSH)

Angiogenesis Inhibitors [adverse effects] [*therapeutic use]; Antibodies, Monoclonal [adverse effects] [therapeutic use]; Antibodies, Monoclonal, Humanized; Antineoplastic Agents [therapeutic use]; Bevacizumab; Indoles [therapeutic use]; Neovascularization,

Pathologic [*drug therapy]; Ovarian Neoplasms [*blood supply] [drug therapy]; Paclitaxel [therapeutic use]; Recombinant Fusion Proteins [adverse effects] [therapeutic use]; Survival Analysis

MeSH check words

Female; Humans