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

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## TABLE OF CONTENTS

[Intervention Review]

# Angiogenesis inhibitors for the treatment of ovarian cancer

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## ABSTRACT

### Background

Many women with ovarian cancer eventually develop resistance to conventional chemotherapy drugs, and so novel agents are being developed to target specific molecular pathways. One such class of drugs inhibits angiogenesis (the development of new blood vessels), which is essential for tumour growth. It is important to establish whether the addition of these new drugs to conventional chemotherapy regimens improves survival, and what the side-effects may be.

### Objectives

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

### Search methods

We sought to identify completed randomised controlled trials (RCTs) by searching The Cochrane Gynaecological Cancer Review Group's Trial Register, The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 10), MEDLINE and EMBASE (1990 to October 2010). We also searched registers of clinical trials, and contacted investigators of completed and ongoing trials for further information.

### Selection criteria

Randomised controlled studies comparing angiogenesis inhibitors with either standard chemotherapy or no treatment, in women with ovarian cancer.

### Data collection and analysis

Two independent authors carried out data collection and extraction. We used a random-effects model for pooling data.

### Main results

We did not find any fully-published, completed RCTs of angiogenesis inhibitors that met our inclusion criteria. We identified five abstracts of completed RCTs of four different angiogenesis-inhibiting agents, with a total of 3701 participants.

Meta-analysis of two trials found no statistically significant difference in overall survival (OS) between women with newly-diagnosed advanced ovarian cancer who received concurrent and maintenance bevacizumab compared to those who received chemotherapy

(carboplatin and paclitaxel) alone. However, women who received concurrent and maintenance bevacizumab had their risk of disease progression reduced by a quarter (hazard ratio (HR) 0.75, 95% confidence interval (CI) 0.68 to 0.83; P < 0.001); they also had a significantly increased risk of severe gastrointestinal adverse events, moderate or severe hypertension and severe bleeding.

One trial also compared chemotherapy to concurrent (but not maintenance bevacizumab), and found no statistically significant difference in OS or progression-free survival (PFS). However, the women who received bevacizumab had a significantly higher risk of moderate or severe hypertension.

A three-armed RCT, of paclitaxel alone or with low- or high-dose AMG 386, in women with recurrent ovarian cancer, found no statistically significant difference in OS. However, women who received low-dose AMG 386 had a third less risk of disease progression than those who received placebo (HR 0.57, 95% CI 0.36 to 0.91; P = 0.02). The trial found no evidence of increased adverse events in the intervention arms.

Two relatively small RCTs (one of VEGF-Trap, the other of BIBF 1120) found no evidence of either significant survival benefit or increased severe adverse events, compared to placebo, but they both lacked statistical power.

All five trials had unclear risk of bias, largely because they have only been published in abstract form, and thus many methodological details are unclear. We identified twelve suitable ongoing trials.

**Authors' conclusions**

There is, as yet, no fully-published RCT evidence for the efficacy or safety of angiogenesis inhibitors for the treatment of ovarian cancer, but some preliminary results are available from five trials. There is some evidence from a meta-analysis of two trials that the addition of concurrent and maintenance bevacizumab to standard chemotherapy may reduce the risk of disease progression, in women with newly-diagnosed advanced ovarian cancer. There is also some evidence from a single trial that low-dose AMG 386 may reduce the risk of disease progression in women with recurrent ovarian cancer. However, there is currently no evidence that angiogenesis inhibitors improve OS, nor is there enough evidence to justify the routine use of angiogenesis inhibitors in treating women with ovarian cancer. We eagerly await both the more detailed results of these five completed trials, and the preliminary results of the several ongoing trials.

## PLAIN LANGUAGE SUMMARY

**Are substances that inhibit the growth of new blood vessels (angiogenesis inhibitors), alone or in combination with conventional chemotherapy, likely to improve outcomes for women with ovarian cancer?**

Ovarian cancer is the seventh most common cancer in women worldwide, with an annual incidence of about 6.3 cases per 100,000 women, and an annual mortality rate of 3.8 per 100,000 women. Standard treatment of advanced ovarian cancer usually involves surgery, to remove as much of the cancer as possible ('debulking'), and platinum-based chemotherapy, with or without the addition of a taxane. However, despite good initial responses to platinum agents and taxanes, most women have disease relapse, require further treatment with chemotherapy, and eventually develop resistance to conventional chemotherapy drugs.

Many researchers are trying to find new drugs, which target different pathways, in order to treat ovarian cancer that has become resistant to standard chemotherapy. One target is the pathway for angiogenesis: the growth of new blood vessels. Although new blood vessels can form as part of the body's normal processes, cancers are especially reliant on angiogenesis, as they need a blood supply in order to grow. It is hoped that drugs that act to inhibit the growth of new blood vessels will slow or stop the progression of the cancer.

In this review we found evidence from five studies, comparing drugs which inhibit angiogenesis against either standard chemotherapy (carboplatin + paclitaxel) or placebo.

Two trials looked at the effect of adding bevacizumab to conventional chemotherapy in women who had just been diagnosed with ovarian cancer and had debulking surgery. Bevacizumab was given both alongside the chemotherapy, and then continued afterwards (called maintenance therapy). Taking the results of these two trials together, there was no significant benefit from adding bevacizumab to standard chemotherapy in terms of survival time, but there was fairly strong evidence that it might slow the growth of the cancer (increased progression-free survival (PFS)). However, the trials also showed that there were worse side effects in women who received bevacizumab in addition to chemotherapy (particularly high blood pressure, serious bowel problems and bleeding). One of these two trials also looked at the effect of giving bevacizumab concurrently with chemotherapy (not continuing afterwards), and found no significant improvement in either survival time or slowing cancer growth, but did find a significant increase in moderate and severe high blood pressure (hypertension).

A third trial looked at adding a different agent, AMG 386, to paclitaxel chemotherapy in women with recurrent ovarian cancer. The trial compared the addition of either a higher or lower dose of AMG 386 to placebo. It found no improvement in survival with either the higher or lower dose of AMG 386, but there were suggestions that it might slow cancer growth. It did not seem to increase side effects.

We identified two other trials; one comparing placebo to BIBF 1120, and the other comparing placebo to VEGF (vascular endothelial growth factor)-Trap. Neither study found evidence of slowing cancer growth/prolonging survival, or worsening side effects. However, these were both relatively small studies, which made them less likely to detect an effect that may or may not have been present.

All of the included trials that we identified reported only preliminary results, which had been presented at conferences, but not yet published in full. It is thus difficult to be sure of the specific details of how these trials were performed, and therefore to assess their risk of bias. We found 12 other on-going studies that fulfilled our inclusion criteria, and some of these are expected to release preliminary results soon.

# BACKGROUND

## Description of the condition

Each year, worldwide, nearly 225,000 women are diagnosed with ovarian cancer and over 140,000 die, corresponding to an annual age-standardised incidence of 6.3 cases per 100,000 women, an annual mortality rate of 3.8 deaths per 100,000, and a cumulative lifetime risk of 0.68% (GLOBOCAN 2008). In terms of both incidence and mortality, it is the seventh most common cancer in women. The onset is often insidious; the symptoms are vague and may mimic other conditions. This may lead to a delay in diagnosis, and currently three-quarters of women with ovarian cancer are diagnosed when the disease has spread throughout the abdomen (stage III or IV) (Shepherd 1989) when the five-year survival rate is 20% to 30% (Jemal 2008). Epithelial ovarian cancer, which arises from the surface of the ovary, 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).

## Description of the intervention

Management of advanced ovarian cancer consists of debulking surgery, and platinum-based chemotherapy, with or without the addition of a taxane (Morrison 2007; Stewart 1999). A recent RCT found that there was no difference in survival, if surgery was performed before or after the first three cycles of chemotherapy (Vergote 2010). However, in women presenting with advanced disease, there has been little change to the five-year survival rate for stage III to IV of the disease over the past 20 to 30 years (Engel 2002). Despite good initial response to platinum agents and taxanes, most women have disease 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 lead 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.

## How the intervention might work

### Angiogenesis and ovarian cancer

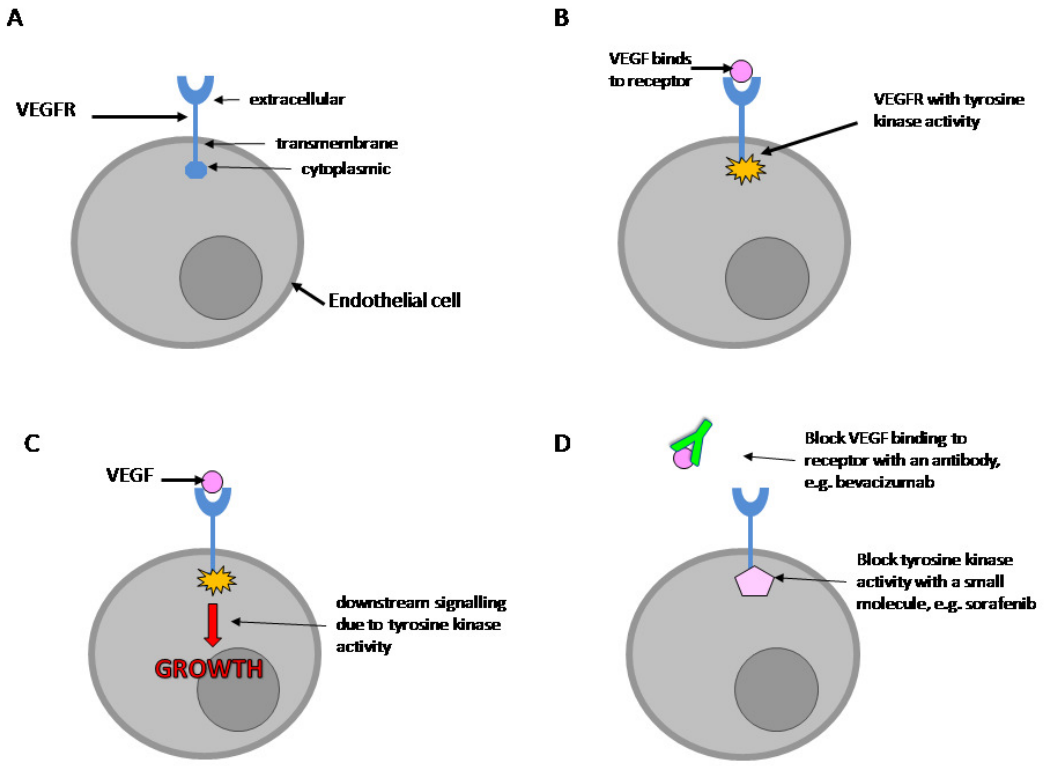
Angiogenesis is the development of new blood vessels. Once a tumour deposit is larger than 1 mm in diameter it cannot receive adequate nutrients or oxygen from surrounding tissues by diffusion alone and it must then stimulate new blood vessel formation to support further growth. Angiogenesis is a vital 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 patients 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).

**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 tyrosine kinase inhibitors

Small molecule inhibitors of VEGF-R tyrosine kinase have been developed and investigated in clinical trials. One advantage of these compounds is that many are orally active.

AZD2171 (cediranib or Recentin$^{TM}$ Astra Zeneca) is a small molecule inhibitor of VEGF-R that has demonstrated benefit in preclinical studies (Wedge 2005). Phase II studies have also shown that AZD2171 is an active drug in patients with recurrent ovarian cancer (Hirte 2008; Matulonis 2008). The most frequent side effects were tiredness, diarrhoea, hypertension and anorexia. A large multicentre phase III study (ICON6: NCT00532194) is evaluating the role of AZD2171 in patients with recurrent platinum-sensitive ovarian cancer.

Pazopanib is a potent selective receptor tyrosine kinase inhibitor of VEGF-R, PDGF-R (platelet derived growth factor receptor) and c-kit that blocks tumour growth and inhibits angiogenesis. It has shown biological activity in patients with CA125-positive recurrent ovarian cancer after primary platinum-based therapy ( Friedlander 2010).

BIBF 1120 is an oral, small molecule, triple angiokinase inhibitor, targeting VEGF-R, FGF-R (fibroblast growth factor receptor) and PDGF-R. A recent phase II study has evaluated its use in maintenance of post-relapse remission in patients who responded to second, third or fourth line chemotherapy (Ledermann 2009).

Sorafenib [*N*-(3-trifluoromethyl-4-chlorophenyl)-*N'*-(4-(2-mehtylcarbamoyl pyridin-4-yl) oxyphenyl) urea; BAY 43-9006/ Nexavar] is a tyrosine kinase inhibitor that directly inhibits VEGF-R in addition to other angiogenic and growth stimulatory pathways (via Raf kinase inhibition) (Mross 2007; Siu 2006). Activity has been demonstrated against ovarian cancer in early clinical trials for pre-treated relapsed disease (Siu 2006) and its role in first-line treatment for ovarian cancer is under evaluation (Hainsworth 2010).

Sunitinib (SU11248) is a VEGF-R tyrosine kinase inhibitor and is being tested for activity in women with relapsed ovarian cancer in a non-randomised, non-blinded, multicentre phase II trial ( Buckstein 2007).

### 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. 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 and 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 (Burger 2010 (GOG-0218)) and the ICON 7 (Perren 2010 (ICON7)) study. These trials are also assessing the role of bevacizumab in the maintenance treatment of these patients.

## 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, it may be possible to use these newer treatments in patients who are not currently taking chemotherapy (so called maintenance treatment), to reduce the chance of, or delay, the recurrence of their ovarian cancer.

# OBJECTIVES

To compare the effectiveness and toxicities of angiogenesis inhibitors in the treatment of 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.

### Types of participants

Adult women with histologically proven ovarian cancer. Women with other concurrent malignancies were excluded.

### Types of interventions

- Angiogenesis inhibitors + conventional chemotherapy versus conventional chemotherapy.
- Angiogenesis inhibitors versus no treatment.

### Types of outcome measures

#### Primary outcomes

Overall survival (OS): survival until death from all causes.

#### Secondary outcomes

1. Progression-free survival (PFS).
2. Quality of life (QoL), measured by a validated scale.
3. Toxicity; grades of toxicity were extracted and grouped (CTEP 2006) as follows:
    - 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.

## Search methods for identification of studies

We sought papers in all languages but no translations were necessary.

### Electronic searches

See: Cochrane Gynaecological Cancer Group methods used in reviews.

We searched the following electronic databases.

- The Cochrane Gynaecological Cancer Review Group's Trial Register.
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 10).
- MEDLINE up to October 2010.
- EMBASE up to October 2010.

The MEDLINE, EMBASE and CENTRAL search strategies based on terms related to the review topic are presented in Appendix 1, Appendix 2 and Appendix 3 respectively.

We searched databases from 1990 to October 2010. These novel agents have been developed recently and so searches before 1990 would not have been relevant.

We had planned that all relevant articles found would have been identified on PubMed and, using the 'related articles' feature, we would have carried out a further search for newly published articles. However, all included trials in this review have thus far only been published in the form of conference abstracts, which were not identifiable on PubMed.

### Searching other resources

We searched the Physicians Data Query, www.controlled-trials.com/rct, www.clinicaltrials.gov, www.cancer.gov/clinicaltrials and the National Research Register (NRR) for ongoing trials. 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) and 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.

As all included trials were reported in abstract form or data were obtained from conference presentations or by contacting trialists, we could not search reference lists of included trials for further relevant trials as specified in the protocol.

#### 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

We downloaded all titles and abstracts retrieved by electronic searching to the reference management database *Endnote*, removed duplicates and two review authors (KG, IM) independently examined the remaining references. We excluded those studies which clearly did not meet the inclusion criteria and obtained copies of the full text of potentially relevant references. Two review authors (KG, IM) independently assessed the eligibility of retrieved papers.. We resolved disagreements by discussion between the two review authors and when necessary by a third review author (JM or SN). We documented 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

- Patient characteristics
  - Age
  - Co-morbidities
  - Previous treatment
- Total study duration
- Total number of intervention groups
- Ovarian cancer details at diagnosis
  - FIGO stage
  - 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 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 Parmar 1998.
- For dichotomous outcomes (e.g. toxicity), we extracted the number of patients in each treatment arm who experienced the outcome of interest and the number of patients assessed at endpoint, in order to estimate a risk ratio (RR).

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 groups to which they were assigned.

We noted the time points at which outcomes were collected and reported.

Two review authors (KG and JM, rather than KG and IM, as in the protocol) 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 (IM or SN) when necessary.

### Assessment of risk of bias in included studies

We assessed the risk of bias in included RCTs using the Cochrane Collaboration's tool. This included assessment of the following.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data: 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 patients 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 patients 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.
- Other possible sources of bias.

Two review authors (JM, KG) independently applied the risk of bias tool and resolved differences by discussion or by appeal to a third review author (SK or HD). 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 the following measures of the effect of treatment.

- For time-to-event data, we used the HR.
- For dichotomous outcomes, we used the RR.

If adjusted results were available, they were preferred; otherwise we used unadjusted results.

### Dealing with missing data

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

### Assessment of heterogeneity

We assessed heterogeneity between studies by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials which cannot be ascribed to sampling variation (Higgins

2003) and by a formal statistical test of the significance of the heterogeneity (Deeks 2001). If there was evidence of substantial heterogeneity, we investigated and reported the possible reasons for this.

### Data synthesis

If sufficient, clinically similar trials were available, we pooled their results in meta-analyses.

- For time-to-event data, we pooled HRs using the generic inverse variance facility of RevMan 5.
- For any dichotomous outcomes, we calculated the RR for each study and then pooled these.

We used random-effects models with inverse variance weighting for all meta-analyses (DerSimonian 1986).

The Burger 2010 (GOG-0218) trial had multiple treatment groups (three-arm trial), and so we divided the control group between the treatment groups, and treated comparisons between each treatment group and a split control group as independent comparisons for all adverse event outcomes. This was not necessary for OS as we obtained HR estimates from a Cox regression model.

### Subgroup analysis and investigation of heterogeneity

As we expected to find few trials, we did not plan any subgroup analyses. However, in the interpretation of heterogeneity we considered factors such as type of intervention (e.g. use as early stage consolidation therapy in chemo-sensitive cancers or use in late stage chemo-resistant cancers) and stage of disease.

## RESULTS

## Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

### Results of the search

From the main search strategy we found 4248 unique references (after we had removed most duplicates); two review authors (IM and KG) independently examined these abstracts. We identified 14 studies as potentially eligible for this review from the title and abstract screening of these references. We excluded seven of these studies after obtaining the full text, for the reasons described in the Excluded studies section. Four of the references were conference abstracts that described RCTs that fulfilled our criteria. Three of these were studies that had completed primary data collection (Burger 2010 (GOG-0218); Karlan 2010; Ledermann 2009). One study was still ongoing at the time of finding the most recent abstract using our search strategy (Mazur 2006, subsidiary reference to Perren 2010 (ICON7)); however, further handsearching and contacting of investigators identified that results had recently been reported at a conference (Perren 2010 (ICON7)). Through searching clinical trial databases we identified a fifth completed RCT; we contacted the investigators who revealed that this had been presented and published as a conference abstract (Vergote 2009), and will be published in full shortly. Three references were to ongoing trials, two of which should be suitable for inclusion when completed (Hainsworth 2010; McGuire 2010), and one of which is awaiting classification (Gordon 2010).

We searched clinical trial databases for ongoing studies and identified 10 further ongoing RCTs that should be suitable for inclusion when completed (some of these studies have now completed early outcomes, and will publish preliminary results shortly, e.g. OCEANS: NCT00434642). We identified another six ongoing trials which we considered for inclusion, but then excluded for the reasons described in the Excluded studies section.

### Included studies

We included five RCTs published in abstract form (Burger 2010 (GOG-0218); Karlan 2010; Ledermann 2009; Perren 2010 (ICON7); Vergote 2009) (with results reported at recent conferences), as they met the inclusion criteria.

Burger 2010 (GOG-0218) was a randomised, double-blind, placebo-controlled, phase III study of bevacizumab in 1873 women with newly-diagnosed epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer. All women were within 1 to 12 weeks of initial debulking surgery, and had stage III-IV disease, with a Gynecologic Oncology Group (GOG) performance status of zero to two. It was a three-armed study, comparing chemotherapy (carboplatin and paclitaxel) plus placebo (arm one = 625 women), versus chemotherapy plus concurrent bevacizumab (arm two = 625 women), versus chemotherapy plus concurrent and maintenance bevacizumab (arm three = 623 women). All women received paclitaxel 175 mg/m$^2$ + carboplatin AUC 6 (AUC = area under the curve) for cycles one to six; women in arm one also received placebo for cycles 2 to 22; women in arm two received bevacizumab 15 mg/kg concurrently with the chemotherapy for cycles two to six, and then placebo for cycles 7 to22; women in arm three received concurrent bevacizumab for cycles two to six, and then maintenance bevacizumab for cycles 7 to 22. The median age in each arm was 60 years. Six hundred and thirty-nine (34%) patients had stage III disease with optimal surgical cytoreduction; 752 (40%) patients had stage III with suboptimal cytoreduction and 482 (26%) had stage IV disease. The primary outcome was PFS; secondary outcomes included OS, safety, QoL and correlative laboratory studies. Preliminary results for PFS, OS and adverse events have been published in conference abstracts and presentations (events had been observed in 24% of

patients at time of data lock). The median length of follow-up (for reported data thus far) was 17.4 months (range 0.0-50.7 months). Randomisation (and hence also analysis) was stratified by GOG performance status and by stage/debulking status.

Perren 2010 (ICON7) was a randomised, open-label, phase III study of bevacizumab (given both concurrently with chemotherapy, and then as maintenance therapy), versus chemotherapy alone, in 1528 women with newly-diagnosed epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer. Women in both study arms received carboplatin AUC6 and paclitaxel 175 mg/m$^2$ once every three weeks for up to six cycles; those in the intervention arm additionally received bevacizumab 7.5 mg/kg once every three weeks, for up to a total of 18 cycles (six cycles with chemotherapy, plus a further 12 cycles). One thousand three hundred and forty (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. One hundred and forty-two (9%) women had FIGO stage I/IIA disease, 315 (21%) had stage IIB to IIIB and 1071 (70%) had stage IIIC/IV disease. The median age was 57 years in both groups. The primary outcome was PFS, defined by Response Evaluation Criteria In Solid Tumors (RECIST) guidelines on radiological, clinical or symptomatic progression. Secondary outcomes included OS, response rate, duration of response and toxicity (with sub-studies planned on QoL, health economics and translation/biomarker research). The median length of follow-up (for data reported thus far) was 19.4 months. Although full results on OS will not be available until 2012, preliminary results on PFS, OS and adverse events have been published as conference abstracts and presentations.

Karlan 2010 was a randomised, double-blind, placebo-controlled, phase II study of AMG 386, an anti-angiopoietin peptibody, which acts to inhibit angiogenesis by interfering with the interaction between angiopoietin-1 and angiopoietin-2 with the Tie-2 receptor (Neal 2010). The trial involved 161 women with recurrent epithelial ovarian cancer (FIGO stage II-IV), or fallopian tube or primary peritoneal cancer, and was a three-armed comparison of paclitaxel chemotherapy with a higher versus lower dose of AMG 386, versus placebo. All women received paclitaxel at 80 mg/m$^2$ once weekly QW (QW = three weeks on/one week off); women in arm A (n=53) also received AMG 386 at 10 mg/kg QW (higher dose); women in arm B (n=53) received AMG 386 at 3 mg/kg QW (lower dose); and women in arm C (n=55) received placebo QW. All patients had radiographically-documented progression, as judged by RECIST or CA125 (GCIG (Gynecologic Cancer InterGroup) criteria), and $\leq$ 3 anti-cancer therapies (but at least one platinum-containing regimen). One hundred and fifty-one (99%) women had a GOG performance status of zero or one. One hundred and thirty-seven (85%) women had ovarian cancer; 21 (13%) women had primary peritoneal cancer; and three (2%) women had fallopian tube cancer. 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. The primary outcome was PFS; secondary outcomes included response as per RECIST, CA125 response, safety and pharmacokinetics. The median length of follow-up (for data reported thus far) was 66.1 weeks in arm A, 65.1 weeks in arm B and 64.4 weeks in arm C. Randomisation (and hence also analysis) was stratified by whether or not women had previously had disease progression within six months of the last chemotherapy regimen, and on whether or not they had had prior anti-VEGF therapy. Preliminary results for PFS, OS and adverse events have been published as conference abstracts and presentations.

Ledermann 2009 was a randomised, double-blind, placebo-controlled, phase II trial to assess the effectiveness of BIBF 1120 versus placebo as a maintenance therapy in women with chemotherapy-responsive relapsed ovarian cancer (or fallopian tube or primary peritoneal cancer). Eighty-four women were recruited: 44 were given oral BIBF 1120 at a dose of 250 mg twice daily for a period of up to nine months; 40 were given placebo. The mean age of participants was 60 years (range 27 to 76 years). The primary outcome was PFS at 36 weeks, as confirmed by CT scan (performed at 12-week intervals). Secondary outcomes included: time to tumour progression (according to RECIST criteria and CA125), PFS at three and six months, OS and incidence/intensity of adverse events at 9 months.

Vergote 2009 was a randomised, double-blind, placebo-controlled trial of VEGF-Trap versus placebo in 55 women with chemotherapy-resistant advanced epithelial ovarian cancer. [VEGF-Trap, also known as aflibercept, is a decoy receptor for VEGF. It is a fusion protein, combining the constant region of immunoglobulin IgG1 with the ligand-binding domains of VEGF receptors; it thus can bind to VEGF, preventing it binding to the VEGF-receptors in the body, and hence inhibiting angiogenesis (Aflibercept 2008)]. Women were only included in the study if they also had recurrent malignant ascites (a collection of fluid in the abdominal cavity, which occurs in some women as a result of ovarian cancer). The primary aim of the study was to see whether VEGF-Trap could reduce the need for paracentesis (the procedure for draining the ascitic fluid), which is not one of the pre-specified outcomes of interest for this review. However, some of the secondary outcomes for this study are relevant to the scope of this review (e.g. OS, adverse events and QoL). Thus, we have included this study, but have only reported and discussed these specific outcomes (i.e. not the paracentesis-related outcomes). Women in the intervention arm received VEGF-Trap IV, at a dose of 4 mg/kg every two weeks; those in the control arm received placebo. The median age was 56 years (range 33 to 88 years). Eighty-four per cent of women had an ECOG Performance Status of one to two. Participants had tried a median of four prior lines of chemotherapy (range 2 to 11). All five of these completed RCTs have published summaries of their methods and main results in abstract form, as presented at conferences. We have discussed their results below, as they represent the current best available data. However, any analysis is pro-

visional, as further details of methods and results are needed.

### Excluded studies

Fron the search strategy we identified seven potentially relevant references, which we later excluded after obtaining the full text, for the following reasons.

- One study (Tew 2007) was a report of preliminary data from a phase II, randomised, double-blind trial comparing two different doses of VEGF-Trap (2 vs 4 mg/kg) in women with recurrent platinum-resistant epithelial ovarian cancer. As detailed in the study protocol (found by searching the clinical trials databases, and included as a supplementary reference), the outcome data for the two treatment arms will be compared to historical controls. [The full results will be published later this year].
- Two references (Burger 2010; Markman 2009) were narrative review articles, and did not include any completed or ongoing studies that met our criteria, and which had not already been identified by our other search methods.
- One reference (Azad 2008) was a conference abstract, describing a phase I dose-finding study of sorafenib and bevacizumab for patients with multiple tumour types, and emphasising the results for the 15 patients with ovarian cancer; there was no control group.
- Two references were to a single article (Osterweil 2010; two linked references), which discussed the results of one of the main included studies (Burger 2010 (GOG-0218)).
- One reference (Sennino 2010) was an article commenting on another study, which compared the activity of bevacizumab to an inhibitor of PDGF-beta in mouse-based models of ovarian cancer.

From our search of the clinical trials databases, we identified six ongoing trials which, although randomised studies of angiogenesis inhibitors in ovarian cancer, did not fulfil our inclusion criteria, and so we excluded them for the following reasons.

- Two studies (NCT00017303; NCT00543049) involved patients being randomised to different dosage schedules of an angiogenesis inhibitor (i.e. with no control group).
- In three ongoing studies (NCT00096200; NCT00886691; NCT01115829) patients were randomised to an angiogenesis inhibitor with or without another agent (as opposed to standard therapy with vs without an angiogenesis inhibitor), so that patients in all trial arms received the angiogenesis inhibitor.
- One ongoing study (NCT01167712) randomised women to one of two different dosage schedules of cytotoxic chemotherapy; although patients in both randomisation arms could also be treated with bevacizumab, the allocation of bevacizumab was made by patient choice, rather than randomisation.

### Risk of bias in included studies

All five included trials (Burger 2010 (GOG-0218); Karlan 2010; Ledermann 2009; Perren 2010 (ICON7); Vergote 2009) have thus far been published only as conference abstracts, so we lacked sufficient information to make an accurate assessment of each trial's quality. In some cases, we were able to obtain access to the PowerPoint slides or poster from the original conference presentation, which provided further detail, but obviously still not as much as would normally appear in a full published paper. Consequently, all five trials had 'unclear' risk of bias: only the trial of Burger 2010 (GOG-0218) satisfied one of the criteria that we used to assess risk of bias. It was 'unclear' in all six risk of bias items in the other four trials and in five of the six in the Burger 2010 (GOG-0218) trial, which assessed a satisfactory proportion of women who had been randomised, at the end of the trial (see Figure 2; Figure 3). When these trials are published in full text we will update the review and make a thorough assessment of risk of bias.

**Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.**

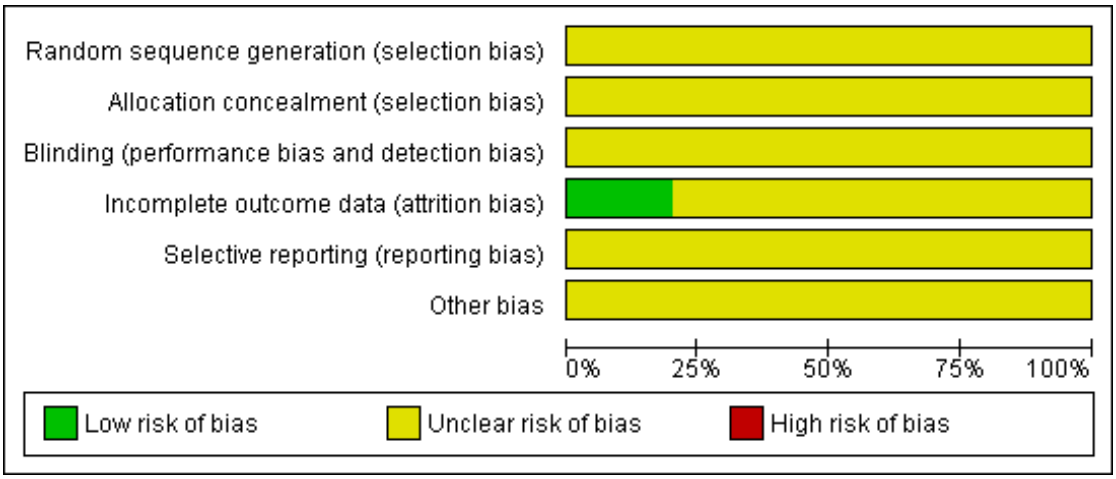
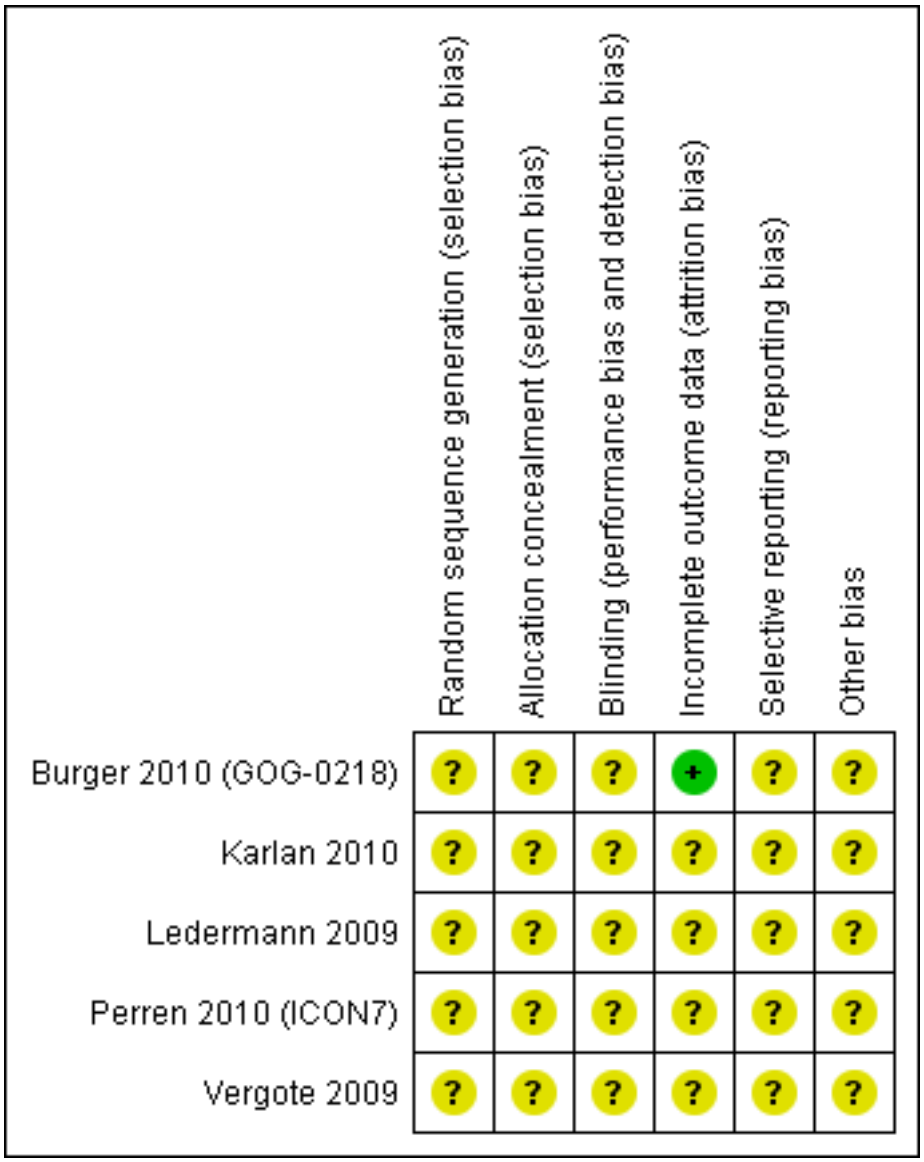


**Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**



## Effects of interventions

For dichotomous outcomes, we were unable to estimate a RR if one or both of the treatment groups experienced no events.

### Overall survival (OS)

**Chemotherapy + concurrent bevacizumab + maintenance placebo versus chemotherapy + concurrent and maintenance placebo**

(See Analysis 1.1)

The trial of Burger 2010 (GOG-0218) found no statistically significant difference in the risk of death in women who received concurrent bevacizumab and maintenance placebo in addition to chemotherapy and those who received concurrent and maintenance placebo in addition to their chemotherapy (HR 1.04, 95% CI 0.83 to 1.30).

**Chemotherapy + concurrent and maintenance bevacizumab versus chemotherapy +/- placebo**

(See Analysis 2.1)

Meta-analysis of two trials (Burger 2010 (GOG-0218); Perren 2010 (ICON7)) found no statistically significant difference in the risk of death in women who received concurrent bevacizumab and maintenance bevacizumab in addition to chemotherapy and those who received concurrent and maintenance placebo or no further treatment in addition to their chemotherapy (HR 0.87, 95% CI 0.73 to 1.03). The percentage of the variability in effect estimates that was due to heterogeneity between studies rather than sampling error (chance) was not important ($I^2$ = 0%).

**Chemotherapy + AMG 386 at 10 mg/kg (high dose) versus chemotherapy + placebo**

(See Analysis 3.1)

In the Karlan 2010 trial, women who received high dose AMG 386 in addition to chemotherapy had in excess of a third-less risk of death compared to women receiving placebo in addition to their chemotherapy, but this difference was not statistically significant (HR 0.60, 95% CI 0.34 to 1.06).

**Chemotherapy + AMG 386 at 3 mg/kg (low dose) versus chemotherapy + placebo**

(See Analysis 4.1)

In the Karlan 2010 trial, women who received low dose AMG 386 in addition to chemotherapy had just over a quarter-less risk of death compared to women receiving placebo in addition to their chemotherapy, but this difference was not statistically significant (HR 0.77, 95% CI 0.45 to 1.31).

**VEGF-Trap versus placebo**

(See Analysis 6.1)

The trial of Vergote 2009 found no statistically significant difference in the risk of death in women who received VEGF-Trap compared to those who received placebo (HR 1.02, 95% CI 0.56 to 1.86).

### Progression-free survival (PFS)

**Chemotherapy + concurrent bevacizumab + maintenance placebo versus chemotherapy + concurrent and maintenance placebo**

(See Analysis 1.2)

The trial of Burger 2010 (GOG-0218) found no statistically significant difference in the risk of disease progression in women who received concurrent bevacizumab and maintenance placebo in addition to chemotherapy and those who received concurrent and maintenance placebo in addition to their chemotherapy, (HR 0.91, 95% CI 0.79 to 1.04).

**Chemotherapy + concurrent and maintenance bevacizumab versus chemotherapy alone +/- placebo**

(See Analysis 2.2)

Meta analysis of two trials (Burger 2010 (GOG-0218); Perren 2010 (ICON7)) found that women who received concurrent bevacizumab and maintenance bevacizumab in addition to chemotherapy had significantly lower risk of disease progression (a quarter-less risk) compared to women who received concurrent and maintenance placebo or no further treatment in addition to their chemotherapy (HR 0.75, 95% CI 0.68 to 0.83). The percentage of the variability in effect estimates that was due to heterogeneity between studies rather than chance was not important ($I^2$ = 0%).

**Chemotherapy + AMG 386 at 10 mg/kg (high dose) versus chemotherapy + placebo**

(See Analysis 3.2)

In the Karlan 2010 trial, women who received high dose AMG 386 in addition to chemotherapy had around a quarter-less risk of disease progression compared to women receiving placebo in addition to their chemotherapy, but this difference was not statistically significant (HR 0.70, 95% CI 0.44 to 1.10).

**Chemotherapy + AMG 386 at 3 mg/kg (low dose) versus chemotherapy + placebo**

(See Analysis 4.2)

In the Karlan 2010 trial, women who received low dose AMG 386 in addition to chemotherapy had in excess of a third-less risk of disease progression compared to women receiving placebo in addition to their chemotherapy (HR 0.57, 95% CI 0.36 to 0.91).

**Continuous BIBF 1120 versus placebo**

(See Analysis 5.1)

In the Ledermann 2009 trial, women who received continuous BIBF 1120 had nearly a third-less risk of disease progression compared to women receiving placebo (HR 0.68, 95% CI 0.42, 1.09). This difference was not statistically significant, although the trial was reported as not being sufficiently powered for a direct comparison of the two interventions. The authors of this trial concluded that a large phase III trial is needed to confirm the efficacy of this drug. The trial reported no deaths during treatment at the end of 36 weeks.

### Severe adverse events

**Chemotherapy + concurrent bevacizumab + maintenance placebo versus chemotherapy + concurrent and maintenance placebo**

The trial of Burger 2010 (GOG-0218) reported on severe adverse events for the above comparison.

**Grade ≥ 2 gastrointestinal adverse events**

(See Analysis 1.3)

Women who received concurrent bevacizumab and maintenance placebo in addition to chemotherapy were more than twice as likely to suffer moderate or severe gastrointestinal adverse events than those who received concurrent and maintenance placebo in addition to their chemotherapy (RR 2.11, 95% CI 0.72 to 6.21), but this was not statistically significant.

**Grade ≥ 2 hypertension**

(See Analysis 1.4)

Women who received concurrent bevacizumab and maintenance placebo in addition to chemotherapy were over two times more likely to suffer moderate or severe hypertension than those who received concurrent and maintenance placebo in addition to their chemotherapy (RR 2.25, 95% CI 1.45 to 3.50).

**Grade ≥ 3 proteinuria**

(See Analysis 1.5)

The trial found no statistically significant difference in the risk of severe proteinuria in women who received concurrent bevacizumab and maintenance placebo in addition to chemotherapy and those who received concurrent and maintenance placebo in addition to their chemotherapy (RR 0.99, 95% CI 0.18 to 5.38).

**Grade ≥ 2 pain**

(See Analysis 1.6)

The trial found no statistically significant difference in the risk of moderate or severe pain in women who received concurrent bevacizumab and maintenance placebo in addition to chemotherapy and those who received concurrent and maintenance placebo in addition to their chemotherapy (RR 1.00, 95% CI 0.85 to 1.18).

**Grade ≥ 4 neutropenia**

(See Analysis 1.7)

The trial found no statistically significant difference in the risk of severe neutropenia in women who received concurrent bevacizumab and maintenance placebo in addition to chemotherapy and those who received concurrent and maintenance placebo in addition to their chemotherapy (RR 1.09, 95% CI 0.98 to 1.23) .

**Febrile neutropenia**

(See Analysis 1.8)

The trial found no statistically significant difference in the risk of febrile neutropenia in women who received concurrent bevacizumab and maintenance placebo in addition to chemotherapy and those who received concurrent and maintenance placebo in addition to their chemotherapy (RR 1.35, 95% CI 0.69 to 2.66).

**Venous thromboembolic event**

(See Analysis 1.9)

The trial found no statistically significant difference in the risk of a venous thromboembolic event in women who received concurrent bevacizumab and maintenance placebo in addition to chemotherapy and those who received concurrent and maintenance placebo in addition to their chemotherapy (RR 0.88, 95% CI 0.50 to 1.54).

**Arterial thromboembolic event**

(See Analysis 1.10)

The trial found no statistically significant difference in the risk of an arterial thromboembolic event in women who received concurrent bevacizumab and maintenance placebo in addition to chemotherapy and those who received concurrent and maintenance placebo in addition to their chemotherapy (RR 0.66, 95% CI 0.15 to 2.94).

**Grade ≥ 3 non-CNS bleeding**

(See Analysis 1.11)

The trial found no statistically significant difference in the risk of severe bleeding outside the central nervous system (CNS) in women who received concurrent bevacizumab and maintenance placebo in addition to chemotherapy and those who received concurrent and maintenance placebo in addition to their chemotherapy (RR 1.32, 95% CI 0.35 to 4.95).

**Chemotherapy + concurrent and maintenance bevacizumab versus chemotherapy +/- placebo**

**Grade ≥ 2 gastrointestinal adverse events**

(See Analysis 2.3)

Meta-analysis of two trials (Burger 2010 (GOG-0218); Perren 2010 (ICON7)) found that women who received concurrent bevacizumab and maintenance bevacizumab in addition to chemotherapy were around two-and-a-half times more likely to suffer moderate or severe gastrointestinal adverse events than those who received concurrent and maintenance placebo or no further treatment in addition to their chemotherapy (RR 2.47, 95% CI 1.08 to 5.67). The percentage of the variability in effect estimates that was due to heterogeneity between studies rather than chance was not important ($I^2$ = 0%).

**Grade ≥ 2 hypertension**

(See Analysis 2.4)

Meta-analysis of two trials (Burger 2010 (GOG-0218); Perren 2010 (ICON7)) found that women who received concurrent bevacizumab and maintenance bevacizumab in addition to chemotherapy were over five times more likely to suffer moderate or severe hypertension than those who received concurrent and maintenance placebo or no further treatment in addition to their chemotherapy (RR 5.13, 95% CI 1.91 to 13.82). The percentage of the variability in effect estimates that was due to heterogeneity between studies rather than chance may represent considerable heterogeneity ($I^2$ = 89%).

**Grade ≥ 3 proteinuria**

(See Analysis 2.5)

Meta-analysis of two trials (Burger 2010 (GOG-0218); Perren 2010 (ICON7)) found that women who received concurrent be-

vacizumab and maintenance bevacizumab in addition to chemotherapy were over two-and-a-half times more likely to suffer severe proteinuria than those who received concurrent and maintenance placebo or no further treatment in addition to their chemotherapy (RR 2.90, 95% CI 0.84 to 10.06), but this was not statistically significant. The percentage of the variability in effect estimates that was due to heterogeneity between studies rather than chance was not important ($I^2$ = 0%).

**Grade ≥ 2 pain**

(See Analysis 2.6)

The trial of Burger 2010 (GOG-0218) found that women who received concurrent bevacizumab and maintenance placebo in addition to chemotherapy had a slightly higher risk of moderate or severe pain than those who received concurrent and maintenance placebo in addition to their chemotherapy (RR 1.13, 95% CI 0.97 to 1.33), but this was not statistically significant.

**Grade ≥ 3 neutropenia**

(See Analysis 2.7)

Meta-analysis of two trials (Burger 2010 (GOG-0218); Perren 2010 (ICON7)) found that women who received concurrent bevacizumab and maintenance bevacizumab in addition to chemotherapy had a slightly higher risk of severe neutropenia than those who received concurrent and maintenance placebo or no further treatment in addition to their chemotherapy (RR 1.09, 95% CI 0.99 to 1.21), but this approached borderline significance (P = 0.08). The percentage of the variability in effect estimates that was due to heterogeneity between studies rather than chance was not important ($I^2$ = 0%).

**Febrile neutropenia**

(See Analysis 2.8)

Meta-analysis of two trials (Burger 2010 (GOG-0218); Perren 2010 (ICON7)) found no statistically significant difference in the risk of febrile neutropenia between women who received concurrent bevacizumab and maintenance bevacizumab in addition to chemotherapy and those who received concurrent and maintenance placebo or no further treatment in addition to their chemotherapy (RR 1.23, 95% CI 0.76 to 1.98). The percentage of the variability in effect estimates that was due to heterogeneity between studies rather than chance was not important ($I^2$ = 0%).

**Venous thromboembolic event**

(See Analysis 2.9)

Meta-analysis of two trials (Burger 2010 (GOG-0218); Perren 2010 (ICON7)) found no statistically significant difference in the risk of a venous thromboembolic event between women who received concurrent bevacizumab and maintenance bevacizumab in addition to chemotherapy and those who received concurrent and maintenance placebo or no further treatment in addition to their chemotherapy (RR 1.64, 95% CI 0.76 to 3.56). The percentage of the variability in effect estimates that was due to heterogeneity between studies rather than chance may represent substantial heterogeneity ($I^2$ = 71%).

**Arterial thromboembolic event**

(See Analysis 2.10)

Meta-analysis of two trials (Burger 2010 (GOG-0218); Perren 2010 (ICON7)) found no statistically significant difference in the risk of an arterial thromboembolic event between women who received concurrent bevacizumab and maintenance bevacizumab in addition to chemotherapy and those who received concurrent and maintenance placebo or no further treatment in addition to their chemotherapy (RR 1.40, 95% CI 0.50 to 3.92). The percentage of the variability in effect estimates that was due to heterogeneity between studies rather than chance may represent moderate heterogeneity ($I^2$ = 42%).

**Grade ≥ 3 bleeding**

(See Analysis 2.11)

Meta-analysis of two trials (Burger 2010 (GOG-0218); Perren 2010 (ICON7)) found that women who received concurrent bevacizumab and maintenance bevacizumab in addition to chemotherapy had around three times the risk of severe bleeding than those who received concurrent and maintenance placebo or no further treatment in addition to their chemotherapy (RR 2.90, 95% CI 1.10 to 7.62), and this was statistically significant (P = 0.03). The percentage of the variability in effect estimates that was due to heterogeneity between studies rather than chance was not important ($I^2$ = 0%).

**Thrombocytopenia**

(See Analysis 2.12)

The trial of Perren 2010 (ICON7) found no statistically significant difference in the risk of severe thrombocytopenia between women who received concurrent bevacizumab and maintenance placebo in addition to chemotherapy and those who received concurrent and maintenance placebo in addition to their chemotherapy (RR 1.75, 95% CI 0.94 to 3.28).

**Chemotherapy + AMG 386 at 10 mg/kg (high dose) versus chemotherapy + placebo**

**Grade ≥ 3 adverse events**

The trial of Karlan 2010 reported on severe adverse events for the above comparison.

The trial found no statistically significant difference in the risk of severe bowel perforation, hypertension, neutropenia, venous and arterial thromboembolic events, proteinuria, cardiac toxicity events and hemorrhagic events in women who received chemotherapy plus high dose AMG 386 and those who received chemotherapy and placebo. There were relatively few severe adverse events reported in each arm (this ranged from no events in either arm for severe hypertension to 6/53 events in the chemotherapy plus high dose AMG arm and 9/55 in the placebo arm for severe venous thromboembolic events).

**Chemotherapy + AMG 386 at 3 mg/kg (low dose) versus Chemotherapy + placebo**

**Grade ≥ 3 adverse events**

The trial of Karlan 2010 reported on severe adverse events for the above comparison.

The comparison of chemotherapy plus low dose AMG 386 versus

chemotherapy and placebo yielded similar results in terms of severe adverse events to the comparison of chemotherapy plus high dose AMG 386 versus chemotherapy and placebo (see above). The trial of Karlan 2010 found no statistically significant difference in the risk of severe bowel perforation, hypertension, neutropenia, venous and arterial thromboembolic events, proteinuria, cardiac toxicity events and hemorrhagic events in women who received chemotherapy plus low dose AMG 386 and those who received chemotherapy and placebo. (The number of events in each arm ranged from no events for severe hypertension to 6/52 events in the chemotherapy plus low dose AMG 386 arm and 9/55 in the placebo arm for severe venous thromboembolic events).

**Continuous BIBF 1120 versus placebo**

**Severe gastrointestinal adverse events**

(See Analysis 5.2)

The trial of Ledermann 2009 found no statistically significant difference in the risk of a severe gastrointestinal adverse event between women who received continuous BIBF 1120 and women who received placebo (RR 1.59, 95% CI 0.50 to 5.03).

**VEGF-Trap versus placebo**

The trial of Vergote 2009 reported on adverse events for the above comparison.

**Fatal gastrointestinal events**

(See Analysis 6.2)

The trial found no statistically significant difference in the risk of fatal gastrointestinal events between women who received VEGF-Trap and women who received placebo (RR 2.69, 95% CI 0.30 to 24.28).

**Other adverse events**

The trial has so far only reported other adverse events observed in patients treated with VEGF-Trap, and where the investigators believed the events were related to VEGF inhibition (i.e. no comparison figures from the control group).

Of those women who received VEGF-Trap, the trialists observed dysphonia in 20%, hypertension in 16.7%, proteinuria in 10% and epistaxis in 6.7%.

# DISCUSSION

## Summary of main results

We found five RCTs comparing angiogenesis inhibitors to either placebo or standard chemotherapy in women with ovarian cancer (Burger 2010 (GOG-0218); Karlan 2010; Ledermann 2009; Perren 2010 (ICON7); Vergote 2009). All five trials have thus far been published only in the form of conference abstracts, and so there are limited data available (even after contacting investigators for further information). Some of the trials are expected to be published in full later this year; others are still awaiting longer-term follow-up data (e.g. for OS).

Burger 2010 (GOG-0218) was a double-blind, placebo-controlled, phase III RCT in 1873 women with newly-diagnosed epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer. The study assessed the effects of adding bevacizumab, a humanised monoclonal antibody that binds to vascular endothelial growth factor, to standard paclitaxel/carboplatin chemotherapy, either concurrently with the chemotherapy, or both concurrently and continuing after the chemotherapy (maintenance therapy). The trial found that the addition of concurrent bevacizumab to standard chemotherapy did not appear to prolong OS (HR 1.04, 95% CI 0.83 to 1.30; P = 0.73) or PFS (HR 0.91, 95% CI 0.79 to 1.04; P = 0.17). However, the women who received concurrent bevacizumab had more than twice the risk of moderate or severe hypertension (RR 2.25, 95% CI 1.45 to 3.50).

The addition of concurrent and maintenance bevacizumab to standard carboplatin/paclitaxel chemotherapy was also assessed in Perren 2010 (ICON7), an open-label phase III randomised trial in 1528 women with newly-diagnosed epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer.

Meta-analysis of the two trials (Burger 2010 (GOG-0218); Perren 2010 (ICON7)) assessing 2707 participants, suggested that the addition of concurrent and maintenance bevacizumab to standard chemotherapy compared to chemotherapy alone (with or without placebo) may prolong OS (HR 0.87, 95% CI 0.73 to 1.03; P = 0.10), but this was not statistically significant and longer follow-up is needed. There was however evidence of a reduction in the risk of disease progression by a quarter (HR 0.75, 95% CI 0.68 to 0.83; P < 0.001). Women who received concurrent and maintenance bevacizumab had an increased risk of severe gastrointestinal adverse events (HR 2.47, 95% CI 1.08 to 5.67; P = 0.03), moderate or severe hypertension (HR 5.13, 95% CI 1.91 to 13.82; P = 0.001) and severe bleeding (HR 2.90, 95% CI 1.10 to 7.62; P = 0.03) compared to women who received chemotherapy alone. There was also an increased risk of severe neutropenia in the concurrent and maintenance bevacizumab group compared to the chemotherapy alone group (HR 1.09, 95% CI 0.99 to 1.21; P = 0.08) but this only approached borderline significance.

The main difference between the two trials was that Burger 2010 (GOG-0218) used bevacizumab at a dose of 15 mg/kg, whereas Perren 2010 (ICON7) used bevacizumab at a dose of 7.5 mg/kg. Additionally, the trial of Burger 2010 (GOG-0218) was double-blind so that patients in the control (chemotherapy only) arm were given placebo in place of bevacizumab, while the Perren 2010 (ICON7) trial was open-label so that patients in the control arm did not receive placebo and were aware that they were not receiving bevacizumab. The lack of blinding in Perren 2010 (ICON7) could potentially have influenced outcomes, in that knowing which treatment group a patient is in could affect the patient's performance, but could also affect the assessment of their doctors (e.g. in terms of judging progression). In terms of par-

ticipants, the main difference was that the women in the Burger 2010 (GOG-0218) trial were, in general, more high risk (all had stage III-IV disease) than those in the Perren 2010 (ICON7) trial (which included women with high-risk stage I-II disease, as well as stage III-IV).

Karlan 2010 was a double-blind, placebo-controlled, phase II RCT of AMG 386, an anti-angiopoietin peptibody, which acts to inhibit angiogenesis by interfering with the interaction between angiopoietin-1 and angiopoietin-2 with the Tie-2 receptor. The trial involved 161 women with recurrent epithelial ovarian cancer (FIGO stage II-IV), or fallopian tube or primary peritoneal cancer, and was a three-armed comparison of paclitaxel chemotherapy with a higher (10 mg/kg) versus lower (3 mg/kg) dose of AMG 386, versus placebo. The trial did not find strong evidence that the addition of high-dose AMG 386 prolonged OS (HR 0.60, 95% CI 0.34 to 1.06; P = 0.08) or PFS (HR 0.70, 95% CI 0.44 to 1.10; P = 0.12), although there was some degree of improvement in both. The addition of low-dose AMG 386 did not appear to improve OS (HR 0.77, 95% CI 0.45 to 1.31; P = 0.34), but there was some evidence of a reduction in the risk of disease progression by over a third (HR 0.57, 95% CI 0.36 to 0.91; P = 0.02). The trial did not find strong evidence of an increased risk of adverse events associated with either low-dose or high-dose AMG 386.

Ledermann 2009 was a double-blind, placebo-controlled, phase II RCT of BIBF 1120, a small molecule inhibitor of three receptors involved in angiogenesis (vascular endothelial growth factor receptor, fibroblast growth factor receptor and platelet-derived growth factor receptor). The trial involved 84 women with chemotherapy-responsive relapsed ovarian, fallopian tube or primary peritoneal cancer. The trial did not find strong evidence that the addition of BIBF 1120 either reduced the risk of disease progression (HR 0.68, 95% CI 0.42 to 1.08; P = 0.10) or increased the risk of severe gastrointestinal adverse events (HR 1.59, 95% CI 0.50 to 5.03).

Vergote 2009 was a double-blind, placebo-controlled, RCT of VEGF-Trap, a fusion-protein decoy-receptor for vascular endothelial growth factor. The trial involved 55 women with chemotherapy-resistant advanced epithelial ovarian cancer and recurrent malignant ascites. The trial found no evidence that VEGF-Trap prolonged OS (HR 1.02, 95% CI 0.56 to 1.86; P = 0.94). There was also no evidence of an increased risk of fatal gastrointestinal events (HR 2.69, 95% CI 0.30 to 24.28).

Overall, the results of these five RCTs are not sufficient to confirm whether or not there is a survival benefit from angiogenesis inhibitors in the treatment of ovarian cancer.

Twelve ongoing trials were identified which, from the methods reported thus far, are likely to meet our inclusion criteria when completed.

- Four studies are of bevacizumab in different settings: as a first-line therapy (NCT01081262); in platinum-resistant disease (AURELIA: NCT00976911); and in recurrent disease (NCT00565851; OCEANS: NCT00434642).
- Three studies are of sorafenib in different settings: as first-line therapy (Hainsworth 2010); in advanced disease (NCT00791778); and in platinum-resistant recurrent disease (NCT01047891).
- One trial is of BIBF 1120 as a first-line therapy (NCT01015118).
- One trial is of AMG 386, in combination with paclitaxel, following surgery and platinum-based chemotherapy (TRINOVA-1: NCT01204749).
- One trial is of pazopanib as a second-line treatment (NCT00866697).
- One trial is of cediranib in relapsed disease (ICON6: NCT00532194).
- One trial is of an antibody to PDGF-R-alpha in platinum-refractory/resistant disease (McGuire 2010).

## Overall completeness and applicability of evidence

Overall, the quality of the evidence was low (GRADE Working Group) as all trials were at an unclear risk of bias, outcomes were incompletely documented, and follow-up was insufficient to adequately assess differences in survival that may or may not have been present. Although we identified five RCTs that met our inclusion criteria, none have yet reported their methods and results in full, and thus they are at an unclear (and potentially high) risk of bias. When the results of these trials have been published in full it is likely that the evidence will be upgraded and by the time the results of the ongoing trials are made available the completeness of evidence should be very thorough. Only two of the trials used the same drug (Burger 2010 (GOG-0218); Perren 2010 (ICON7), both of bevacizumab), while the other three trials examined thee different agents, in slightly different populations. At least two of these (Ledermann 2009; Vergote 2009) probably lacked the statistical power to detect an effect, even if present, due to relatively small sample sizes. This makes it more difficult to draw general conclusions about the efficacy of angiogenesis inhibitors in treating ovarian cancer. Furthermore, we found no good-quality, non-randomised studies with concurrent comparison groups, making it difficult to test the robustness of the findings of these varied trials.

Although we specified QoL as an outcome, none of the five trials we identified have yet reported QoL data. However, two of them (Burger 2010 (GOG-0218); Perren 2010 (ICON7)) have specified QoL as a planned outcome, and are expected to report on this when full data are available.

Angiogenesis inhibitors are not currently in routine use as first- or second-line treatment of epithelial ovarian, fallopian tube or primary peritoneal cancers. These trials present limited evidence that angiogenesis inhibitors (in particular, bevacizumab and AMG 386) might benefit patients with newly-diagnosed high risk/advanced ovarian cancer or recurrent disease.

This review summarises the current available evidence, but new results are being released on a regular basis. For example, as this review went to press, updated results for one of the trials included in this review (Perren 2010 (ICON7)) were presented at a conference, as were preliminary results for an ongoing trial (OCEANS: NCT00434642). This review will be updated shortly, to incorporate the newly-available data.

## Quality of the evidence

Five trials of four different anti-angiogenic agents, involving a total of 3701 patients, met the inclusion criteria for the review. These trials were at an unclear (and potentially high) risk of bias, largely because of the preliminary nature of the available data. All five trials have been presented at conferences, and thus far published only as abstracts; the brief nature of these inevitably means that much of the methodological detail, which is necessary for the assessment of risk of bias, is absent. None of the trials commented on the methods used to generate the sequence of random numbers to allocate women in the different treatment arms. Neither was it clear whether there was adequate concealment of allocation from patients and healthcare professionals involved in the trial. Inadequate concealment of allocation is often associated with an over-estimate of the effects of treatment (Moher 1998; Schulz 1995). Thus, the evidence on OS may be more robust than that for PFS, as blinding of outcome assessors has less potential for influence on death than disease progression. Four of the trials were described as 'double-blind' (Burger 2010 (GOG-0218); Karlan 2010; Ledermann 2009; Vergote 2009), suggesting that at least the trialists intended to blind both patients and healthcare professionals to the treatments that were received, although it was not clear whether the outcome assessor was blinded. One trial (Perren 2010 (ICON7)) was described as 'open-label,' suggesting that there was no attempt at blinding.

The trials all reported survival outcomes using a HR, which is the best statistic to summarise the difference in risk between two treatment groups over the duration of a trial, when there is "censoring" i.e. the time to death (or disease progression) is unknown for some women as they were still alive (or disease-free) at the end of the trial.

Some of the trials have only reported preliminary data, particularly for outcomes that require longer-term follow-up, such as OS and PFS.

In the trial of Burger 2010 (GOG-0218), the PFS and preliminary OS analyses were performed after 1201 (64%) PFS events were observed and 444 (24%) deaths. More mature OS data (i.e. after a longer period of follow-up) and QoL data, are still awaited. The authors reported in detail on selected moderate and severe adverse events in each trial arm.

In the trial of Perren 2010 (ICON7), the PFS and preliminary OS analyses were performed after 759 (50%) cases of disease progression and 241 (16%) deaths. More mature OS data (i.e. after a longer period of follow-up) and QoL data, are still awaited; updated OS results should be available in 2012. The authors reported in detail on selected adverse events in each trial arm (both severe and all grades).

In the Karlan 2010 trial, both PFS and OS data are mature, but it was not possible to deduce the number of deaths or cases of disease progression from the Kaplan Meier plots. QoL was not a planned outcome in the trial. The authors reported in detail on selected adverse events in each trial arm (both severe and those of special interest).

In the trial of Ledermann 2009, the PFS analysis was performed at 36-weeks (as prospectively planned); the authors reported that there were no deaths on treatment. QoL was not a planned outcome in the trial. The authors reported briefly on the percentage of patients in each trial arm who experienced severe adverse events, but only reported in detail on gastrointestinal toxicities.

In the Vergote 2009 trial, it was not reported how many deaths had occurred at the time of analysis, as the trial was primarily concerned with reducing the need for paracentesis in women with malignant ascites, rather than prolonging survival. The authors reported on fatal gastrointestinal events separately by trial arm, but did not report on other adverse events.

It was not clear in four of the five trials how many women were lost to follow-up, although survival analyses used a HR in all trials which correctly accounts for censoring. This is more relevant to severe adverse event outcomes that were reported but it would be assumed that loss to follow-up would be low for acute toxicity, and more considerable for survival outcomes and longer-term adverse events.

## Potential biases in the review process

We performed a comprehensive search, including a thorough search of the grey literature. At least two reviewers sifted and independently extracted data for all studies. We restricted the included studies to RCTs as they provide the strongest level of evidence available. Hence we have attempted to reduce bias in the review process.

The greatest threat to the validity of the review is likely to be the possibility of publication bias, i.e. studies that did not find angiogenesis inhibitors for the treatment of ovarian cancer to have been effective may not have been published; we were unable to assess this possibility.

## Agreements and disagreements with other studies or reviews

Other than the five trials discussed above, we are not aware of any other completed RCTs of angiogenesis inhibitors compared to normal chemotherapy and/or placebo in patients with ovarian cancer. However, there have been many phase I and phase II

studies without control groups. Results of some of the larger non-controlled phase II studies are discussed below.

**Bevacizumab**

Bevacizumab is probably the most-studied of the angiogenesis inhibitors, and there have been several uncontrolled phase II trials. The studies generally concluded that there was some degree of disease response (although this is difficult to assess objectively without a concurrent control group), and several also identified gastrointestinal adverse events (particularly perforation) and hypertension as important side-effects.

A retrospective analysis of 43 patients from six centres, all of whom received bevacizumab with chemotherapy for heavily-pretreated ovarian cancer, found an objective response rate of 40%, with a median time to progression of 3.8 months (Asmane 2010). Grade three to four toxicities were reported in 13 (30.2%) women, including proteinuria, hypertension, haemorrhage, pelvic abscess and psychiatric disorders. Three (7.0%) women suffered gastrointestinal perforations and six (13.9%) had fistulas.

A phase II study of bevacizumab was conducted in 62 women with persistent/recurrent ovarian cancer or primary peritoneal cancer (Burger 2007). Bevacizumab was given at a dose of 15 mg/kg IV once every 21 days until disease progression or prohibitive toxicity. Median PFS was 4.7 months; median OS was 17 months. Twenty-five (40.3%) patients survived progression-free for at least six months.

Cannistra 2007 was another phase II study of bevacizumab, again given at 15 mg/kg, once every three weeks. It involved 44 women with platinum-resistant epithelial ovarian cancer or peritoneal serous carcinoma, all of whom had experienced disease progression during, or within three months of discontinuing treatment with topotecan or liposomal doxorubicin. The overall incidence of gastrointestinal perforation in this study was 11.4%, but 23.8% in those women who had three prior chemotherapy regimens (compared to 0% in those who had two prior chemotherapy regimens). Median PFS was 4.4 months (95% CI 3.1 to 5.5 months). Median OS was 10.7 months at the end of the study.

A study of bevacizumab 15 mg/kg, once every three weeks, was also conducted in 32 patients with recurrent advanced ovarian cancer, who had failed multiple prior chemotherapeutic regimens (Monk 2006). Some patients also received cytotoxic chemotherapy. Median PFS was 5.5 months; median OS was 6.9 months. Grade three toxicities seen included hypertension, proteinuria and enterocutaneous fistula.

A phase II study of bevacizumab (10 mg/kg, once every two weeks) and cytotoxic chemotherapy (metronomic oral cyclophosphamide) was conducted in 70 women with recurrent ovarian cancer (Garcia 2008). Median PFS was 7.2 months; median OS was 16.9 months. There were four episodes of gastrointestinal perforation or fistula, amongst other adverse events. A very similar study of bevacizumab and metronomic oral cyclophosphamide was conducted in 38 patients with heavily-pretreated, recurrent ovarian cancer (Sanchez-Munoz 2010). This trial found a median PFS of 4.5 months, and a median OS of 10.7 months; there were no cases of gastrointestinal perforation.

Another study trialled bevacizumab with carboplatin/paclitaxel chemotherapy (given IV initially, then intraperitoneally) in 40 patients with ovarian cancer (Krasner 2010). There was no progressive disease during the (unspecified) follow-up period. Significant grade three to four adverse events included: abdominal pain (5), fatigue (6), neutropenia (10), thrombocytopenia (5) and nausea (4).

A phase II study of carboplatin/paclitaxel with bevacizumab as concurrent and then maintenance therapy in 62 women with advanced Mullerian tumours (73% with ovarian cancer) found a PFS of 58% at 36-months (Penson 2010). Two gastrointestinal perforations and two pulmonary emboli occurred, both during the chemotherapy phase.

Preliminary data from a phase II study of bevacizumab as concurrent (with oxaliplatin and docetaxel cytotoxic chemotherapy) and then maintenance therapy in 110 women with advanced ovarian, peritoneal or fallopian tube cancer (Rose 2009) showed one case of colonic perforation associated with bevacizumab. Common grade three to four adverse events included neutropenia (39%), leukopenia (11%), hypertension (9%) and fatigue (7%).

A phase II study of nab-paclitaxel and bevacizumab in 48 women with recurrent, platinum-resistant ovarian cancer found a median PFS of 8.3 months and median OS of 16.5 months (Tillmanns 2010). Bowel obstruction was reported in 3.8% of patients. Other common toxicities included neutropenia, anaemia, nausea, nosebleed, neuropathy and infection.

Given that several trials of angiogenesis inhibitors have reported gastrointestinal perforations and/or fistulae as adverse events, some studies have also been conducted to look specifically at this as a potential sideeffect. A retrospective study of the medical records of 160 patients with ovarian cancer, who had been treated with bevacizumab off-protocol at one institution (Diaz 2010), found that six (4%) developed gastrointestinal perforations.

Another retrospective chart review was conducted of patients with recurrent ovarian cancer who had been treated in a centre in the USA, comparing 68 patients who had received bevacizumab (67% in combination with chemotherapy) to 195 patients who had received standard chemotherapy alone (Sfakianos 2009). The study found that, amongst women treated with bevacizumab (with or without chemotherapy), five (7.2%) developed a gastrointestinal perforation and/or fistula, compared to 13 (6.5%) women amongst those treated with chemotherapy alone (RR 1.09, 95% CI 0.40 to 2.96). The authors therefore concluded that "bevacizumab does not significantly increase gastrointestinal toxicity compared to standard salvage chemotherapy." However, as this was not a randomised study, the two groups of women almost certainly also differed in other ways, and so one must be cautious about drawing conclusions of comparative safety.

A third retrospective study assessed the incidence of bowel perforation and hypertension amongst 32 women with advanced ovar-

ian cancer, who had been treated with one of two dosage regimens of carboplatin, paclitaxel and bevacizumab (Abaid 2010). The authors reported no cases of bowel perforation and two cases of "clinically significant" hypertension.

A fourth retrospective study was aimed at assessing the efficacy and adverse events associated with use of bevacizumab amongst 64 women with recurrent ovarian cancer who had been treated with bevacizumab plus chemotherapy (Cheng 2009). The authors reported that fifteen (23.4%) patients had grade three or four adverse events, and that gastrointestinal perforations occurred in two (3.1%) patients.

A fifth retrospective study of 51 women with recurrent ovarian cancer who had received paclitaxel chemotherapy and bi-weekly bevacizumab, found an overall median PFS of 7 months and a median OS of 12 months (Hurt 2009). Three (5%) patients suffered bowel perforations.

**Other angiogenesis inhibitors**

A phase II open-label study of pazopanib (given 800 mg daily, orally) was conducted in 36 women with recurrent ovarian cancer and an elevated CA125, who had previously had a complete CA125 response to platinum-based chemotherapy (Friedlander 2010). The authors reported that eleven (31%) women had a CA125 response, and PFS at six months was 17% (95% CI 6% to 33%).

One phase II study of imatinib (given 400 mg daily, orally), in 35 women with ovarian cancer in second or greater remission, found that the PFS was not prolonged beyond the historical estimate (Juretzka 2008); the authors also reported that they found no association between PDGF-R staining and PFS.

Another phase II trial of daily imatinib was conducted in women with recurrent ovarian cancer (Alberts 2007), this time limited to those with tumours expressing one of two targets against which imatinib acts (c-kit/CD117 or PDGF-R). Although 34 women were registered for the trial, 15 were ineligible or not evaluable. Of the 19 women who were evaluable, two (11%) had tumours which tested positive for c-kit and 17 (89%) for PDGF-R. However, no women showed an objective response. Median PFS was 2 months and median OS was 10 months.

A phase II study of daily sorafenib (in combination with weekly gemcitabine) in 43 women with recurrent ovarian cancer found a median time to progression of 5.4 months, and a median OS of 13.0 months (Welch 2010). Common adverse events reported included haematologic toxicity, hand-foot syndrome, fatigue, hypokalaemia and diarrhoea.

A phase II study of daily cediranib amongst 47 women with recurrent ovarian cancer found that median PFS was 5.2 months (Matulonis 2009). In terms of side-effects, grade three hypertension occurred in 46%, fatigue in 24% and diarrhoea in 13%. The authors reported no bowel perforations or fistulas.

Previous studies have suggested that hypertension and proteinuria are common adverse events associated with inhibitors of the VEGF pathway. Thus, one phase II study of cediranib in 31 women with recurrent epithelial ovarian cancer incorporated detailed monitoring of hypertension and proteinuria (Robinson 2010). The trial found that 31 (67%) women had developed hypertension by day three of therapy and 87% by the end of the study. Forty-three per cent developed grade $\geq$ 3 hypertension. Fourteen (30%) women developed proteinuria, in seven of whom it occurred in the first two weeks of starting therapy.

# AUTHORS' CONCLUSIONS

## Implications for practice

Available data suggest an improvement in PFS, if concurrent and maintenance bevacizumab is added to conventional chemotherapy, but no significant effect on OS, for patients with ovarian cancer. Adverse events were more common in the bevacizumab arm compared to the placebo arm, several significantly so (severe gastrointestinal events, severe bleeding, and moderate and severe hypertension). There was no evidence of an increase in either OS or PFS with the addition of concurrent (but not maintenance) bevacizumab to standard chemotherapy, but there was a significant increase in the risk of moderate and severe hypertension in the bevacizumab arm.

These results are relatively promising, suggesting that the combination of concurrent and maintenance bevacizumab may have a role, in addition to standard debulking surgery and chemotherapy, in delaying disease progression in women with newly-diagnosed ovarian cancer. However, some cautions must be borne in mind. Firstly, longer-term follow-up data are needed, in order to see whether the improvement in PFS is accompanied by any significant improvement in OS. Secondly, the finding of improved PFS is based on only two trials, and one would ideally seek further confirmation. Thirdly, the data have thus far been published only as conference abstracts, and must be judged as being at high risk of bias until further details are known. Fourthly, one of the two trials on which this finding was based was open-label (i.e. no attempt at blinding), and thus is particularly open to bias in clinician-assessed outcomes such as disease progression. Fifthly, there is also evidence of increased risks of adverse events with bevacizumab therapy, particularly of gastrointestinal events, hypertension and bleeding, in keeping with findings from non-controlled phase II studies.

Data show little or weak evidence of improvement in OS and PFS if high-dose AMG 386 is added to chemotherapy. The addition of low-dose AMG 386 to chemotherapy was associated with a significant improvement in PFS, but there was no evidence of an effect on OS. There was no evidence of significant difference in the toxicities of the two arms. These results are also encouraging, particularly the lack of evidence for increased risk of adverse events.

However, there is currently insufficient evidence to support the routine use of angiogenesis inhibitors alone or in combination with chemotherapeutic agents in ovarian, fallopian tube or primary peritoneal cancer. Further research is needed to confirm or contradict the results available thus far, both in the form of further data from the existing trials, and other trials of these and other anti-angiogenic agents.

### Implications for research

There is still considerable uncertainty regarding the circumstances in which angiogenesis inhibitors should be used in treating ovarian cancer, if at all. Given their specific mechanism of action, it seems likely that any effect would be greater in those patients with particularly high levels of angiogenesis (e.g. with over-expression of VEGF). Several of the completed and ongoing trials thus also include sub-studies, looking at expression of pro-angiogenesis markers, and their correlation with disease response. In the ongoing quest for patient-specific medicine, the identification of those patients who are likely to respond to a drug (and perhaps more importantly, those who are not likely to respond, and thus should be spared the unnecessary drug and its attendant sideeffects), continues to be a priority.

The limited current data (as represented by the five included trials) highlight the gaps in knowledge. One is the issue of whether angiogenesis inhibitors can affect OS as well as PFS; this is largely a question of longer-term follow-up, and should be answered (at least in part for bevacizumab) as more data become available from the existing (e.g. Burger 2010 (GOG-0218) and Perren 2010 (ICON7)) and ongoing trials. We identified four ongoing trials of bevacizumab, one of which has just released preliminary results (OCEANS: NCT00434642). Importantly, the fuller reports of results should include data on QoL outcomes for at least some studies. Given the growing evidence of the risk of adverse events associated with at least some angiogenesis inhibitors, both QoL and OS data will be important information to help clinicians and patients balance potential risks and benefits.

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## REFERENCES

### References to studies included in this review

**Burger 2010 (GOG-0218)** ***{published and unpublished data}***

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;**21:8s:**(Suppl; abstr 978PD): viii307.

Burger RA, Brady MF, Bookman MA, Monk BJ, Walker JL, Homesley HD, et al. Gynecologic Oncology Group study. Safety and subgroup efficacy analyses in GOG-0218, a Phase III trial of bevacizumab in the primary treatment of advanced epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer. Conference Poster from ESMO 2010.

Burger RA, Brady MF, Bookman MA, Walker JL, Homesley HD, Fowler Jet al, Gynecologic Oncology Group (GOG) study. Phase III trial of Bevacizumab in the Primary Treatment of Advanced Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer. Powerpoint Presentation from ASCO 2010 Conference.

* Burger RA, Brady MF, Bookman MA, Walker JL, Homesley HD, Fowler Jet 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 (Meeting Abstracts)* 2010;**28:18s**:(Suppl; abstr LBA1).

**Karlan 2010** ***{published and unpublished data}***

Amgen. Phase 2, AMG 386 (20060342) in combination with paclitaxel for subjects with advanced recurrent epithelial ovarian or primary peritoneal cancer. MetaRegister of Controlled Trials. Protocol Registered: May 24, 2007.

Karlan BY, Oza AM, Hansen VL, Richardson GE, Provencher D, Ghatage P, et al. Randomized, double-blind, placebo-controlled phase 2 study of AMG 386 combined with weekly paclitaxel in patients with recurrent ovarian carcinoma. Powerpoint Presentation from ASCO 2010.

* 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 (Meeting Abstracts)* 2010;**28:15s**:(Suppl; abstr 5000).

Lu J, Rasmussen E, Navale L, Kuchimanchi M, Hurh E, Karlan B Y, 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 modeling. *Annals of Oncology (Meeting Abstracts)* 2010;**21**(Suppl 8; abstr 983P):viii308.

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) modeling to facilitate phase III dose selection. *Journal of Clinical Oncology (Meeting Abstracts)* 2010;**28**(15˙suppl):5042.
Vergote I B, Oza A M, Hansen V L, Richardson G E, Provencher D, Ghatage P, Tassoudji M, Sun Y-N, Stepan D E, Karlan B Y. A Randomized, Double-blind, Placebo-controlled Phase 2 Study of AMG 386 Plus Weekly Paclitaxel in Patients with Advanced Ovarian Cancer. Conference Poster from ESMO 2010.
Vergote IB, Oza AM, Hansen VL, Richardson GE, Provencher DM, 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;**21:8s:**(Suppl; abstr 975PD): viii305–6.

**Ledermann 2009** ***{published data only (unpublished sought but not used)}***
Boehringer Ingelheim Pharmaceuticals. A randomized placebo-controlled Phase II study of continuous maintenance treatment with BIBF 1120 following chemotherapy in patients with relapsed ovarian cancer. MetaRegister of Controlled Trials. Protocol Registered: July 3, 2008.
* 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 (Meeting Abstracts)* 2009;**27:15s**:(Suppl; abstr 5501).

**Perren 2010 (ICON7)** ***{published and unpublished data}***
Mazur, Collinson F, et al. 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 30–Dec; Vol. 1:92.
National Cancer Institute, Medical Research Council. 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. MetaRegister of Controlled Trials. Date ISRCTN assigned: 25th Jan 2006.
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 ESMO 2010.
* Perren T, Swart AM, Pfisterer J, Ledermann J, Lortholary A, Kristensen G, GCIG ICON7 collaborators. 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 (Meeting Abstracts)* 2010;**21 (Suppl 8; abstr LBA4)**.

**Vergote 2009** ***{published data only}***
Sanofi-Aventis, Regeneron Pharmaceuticals. Study of the effect of intravenous AVE0005 (VEGF Trap) in advanced ovarian cancer patients with recurrent symptomatic malignant ascites. MetaRegister of Controlled Trials Protocol Registered: May 16, 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 forthcoming full published version of the study).
* Vergote I, Amant F, Advani F, Goswami 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 (Meeting Abstract).* October 2009;**19**: (Suppl 2).

## References to studies excluded from this review

**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 [abstract]. Gynecologic Oncology 2008; Vol. 108, issue 3 Suppl 1: S23,.

**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.

**Markman 2009** ***{published data only}***
Markman M. Antiangiogenic drugs in ovarian cancer.. *Expert Opinion on Pharmacotherapy* 2009;**10**(14):2269–77.

**NCT00017303** ***{published data only}***
National Cancer Institute, Cytran. Combination chemotherapy plus IM-862 in treating patients with resected Stage III ovarian cancer or primary peritoneal cancer. MetaRegister of Controlled Trials Protocol Registered: June 6, 2001.

**NCT00096200** ***{published data only}***
Case Comprehensive Cancer Center, National Cancer Institute. BAY 43-9006 plus paclitaxel/carboplatin in women with GYN tumors. MetaRegister of Controlled Trials Protocol Registered: Nov 9, 2004.

**NCT00543049** ***{published data only}***
AGO Ovarian Cancer Study Group. Randomized multicenter trial with SU11248 evaluating dosage, tolerability, toxicity and effectiveness of a multitargeted receptor tyrosine kinase inhibitor. MetaRegister of Controlled Trials Protocol Registered: Oct 10, 2007.

**NCT00886691** *{published data only}*

National Cancer Institute, Gynecologic Oncology Group. Bevacizumab with or without everolimus in treating patients with recurrent or persistent ovarian epithelial cancer, fallopian tube cancer, or primary peritoneal cancer. MetaRegister of Controlled Trials Protocol Registered: April 22, 2009.

**NCT01115829** *{published data only}*

National Cancer Institute, Dana-Farber Cancer Institute. Cediranib Maleate and Olaparib in Treating Patients With Recurrent Ovarian Epithelial Cancer, Fallopian Tube Cancer, Peritoneal Cancer, or Recurrent Triple-Negative Breast Cancer. MetaRegister of Controlled Trials. Protocol Registered: April 30, 2010.

**NCT01167712** *{published data only}*

National Cancer Institute, Gynecologic Oncology Group. 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. Protocol Registered: July 21, 2010.

**Osterweil 2010** *{published data only}*

Markman M. Bevacizumab plus chemo extends progression-free survival: Comment. Oncology Report 2010, issue July–August:25.

Osterweil N. Bevacizumab plus chemo extends progression-free survival: Comment. Oncology Report 2010, issue July–August:25.

**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.

**Tew 2007** *{published data only (unpublished sought but not used)}*

Sanofi-Aventis, Regeneron Pharmaceuticals. NCT00327171: study of AVE0005 (VEGF Trap) in patients with chemoresistant advanced ovarian cancer. MetaRegister of Controlled Trials. Protocol Registered: May 16, 2006.

* 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 (Meeting Abstracts)* 2007;**25:18s:(Suppl; abstr 5508)**.

## References to studies awaiting assessment

**Gordon 2010** *{published data only}*

Exelixis. NCT00940225: study of cabozantinib (XL184) in adults with advanced malignancies. MetaRegister of Controlled Trials. Protocol Registered: July 12, 2009.

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 (Meeting Abstracts)* 2010;**28**(15s):(Suppl; abstr TPS188).

## References to ongoing studies

**AURELIA: NCT00976911** *{published data only}*

Hoffmann-La Roche. AURELIA: A study of Avastin (bevacizumab) added to chemotherapy in patients with platinum-resistant ovarian cancer. MetaRegister of Controlled Trials. Protocol Registered: Sept 14, 2009.

**Hainsworth 2010** *{published data only}*

* 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 (Meeting Abstracts)* 2010;**28**(15˙Suppl):TPS257.

Sarah Cannon Research Institute, Bayer. NCT00390611: Paclitaxel and Carboplatin with or without sorafenib in the first-line treatment of patients with ovarian cancer. MetaRegister of Controlled Trials. Protocol Registered: Oct 19, 2006.

**ICON6: NCT00532194** *{published data only (unpublished sought but not used)}*

Gynecologic Cancer InterGroup. A double-blind, placebo-controlled, three-arm, randomised, multi-centre Gynecologic Cancer InterGroup trial of cediranib (AZD2171), in combination with platinum-based chemotherapy and as a single agent maintenance therapy, in women with ovarian cancer relapsing more than 6 months following completion of first line platinum-based treatment. MetaRegister of Controlled Trials. ISRCTN Assigned: 13 Aug, 2007.

**McGuire 2010** *{published data only}*

ImClone LLC. NCT00913835: a study of Liposomal Doxorubicin with or without IMC-3G3 in platinum-refractory or resistant advanced ovarian cancer. *MetaRegister of Controlled Trials.* Protocol Registered: June 2, 2009.

* 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 (Meeting Abstracts)* 2010;**28**(15˙suppl): TPS256.

**NCT00565851** *{published data only}*

National Cancer Institute, Gynecologic Oncology Group. Carboplatin and paclitaxel with or without Bevacizumab after surgery in treating patients with recurrent ovarian epithelial cancer, primary peritoneal cancer, or fallopian tube cancer. MetaRegister of Controlled Trials. Protocol Registered: Nov 29, 2007.

**NCT00791778** *{published data only}*

Bayer. Comparison of Nexavar/placebo as maintenance therapy for patients with advanced ovarian or primary peritoneal cancer. MetaRegister of Controlled Trials. Protocol Registered: Nov 14, 2008.

**NCT00866697** *{published data only}*

* GlaxoSmithKline. Efficacy and safety of pazopanib monotherapy after first line chemotherapy in ovarian,

fallopian tube, or primary peritoneal cancer. MetaRegister of Controlled Trials. Protocol Registered: March 19, 2009.

GlaxoSmithKline. NCT01227928: a study to evaluate efficacy and safety of pazopanib monotherapy in Asian women who have not progressed after first-line chemotherapy for advanced ovarian, fallopian tube or primary peritoneal carcinoma - an extension study to VEG110655. MetaRegister of Controlled Trials. Protocol Registered: Oct 21, 2010.

**NCT01015118** ***{published data only}***

Boehringer Ingelheim Pharmaceuticals. BIBF 1120 or placebo in combination with paclitaxel and carboplatin in first line treatment of ovarian cancer. MetaRegister of Controlled Trials. Protocol Registered: Nov 9, 2009.

**NCT01047891** ***{published data only}***

TRIAS 2009 - efficacy and safety study of sorafenib with topotecan in patients with platinum-resistant recurrent ovarian cancer. MetaRegister of Controlled Trials. Protocol Registered: January 12, 2010.

**NCT01081262** ***{published data only}***

National Cancer Institute, Gynecologic Oncology Group. Carboplatin and paclitaxel or oxaliplatin and capecitabine, with or without bevacizumab, as first-line therapy in treating patients with newly diagnosed Stage II, Stage III, Stage IV, or recurrent Stage I epithelial ovarian cancer or fallopian tube cancer. MetaRegister of Controlled Trials. Protocol Registered: March 4, 2010.

**OCEANS: NCT00434642** ***{published data only}***

Genentech. A study of carboplatin and gemcitabine plus bevacizumab in patients with ovary, peritoneal, or fallopian tube carcinoma (OCEANS). MetaRegister of Controlled Trials. Protocol Registered: Feb 9, 2007.

**TRINOVA-1: NCT01204749** ***{published data only}***

Amgen. 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. MetaRegister of Controlled Trials. Protocol Registered: Aug 26, 2010.

## Additional references

**Abaid 2010**

Abaid LN, Lopez KL, Micha JP, Rettenmaier MA, Brown III JV, Goldstein BH. Bevacizumab, paclitaxel and carboplatin for advanced ovarian cancer: Low risk of gastrointestinal and cardiovascular toxicity. *European Journal of Gynaecological Oncology* 2010;**31**(3):308–311.

**Aflibercept 2008**

Aflibercept: AVE 0005, AVE 005, AVE0005, VEGF Trap - Regeneron, VEGF Trap (R1R2), VEGF Trap-Eye. *Drugs in Research and Development* 2008;**9**(4):261–9.

**Alberts 2007**

Alberts DS, Liu PY, Wilczynski SP, Jang A, Moon J, Ward JH, et al. Phase II trial of imatinib mesylate in recurrent, biomarker positive, ovarian cancer (Southwest Oncology Group Protocol S0211). *International Journal of Gynecological Cancer* 2007;**17**(4):784–8.

**Asmane 2010**

Asmane I, Guastalla JP, Meeus P, Moullet I, Ardisson P, Vincent L, et al. Feasibility of bevacizumab (BEV) plus chemotherapy in heavily pretreated ovarian cancer (OC) patients (pts): A retrospective study. *Journal of Clinical Oncology (Meeting Abstracts)* 2010;**28**(15˙suppl):e15509.

**Bucher 1997**

Bucher HC, Guyatt GH, Griffith LE, Walter SD. The Results of Direct and Indirect Treatment Comparisons in Meta-Analysis of Randomized Controlled Trials. *Journal of Clinical Epidemiology* 1997;**50**(6):683–91.

**Buckstein 2007**

Buckstein R, Meyer RM, Seymour L, Biagi J, Mackay H, Laurie S, et al. Phase II testing of sunitinib: the National Cancer Institute of Canada Clinical Trials Group IND Program Trials IND.182-185. *Current Oncology* 2007;**14** (4):154–61.

**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.

**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.

**Cheng 2009**

Cheng X, Moroney JW, Levenback CF, Fu S, Jaishuen A, Kavanagh JJ. What is the benefit of bevacizumab combined with chemotherapy in patients with recurrent ovarian, fallopian tube or primary peritoneal malignancies?. *Journal of Chemotherapy* 2009;**21**(5):566–72.

**CTEP 2006**

Cancer Therapy Evaluation Program (CTEP), Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS. (http://ctep.cancer.gov) 2006.

**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 editor(s). *Systematic Reviews in Health Care: Meta-Analysis in Context*. 2nd Edition. London: BMJ Publication group, 2001.

**DerSimonian 1986**

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**(3):177–88.

**Diaz 2010**

Diaz JP, Tew WP, Zivanovic O, Konner J, Sabbatini PJ, Dos Santos LA, et al. Incidence and management of bevacizumab-associated gastrointestinal perforations in

patients with recurrent ovarian carcinoma. *Gynecologic Oncology* 2010;**116**(3):335–9.

**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.

**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.

**Friedlander 2010**
Friedlander M, Hancock KC, Rischin D, Messing MJ, Stringer CA, Matthys GM, et al. A Phase II, open-label study evaluating pazopanib in patients with recurrent ovarian cancer. *Gynecologic Oncology* 2010;**119**(1):32–7.

**Garcia 2008**
Garcia AA, Hirte H, Fleming G, Yang D, Tsao-Wei DD, Roman L, et al. California, Chicago, and Princess Margaret Hospital phase II consortia. Phase II clinical trial of bevacizumab and low-dose metronomic oral cyclophosphamide in recurrent ovarian cancer. *Journal of Clinical Oncology* 2008;**26**(1):76–82.

**GLOBOCAN 2008**
Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide. IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr. Lyon: IARCPress.

**GRADE Working Group**
Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grade Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328** (7454):1490–4.

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

**Hirte 2008**
Hirte HW, Vidal L, Fleming GF, Sugimoto AK, Morgan RJ, Biagi JJ, et al. A phase II study of cediranib (AZD2171) in recurrent or persistent ovarian, peritoneal or fallopian tube cancer: Final results of a PMH, Chicago and California consortia trial. *Journal of Clinical Oncology* 2008;**26**:5521.

**Hurt 2009**
Hurt JD, Richardson DL, Seamon LG, Fowler JF, Copeland LJ, Cohn DE, et al. Sustained progression-free survival with weekly paclitaxel and bevacizumab in recurrent ovarian cancer. *Gynecologic Oncology* 2009;**115**(3):396–400.

**Jemal 2008**
Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, et al. Cancer statistics. *CA: a Cancer Journal for Clinicians* 2008; **58**(2):71–96.

**Juretzka 2008**
Juretzka M, Hensley ML, Tew W, Konner J, Aghajanian C, Leitao M, et al. A phase 2 trial of oral imatinib in patients with epithelial ovarian, fallopian tube, or peritoneal carcinoma in second or greater remission. *European Journal of Gynaecological Oncology* 2008;**29**(6):568–72.

**Krasner 2010**
Krasner CN, Seiden M, Roche M, Morgan MA, Matulonis U, Wolf J. Tolerability and pharmacokinetics of intraperitoneal carboplatin and paclitaxel with intravenous bevacizumab. *Journal of Clinical Oncology (Meeting Abstracts)* 2010;**28**(15˙suppl):5037.

**Matulonis 2008**
Matulonis UA, Berlin ST, Krasner CN, Tyburski K, Lee J, Roche M, et al. Cediranib (AZD2171) is an active agent in recurrent epithelial ovarian cancer. *Journal of Clinical Oncology (Meeting Abstracts)* 2008;**26**(15˙suppl):5501–.

**Matulonis 2009**
Matulonis UA, Berlin S, Ivy P, Tyburski K, Krasner C, Zarwan C, et al. Cediranib, an oral inhibitor of vascular endothelial growth factor receptor kinases, is an active drug in recurrent epithelial ovarian, fallopian tube, and peritoneal cancer. *Journal of Clinical Oncology* 2009;**27**(33):5601–6.

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

**Moher 1998**
Moher D, Pham D, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? . *Lancet* 1998;**352**(9128):609–13.

**Monk 2006**
Monk BJ, Han E, Josephs-Cowan CA, Pugmire G, Burger RA. Salvage bevacizumab (rhuMAB VEGF)-based therapy after multiple prior cytotoxic regimens in advanced refractory epithelial ovarian cancer. *Gynecologic Oncology* 2006;**102**(2):140–4.

**Morrison 2007**
Morrison J, Swanton A, Collins S, Kehoe S. Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer. *Cochrane Database of Systematic Reviews* 2007, Issue 4.. [DOI: 10.1002/14651858.CD005343]

**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.

**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.

**Oehler 2000**

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

**Parmar 1998**

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24): 2815–34.

**Penson 2010**

Penson RT, Dizon DS, Cannistra SA, Roche MR, Krasner CN, Berlin ST, et al. Phase II Study of Carboplatin, Paclitaxel, and Bevacizumab With Maintenance Bevacizumab As First-Line Chemotherapy for Advanced Mullerian Tumors. *Journal of Clinical Oncology* 2010;**28**(1): 154–9.

**Quinn 2001**

Quinn M, Babb B, Brock A, Jones J. *Cancer Trends in England and Wales*. London: The Stationery Office, 2001.

**Robinson 2010**

Robinson ES, Matulonis UA, Ivy P, Berlin ST, Tyburski K, Penson RT, et al. Rapid development of hypertension and proteinuria with cediranib, an oral vascular endothelial growth factor receptor inhibitor. *Clinical Journal of the American Society of Nephrology* 2010;**5**(3):477–83.

**Rose 2009**

Rose PG, Drake R, Braly PS, Bell MC, Wenham RM, Hines JH, et al. Preliminary results of a phase II study of oxaliplatin, docetaxel, and bevacizumab as first-line therapy of advanced cancer of the ovary, peritoneum, and fallopian tube. *Journal of Clinical Oncology* 2009;**27**(15):5546).

**Sanchez-Munoz 2010**

Sanchez-Munoz A, Mendiola C, Rodriguez CA, Perez-Ruiz E, Jurado JM, Alonso-Carrion L, et al. Bevacizumab plus low-dose metronomic oral cyclophosphamide in heavily pretreated recurrent ovarian cancer. *Journal of Clinical Oncology (Meeting Abstracts)* 2010;**28**(15˙suppl):e15507.

**Schulz 1995**

Schulz KF, Chalmers I, Hayes RJ, Altman D. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**(5):408–12.

**Sfakianos 2009**

Sfakianos GP, Numnum TM, Halverson CB, Panjeti D, Kendrick JE, Straughn J M Jr. The risk of gastrointestinal perforation and/or fistula in patients with recurrent ovarian cancer receiving bevacizumab compared to standard chemotherapy: a retrospective cohort study. *Gynecologic Oncology* 2009;**114**(3):424–6.

**Shepherd 1989**

Shepherd JH. Revised FIGO staging for gynaecological cancer. *British Journal of Obstetrics and Gynaecology* 1989; **96**(8):889–92.

**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.

**Stewart 1999**

Stewart L, Advanced Ovarian Cancer Trialists Group. Chemotherapy for advanced ovarian cancer. *Cochrane Database of Systematic Reviews* 1999, Issue 1 10.1002/14651858.CD001418. [DOI: 10.1002/ 14651858.CD001418]

**Tillmanns 2010**

Tillmanns TD, Lowe MP, Schwartzberg LS, Walker MS, Stepanski EJ. A phase II study of bevacizumab with nab-paclitaxel in patients with recurrent, platinum-resistant primary epithelial ovarian or primary peritoneal carcinoma. *Journal of Clinical Oncology (Meeting Abstracts)* 2010;**28** (15˙suppl):5009.

**Vergote 2010**

Vergote I, Tropé CG, Amant F, Kristensen GB, Sardi JE, Ehlen T, et al. European Organization for Research and Treatment of Cancer-Gynaecological Cancer Group, NCIC Clinical Trials Group. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *New England Journal of Medicine* 2010;**363**(10):943–53.

**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.

**Welch 2010**

Welch SA, Hirte HW, Elit L, Schilder RJ, Wang L, MacAlpine K, et al. Sorafenib in combination with gemcitabine in recurrent epithelial ovarian cancer: A study of the princess margaret hospital phase II consortium. *Interntional Journal of Gynecological Cancer* 2010;**20**(5): 787–93.

* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

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

**Burger 2010 (GOG-0218)**

| | |
|---|---|
| Methods | Randomised, double-blind, placebo-controlled phase III trial |
| Participants | 1873 women were enrolled from 336 sites (in the US, Canada, South Korea and Japan)<br>625 patients were treated in arm I (chemotherapy alone), 625 in arm 2 (chemotherapy + concurrent bevacizumab) and 623 in arm 3 (chemotherapy + concurrent bevacizumab + maintenance bevacizumab) (see Interventions below for details)<br>All patients had newly diagnosed (confirmed by histology), previously untreated (i.e. no prior chemotherapy), advanced epithelial ovarian, fallopian tube or primary peritoneal cancer. All patients were within 1-12 weeks of initial abdominal surgery for staging and tumour debulking, after which they had stage III optimal (macroscopic residual disease $\leq$ 1 cm) or sub-optimal (> 1 cm) disease or stage IV disease All patients had a Gynecologic Oncology Group (GOG) Performance Status (PS) of 0-2<br>Patients were excluded if they had a history of significant vascular events, or evidence of intestinal obstruction requiring parenteral support<br>The median age in each arm was 60 years (range 25-86 years in arm 1; 24-88 years in arm 2; 22-89 years in arm 3)<br>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<br>931 (50%) women had GOG performance status 0, 809 (43%) had status 1 and 133 (7%) had status 2<br>639 (34%) patients had stage III disease with optimal cytoreduction; 752 (40%) patients had stage III sub-optimal and 482 (26%) had stage IV disease<br>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<br>Baseline characteristics were similar between all three study arms |
| Interventions | Patients were randomised to one of three treatment arms (in ratio 1:1:1, stratified by GOG performance status and by stage/debulking status). 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)<br>Arm 1: paclitaxel/carboplatin chemotherapy for cycles 1-6 [IV paclitaxel 175 mg/m$^2$ + carboplatin AUC 6 (AUC = area under the curve)] + placebo for cycles 2-22<br>Arm 2: paclitaxel/carboplatin chemotherapy as per arm 1 + concurrent bevacizumab (15 mg/kg) for cycles 2-6 + placebo for cycles 7-22<br>Arm 3: paclitaxel/carboplatin chemotherapy as per arm 1 + concurrent bevacizumab (15 mg/kg) for cycles 2-6 + maintenance bevacizumab for cycles 7-22 |
| Outcomes | Primary:<br>• progression-free survival (PFS) (as judged by radiographic, CA125, clinical criteria or death)<br>Secondary:<br>• overall survival (OS)<br>• safety<br>• quality of Life |

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| | • correlative laboratory studies |
| Notes | The key protocol amendments were: a) the inclusion of patients with optimally debulked (macroscopic residual) disease and b) the change of the primary end-point from OS to PFS (with unblinding to treatment assignment allowed at the time of disease progression)<br>The median length of follow-up (for the data reported thus far) was 17.4 months (range 0.0-50.7 months)<br>Analysis for efficacy was by intent-to-treat (ITT) (n = 1873); analysis for safety was by ITT as of cycle 2 (n = 1816)<br>The data thus far are from a data lock when events had been observed in 24% of patients 86 (14%) patients in arm 1, 82 (13%) patients in arm 2, and 117 (19%) patients in arm 3, were on treatment at time of analysis<br>100 (16%) patients in arm 1, 104 (17%) patients in arm 2, and 148 (24%) patients in arm 3, completed the regimen<br>There were a range of different reasons for discontinuation of study treatment<br>In arm 1: 299 (48%) patients had disease progression; 69 (11%) had adverse events, of which 57 (9%) occurred in cycles 1-6, and 12 (2%) occurred in cycles ≥ 7; 8 (1%) patients died; 44 (7%) patients refused treatment; 19 (3%) patients discontinued treatment for other reasons<br>In arm 2: 264 (42%) patients had disease progression; 86 (14%) had adverse events, of which 73 (12%) occurred in cycles 1-6, and 13 (2%) occurred in cycles ≥ 7; 7 (1%) patients died; 55 (9%) patients refused treatment; 27 (4%) patients discontinued treatment for other reasons<br>In arm 3: 164 (26%) patients had disease progression; 94 (15%) had adverse events, of which 59 (9%) occurred in cycles 1-6, and 35 (6%) occurred in cycles ≥ 7; 13 (2%) patients died; 50 (8%) patients refused treatment; 37 (6%) patients discontinued treatment for other reasons<br>Median time-to-event data were estimated using the Kaplan-Meier method. The analysis was stratified by GOG performance status and by stage/debulking status<br>At the time of analysis, disease progression was judged to have occurred in 423 (67.7%) patients in arm 1, in 418 (66.9%) patients in arm 2, and in 360 (57.8%) patients in arm 3. The 95% CI for arm 2 versus arm 1 was 0.76 to 1.04 in the original data and abstract, but it was not possible to tweak the ln(HR) and SE(ln(HR)) so that the RevMan estimate corresponded (outcome 1.2, 95% CI 0.79 to 1.04)<br>The median PFS was 10.3 months in arm 1, 11.2 months in arm 2 and 14.1 months in arm 3<br>At the time of analysis, 156 (25%) patients had died in arm 1, 150 (24%) patients had died in arm 2 and 138 (22%) patients had died in arm 3<br>The median length of OS was 39.3 months in arm 1, 38.7 months in arm 2 and 39.7 months in arm 3<br>The 1-year OS rate was 90.6% in arm 1, 90.4% in arm 2 and 91.3% in arm 3<br>————————————————————————————<br>Please note trial results only published in Abstract form<br>Data from:<br>1. conference abstract from ASCO 2010 (conference of the American Society of Clinical Oncology)<br>2. Powerpoint presentation from ASCO 2010 (supplied by study investigators)<br>3. conference abstract from ESMO 2010 (conference of the European Society of Medical |

**Burger 2010 (GOG-0218)** (*Continued*)

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| | Oncology)<br>4. poster from ESMO 2010 (available from ESMO 2010 website http://esmo.poster-submission.com/search/download/9801) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "Randomly allocated regimens". However, this was a GOG study, so it is likely that adequate sequence generation was used |
| Allocation concealment (selection bias) | Unclear risk | Abstract did not report whether an attempt was made to conceal the allocation |
| Blinding (performance bias and detection bias)<br>All outcomes | Unclear risk | Not reported. Study was reported as double-blind, but unclear as to whether outcome assessors were blinded |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | % analysed: 1816/1873 (97%) for outcomes on safety. All patients analysed for survival outcomes using ITT approach |
| Selective reporting (reporting bias) | Unclear risk | No QoL data yet - but this is a common problem with the preliminary data reporting in abstracts, and applies to some of the other studies as well |
| Other bias | Unclear risk | Insufficient information to assess whether an additional form of bias may have been present |

**Karlan 2010**

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| Methods | 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)<br>53 patients 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)<br>All patients had radiographically documented progression, as judged by RECIST or CA125 (GCIG criteria), and $\leq$ 3 anticancer therapies (but at least one platinum-containing regimen). All patients had a GOG performance status of 0 or 1, and adequate renal and hepatic function<br>The median age was 59 years (range 27-80 years) in arm A, 60 years (28-85) in arm B and 62 years (38-83) in arm C<br>137 (85%) women had ovarian cancer; 21 (13%) women had primary peritoneal cancer; |

| | |
|---|---|
| | 3 (2%) women had fallopian tube cancer<br>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<br>88 (55%) women had GOG performance status 0, 71 (44%) women had status 1, and 2 (1%) women had status 2-3<br>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<br>87 (54%) women had a history of disease progression on or within 6 months of the last chemotherapy regimen<br>8 (5%) women had previously been treated with anti-VEGF therapy<br>145 (90%) women had measurable disease at baseline<br>61 (38%) women had a history of one prior anticancer therapy; 100 (62%) had a history of two or more therapies<br>86 (53%) women had a history of one prior platinum regimen; 75 (47%) had a history of two or more<br>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 6-12 months), and 31 (19%) women were platinum-sensitive (PFI > 12 months); data were unavailable on platinum sensitivity status for 2 (1%) women<br>Baseline characteristics were fairly similar between all three study arms |
| Interventions | Patients 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)<br>Arm A: paclitaxel at 80 mg/m$^2$ IV once weekly QW (3 weeks on/1 week off) plus AMG 386 at 10 mg/kg IV QW<br>Arm B: paclitaxel at 80 mg/m$^2$ IV QW (3 weeks on/1 week off) plus AMG 386 at 3 mg/kg IV QW<br>Arm C: paclitaxel at 80 mg/m$^2$ IV QW (3 weeks on/1 week off) plus placebo IV QW<br>Patients 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<br>Patients 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:<br>• PFS (defined as time from randomisation to disease progression per RECIST, CA125 (GCIG criteria), clinical progression or death)<br>Secondary:<br>• response as per RECIST (ORR)<br>• CA125 response (per GCIG)<br>• safety<br>• pharmacokinetics |
| Notes | The median follow-up time was 66.1 weeks in arm A, 65.1 weeks in arm B and 64.4 weeks in arm C<br>Median PFS was 7.3 months in arm A, 7.4 months in arm B and 5.0 months in arm C<br>Hazard ratios (HRs) for PFS were obtained using a Cox regression model (stratified by prior anti-VEGF therapy, and progression within 6 months of the last chemotherapy |

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| | regimen). Comparing the hazard of PFS for arm A (10 mg/kg AMG 386) vs arm C (placebo), the HR was 0.70 (80% CI 0.52to 0.93; P = 0.113). The HR for arm B (3 mg/kg AMG 386) vs arm C (placebo) was 0.57 (80% CI 0.42 to 0.77; P = 0.016). The combined HR for Arms A and B (AMG 386) versus arm C (placebo) was 0.64 (80% CI 0.50 to0.82 P = 0.022)<br>Median OS was 22.5 months for arm A, 20.4 months for arm B and 20.9 months for arm C<br>HRs for OS obtained using a Cox regression model were 0.60 (80% CI 0.42 to0.88; P = 0.081) for arm A vs arm C and 0.77 (80% CI 0.54 to 1.09; P = 0.330) for arm B vs arm C<br>The analysis of safety data was restricted to treated patients (52 patients in arm A, 53 in arm B and 55 in arm C)<br>————————————————————<br>Please note trial results only published in abstract form<br>Data from:<br>1. conference abstract from ASCO 2010<br>2. Powerpoint presentation from ASCO 2010 (supplied by study investigators)<br>3. conference abstract from ESMO 2010. [Please note this was presented as Vergote et al, but is about the same study, and by the same team, but with a different order of authors]<br>4. poster from ESMO 2010 (available from ESMO 2010 website http://esmo.poster-submission.com/search/download/9798). [Again, authors listed in different order to ASCO 2010, i.e. Vergote et al.]<br>5. trial protocol at http://www.clinicaltrials.gov/show/NCT00479817<br>6. conference abstracts of the pharmacokinetic analysis of the trial, by Lu et al., from ASCO 2010 and ESMO 2010 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported, "Randomised" was used in abstract but further details were not provided |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Blinding (performance bias and detection bias)<br>All outcomes | Unclear risk | Not reported. Study was reported as "double-blind", but unclear as to whether outcome assessors were blinded |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Unclear |
| Selective reporting (reporting bias) | Unclear risk | Only limited data presented in abstract/ Powerpoint poster |
| Other bias | Unclear risk | Insufficient information to assess whether an additional form of bias may have been present |

**Ledermann 2009**

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| Methods | Randomised, double-blind, placebo-controlled phase II trial |
| Participants | 84 women with chemotherapy-responsive relapsed ovarian cancer were recruited. [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.]<br>44 women were in the intervention (BIBF 1120) arm and 40 in the placebo arm<br>The mean age was 60 years (range 27-76 years)<br>41% of women had had a treatment-free interval before prior chemotherapy of < 6 months; 59% had had an interval of 6-12 months |
| Interventions | BIBF 1120 (250 mg, oral, twice daily, given for up to 9 months)<br>versus<br>Placebo |
| Outcomes | Primary:<br>• PFS Rate at 36 weeks [confirmed by CT assessment, performed at 12-week intervals]<br>Secondary:<br>• time to tumour progression according to RECIST and the tumour marker CA125<br>• PFS at 3 and 6 months<br>• survival and Incidence and Intensity of Adverse Events at 9 months |
| Notes | The median duration of treatment was 116 days (range 2-281 days) in the intervention (BIBF 1120) arm and 101 days (range 2-239 days) in the placebo arm<br>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<br>The PFS HR was 0.68 (95% CI 0.42 to 1.09)<br>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<br>The fact that only the abstract was available meant the results (including adverse events) were not very detailed:<br>grade 3 adverse events occurred in 54% of patients in the BIBF 1120 arm and 25% of patients in the placebo arm;<br>grade 4 adverse events occurred in 7% of patients in the BIBF 1120 arm and 3% of patients in the placebo arm; and<br>grade 3 gastrointestinal toxicities were seen in 16% of patients in the BIBF 1120 arm and 10% of patients in the placebo arm<br>Elevated liver enzymes were noted in 43% of patients in the BIBF 1120 arm and 6.3% of patients in the placebo arm<br>————————————————————<br>Information from:<br>1. Conference Abstract from ASCO 2009<br>2. Trial Protocol at http://www.clinicaltrials.gov/show/NCT00710762 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
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**Ledermann 2009** (*Continued*)

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|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported: "randomised" was used in title, but no further details were provided elsewhere in the abstract |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Blinding (performance bias and detection bias)<br>All outcomes | Unclear risk | Not reported. Study was reported as "double-blind", but unclear as to whether outcome assessors were blinded |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Unclear |
| Selective reporting (reporting bias) | Unclear risk | Only limited data presented in abstract |
| Other bias | Unclear risk | Insufficient information to assess whether an additional form of bias may have been present |

**Perren 2010 (ICON7)**

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| 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)<br>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<br>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]<br>The median age was 57 years (range 18-81) in the control group, and 57 years (range 24-82) in the bevacizumab group<br>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<br>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<br>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%)<br>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<br>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<br>1111 (73%) women had optimal surgery ($\leq$ 1 cm residual disease), 387 (25%) women |

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| | had sub-optimal surgery (> 1 cm residual disease) and 30 (2%) women had not had surgery<br>Baseline characteristics were similar between the two study arms<br>**Stratification variables**<br>*FIGO stage and residuum*<br>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<br>*Intent to start chemotherapy*<br>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<br>Randomisation was stratified on three variables: the stage and extent of debulking (stage I-III debulked ≤ 1 cm vs stage I-III debulked > 1 cm vs stage IV and inoperable stage III); the timing of starting the intended treatment (≤ 4 vs ≥ 4 weeks after surgery); and GCIG group<br>Control arm: carboplatin AUC 6 (AUC = area under the curve) IV over 30-60 mins + 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<br>Intervention arm: carboplatin + paclitaxel as in the control arm, plus bevacizumab 7.5 mg/kg IV over 30-90 minutes on the same day Patients 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<br>Patients 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<br>Patients had clinical assessments/CA125 measurements at every chemotherapy cycles, 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:<br>• PFS [disease progression defined by RECIST guidelines on radiological, clinical or symptomatic progression; CA125 elevation alone was not defined as disease progression]<br>Secondary:<br>• OS (results due in 2012)<br>• response rate<br>• duration of response<br>• toxicity<br>Substudies:<br>• quality of life<br>• health economics<br>• translational (biomarker) research |
| Notes | The median length of follow-up (at the time of reporting data thus far) was 19.4 months. At this point, 2 patients were still on treatment, and there had been 759 events (progres- |

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| | sions or deaths)<br>For the purposes of the regulatory analysis, PFS censoring was at the time of most recent CT scan<br>[An academic analysis was also performed, for which PFS censoring was at the latter of either the most recent CT scan or the last clinical follow-up. In the interests of simplicity, we have not reported these results here]<br>The median length of PFS was 16 months in the placebo group, and 18.3 months in the intervention (bevacizumab) group (HR 0.79, 95% CI 0.68 to0.91; P = 0.001 - from log-rank test)<br>In a preliminary analysis of OS, 130 (17%) women in the placebo arm had died, compared to 111 (15%) women in the bevacizumab arm (HR 0.81, 95% CI 0.63 to1.04; P = 0.098 - log-rank test)<br>---<br>Data from:<br>1. conference presentation from ESMO 2010 (at http://www.icon7trial.org)<br>2. conference abstract from ESMO 2010<br>3. trial protocol http://www.controlled-trials.com/isrctn/pf/91273375 |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not reported: "randomised" was mentioned in abstract and protocol, but no further details were provided |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Blinding (performance bias and detection bias)<br>All outcomes | Unclear risk | "Open label" trial, so by implication no blinding attempted |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Unclear |
| Selective reporting (reporting bias) | Unclear risk | Only Conference Presentation data available so far, but no obviously selective reporting of outcomes |
| Other bias | Unclear risk | Insufficient information to assess whether an additional form of bias may have been present |

**Vergote 2009**

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| Methods | A randomised, double-blind, placebo-controlled trial |
| Participants | 55 women with advanced ovarian cancer, resistant to chemotherapy (platinum-resistant, and topotecan-resistant and/or liposomal doxorubicin-resistant)<br>All women also had symptomatic malignant ascites, for which they needed paracentesis 1-4 times per month<br>Patients were excluded 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 |
| Interventions | Women were randomised to either VEGF-Trap (n = 29, 4 mg/kg IV every 2 weeks), also known as Aflibercept, or placebo (n=26)<br>After 60 days, women could cross-over and receive VEGF-Trap in an open-label phase |
| Outcomes | Primary:<br>• time to repeat paracentesis<br>Secondary:<br>• other paracentesis-related parameters<br>• OS (not mentioned as outcome in protocol, but reported in abstract)<br>• tolerability<br>• safety/adverse events<br>• quality of life (not reported in abstract, but mentioned as outcome in protocol)<br>• patient-reported outcomes (not reported in abstract, but mentioned as outcome in protocol) |
| 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 those outcomes which are of relevance to this specific review, i.e. survival and adverse events<br>This trial has so far only been presented at a conference (and subsequently published as an abstract), and hence the data available are currently very limited. The full report is expected to be published within the next few months<br>The median age of participants was 56 years (range 33-88 years)<br>84% of women had ECOG Performance Status of 1-2<br>Patients had a median of 4 prior lines of chemotherapy (range 2-11)<br>There was no evidence of a difference between the VEGF-Trap vs placebo groups in terms of OS (HR 1.023, 95% CI 0.562 to 1.863)<br>The authors report four fatal gastrointestinal events: three patients in the VEGF-Trap arm had intestinal perforations, and one patient on placebo developed a fistula, followed by sepsis<br>The authors also report the following other adverse events, which were observed amongst women treated with VEGF-Trap: dysphonia (20%), hypertension (16.7%), proteinuria (10%), epistaxis (6.7%). [The precise number of women who suffered each adverse event was unclear]<br>———————————————————————<br>Date from:<br>1. conference abstract from ESGO 2009<br>2. abstract to forthcoming full published report of the study (kindly provided by study |

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| | investigators)<br>3. trial Protocol http://www.clinicaltrials.gov/ct2/show/NCT00327444 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Title and abstract say that allocation was "randomised," but details of sequence generation are not reported |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Blinding (performance bias and detection bias)<br>All outcomes | Unclear risk | Protocol, title and abstract all mention that study was "double-blind", and patients in the control arm received placebo Precise details of blinding are not reported |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Unclear |
| Selective reporting (reporting bias) | Unclear risk | Only limited data presented in abstract |
| Other bias | Unclear risk | Insufficient information to assess whether an additional form of bias may have been present |

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

| Study | Reason for exclusion |
|---|---|
| Azad 2008 | Not an RCT. This was a phase I dose-finding study of sorafenib and bevacizumab for patients with multiple tumour types; this report emphasises results for the 15 patients with ovarian cancer |
| Burger 2010 | Comprehensive narrative review of literature on VEGF inhibitors for gynaecologic malignancies, including summary tables of completed and ongoing trials. Not a systematic review |
| Markman 2009 | A narrative review of the literature on angiogenesis inhibitors in ovarian cancer |
| NCT00017303 | Ongoing randomised phase II study of IM-862 (which has anti-angiogenic action) in patients with resected stage III ovarian cancer. Study excluded because all patients receive IM-862, randomised to one of three different dosage schedules (i.e. patients are not randomised to therapy with vs without angiogenesis inhibitor) |
| NCT00096200 | Ongoing randomised phase II study in patients with recurrent ovarian cancer. All patients receive sorafenib; one group receives sorafenib only, while the other group receives sorafenib plus carboplatin and paclitaxel. Study |

(*Continued*)

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| | excluded as it does not compare treatment with vs without angiogenesis inhibitor |
| NCT00543049 | Ongoing randomised phase II study in patients with platinum-refractory ovarian cancer. All patients receive sunitinib; they are randomised to one of two different dosage schedules. Study excluded as it does not compare treatment with vs without angiogenesis inhibitor |
| NCT00886691 | Ongoing randomised phase II study in patients with recurrent/persistent ovarian cancer, comparing therapy with bevacizumab alone vs bevacizumab + everolimus (an inhibitor of a serine-threonine kinase). [Thus, the trial is not comparing therapy with vs without an angiogenesis inhibitor] |
| NCT01115829 | An ongoing randomised phase I/II study of cediranib with vs without olaparib (a PARP-inhibitor, which targets tumour growth via a different pathway to angiogenesis inhibitors). Study excluded because all patients receive the angiogenesis inhibitor cediranib (i.e. patients are not randomised to treatment with vs without angiogenesis inhibitor) |
| NCT01167712 | Ongoing randomised phase III trial of two different dosage schedules of paclitaxel and carboplatin in patients with Stage II/IV ovarian cancer. Study excluded because, although patients in both randomisation arms may have their chemotherapy with or without bevacizumab, the decision of whether or not to include bevacizumab is made by patient choice, rather than randomisation |
| Osterweil 2010 | Not an RCT. Two different references to a single article, reporting and commenting on a conference abstract about a phase III RCT (Burger 2010 (GOG-0218)) |
| Sennino 2010 | Not an RCT. An article commenting on another paper, which compared the activity of bevacizumab to an inhibitor of PDGF-beta in mouse-based models of ovarian cancer |
| Tew 2007 | Phase II study, involving 162 patients 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) |

## Characteristics of studies awaiting assessment *[ordered by study ID]*

### Gordon 2010

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|---|---|
| Methods | *An adaptive randomised discontinuation trial of XL184 (BMS-907351) in patients (pts) with advanced solid tumours.* An ongoing, phase II, randomised discontinuation trial, comprising an open-label Lead-In tage (stage 1), and a double-blinded Randomised stage (stage 2). [The stage 2 results would constitute an RCT, and so would be relevant to this review] |
| Participants | Patients with advanced solid tumours will be recruited into nine tumour-specific cohorts (breast, gastric/gastro-oesophageal junction, small cell lung, non-small cell lung, ovarian, pancreatic, hepatocellular, melanoma and prostate cancer). [Obviously, only the ovarian cancer cohort would be relevant to this review.] |
| Interventions | Stage 1 (open-label, non-randomised): All patients receive XL 184 (an oral inhibitor of multiple tyrosine kinases, including VEGF-R2, MET and RET) at a dose of 100 mg daily for 12 weeks. Those with a partial or complete response (as judged by modified RECIST criteria) will continue with daily XL 184 until disease progression. Those with stable disease will continue to Stage 2 (randomisation)<br>Stage 2 (double-blind, randomised): patients with stable disease are randomised 1:1 to receive either daily XL184 or |

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| | placebo, until disease progression<br>A 'non-randomised expansion cohort' is also planned, in which all subjects receive open-label Xl 184 (100 mg daily) until disease progression |
| Outcomes | Primary:<br>• stage 1: objective response rate<br>• stage 2: PFS<br>Secondary:<br>• safety and tolerability<br>• correlation between clinical outcome and factors such as: the pathway dysfunction of disease-related genes, specific proteins (e.g. MET), or downstream signalling molecules<br>• pharmacokinetics/pharmacodynamics |
| Notes | This ongoing trial may or may not be suitable for inclusion, depending on whether or not the cohort of patients with ovarian cancer proceed to stage 2 (i.e. a double-blind, randomised trial of XL184)<br>The protocol has been published on ClinicalTrials.gov:<br>http://www.clinicaltrials.gov/ct2/show/NCT00940225 |

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

**AURELIA: NCT00976911**

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| Trial name or title | AURELIA: a study of Avastin (bevacizumab) added to chemotherapy in patients with platinum-resistant ovarian cancer |
| Methods | Phase III, randomised, open-label, two-arm, multi-centre study |
| Participants | Women ≥ 18 years old with platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer |
| Interventions | Randomisation to chemotherapy (paclitaxel, topotecan and liposomal doxorubicin) with bevacizumab, or chemotherapy alone |
| Outcomes | Primary:<br>• PFS<br>Secondary:<br>• objective response rate, biological PFS, OS<br>• quality of life: EORTC, HADS, FOSI<br>• safety and tolerability: AEs, laboratory parameters, ECOG performance status, vital signs |
| Starting date | October 2009 |
| Contact information | Developing drug company: Roche/Genentech<br>Roche medical information contact: Dr Isabelle Widmer (isabelle.widmer@roche.com) |
| Notes | Protocol online at: http://clinicaltrials.gov/show/NCT00976911 |

**Hainsworth 2010**

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| Trial name or title | Paclitaxel and carboplatin with or without sorafenib in the first-line treatment of patients with ovarian cancer |
| Methods | Phase II, randomised, active control, open-label |
| Participants | Women ≥ 18 years old, with histologically-confirmed stage III or IV epithelial ovarian cancer, who have undergone cytoreductive surgery, and who do not have residual large volume disease (no tumour nodules > 3 cm in size), bowel involvement or intestinal obstruction |
| Interventions | Randomised to standard chemotherapy (paclitaxel and carboplatin), either with or without sorafenib |
| Outcomes | Primary:<br>• PFS |
| Starting date | October 2006 |
| Contact information | Principal Investigator: John D. Hainsworth, MD, Sarah Cannon Research Institute<br>tel: 1-877-MY-1-SCRI<br>asksarah@scresearch.net<br>jhainsworth@tnonc.com |
| Notes | Protocol online at: http://www.clinicaltrials.gov/show/NCT00390611<br>Also presented as ongoing trial poster/abstract at ASCO 2010 |

**ICON6: NCT00532194**

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| Trial name or title | ICON6 - a double-blind, placebo-controlled, three-arm, randomised, multi-centre Gynaecologic Cancer InterGroup trial of cediranib (AZD2171), in combination with platinum-based chemotherapy and as a single agent maintenance therapy, in women with ovarian cancer relapsing more than 6 months following completion of first line platinum-based treatment |
| Methods | Phase III, double-blind, placebo-controlled, three-arm, randomised, multicentre study |
| Participants | 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 six months since completion of first-line platinum-based chemotherapy |
| Interventions | Randomisation to one of three different study arms<br>Arm A (reference): standard platinum-based chemotherapy 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<br>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<br>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 |

**ICON6: NCT00532194** (*Continued*)

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| Outcomes | Primary:<br>• stage 1: safety<br>• stage 2: PFS<br>• stage 3: OS<br>Secondary:<br>• stage 1: none<br>• stage 2: OS and toxicity<br>• stage 3: PFS, toxicity and QoL |
| Starting date | November 2007 |
| Contact information | Prof Jonathan Ledermann, University College London, Cancer Research UK and UCL Cancer Trials Centre, 90 Tottenham Court Road, London W1T 4TJ, United Kingdom |
| Notes | Protocol online at: http://www.controlled-trials.com/mrct/trial/724143 |

**McGuire 2010**

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| Trial name or title | Randomised phase II trial of pegylated liposomal doxorubicin (PLD) with or without anti-platelet-derived growth factor receptor-alpha (PDGF-R-alpha) monoclonal antibody IMC-3G3 in platinum-refractory/resistant advanced ovarian cancer |
| Methods | Phase II, open-label, randomised controlled trial |
| Participants | Women with platinum-refractory/resistant ovarian cancer from 13-15 North American and European centres. A total of 110 enrolled patients is aimed for; 25 patients had been enrolled at 6 sites as of January 2010 |
| Interventions | Randomisation to either arm A or arm B, continuing until disease progression or other withdrawal criteria:<br>arm A: doxorubicin (40 mg/m$^2$) every 4 weeks + IMC-3G3 (20 mg/kg) every 2 weeks<br>arm B: doxorubicin (40 mg/m$^2$) every 4 weeks<br>Patients in arm B may receive IMC-3G3 monotherapy upon disease progression<br>[IMC-3G3 is an inhibitor of PDGF-R-alpha, another tyrosine-kinase enzyme involved in angiogenesis, and which is often associated with VEGF-R.] |
| Outcomes | Primary:<br>• PFS<br>Secondary:<br>• OS<br>• objective response rate<br>• median duration of response<br>• adverse events<br>• IMC-3G3 antibody and pharmacokinetic assessments |
| Starting date | June 2009 |
| Contact information | Email: ClinicalTrials@ImClone.com |

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| Notes | Protocol online at: http://www.clinicaltrials.gov/show/NCT00913835<br>Also presented as ongoing trial poster/abstract at ASCO 2010 |

**NCT00565851**

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| Trial name or title | Carboplatin and paclitaxel with or without bevacizumab after surgery in treating patients with recurrent ovarian epithelial cancer, primary peritoneal cavity cancer, or fallopian tube cancer |
| Methods | Phase III, randomised, multi-centre study |
| Participants | Women ≥ 18 years old, with recurrent ovarian epithelial carcinoma, primary peritoneal carcinoma or fallopian tube carcinoma |
| Interventions | All patients have surgical cytoreduction if appropriate. Whether or not they have surgery, patients are then randomised to one of two treatment arms<br>Arm I: chemotherapy (carboplatin plus either paclitaxel or docetaxel)<br>Arm II: chemotherapy as per arm I, plus bevacizumab |
| Outcomes | Primary:<br>• OS<br>Secondary:<br>• PFS<br>• frequency and severity of adverse events |
| Starting date | December 2007 |
| Contact information | Study Chair: Robert L Coleman, MD<br>M.D. Anderson Cancer Center<br>Email: rcoleman@mdanderson.org |
| Notes | Protocol online at: http://clinicaltrials.gov/show/NCT00565851 |

**NCT00791778**

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|---|---|
| Trial name or title | Comparison of Nexavar/placebo as maintenance therapy for patients with advanced ovarian or primary peritoneal cancer |
| Methods | Phase II, randomised, double-blind, placebo-controlled |
| 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 |
| Interventions | Randomisation to sorafenib (also known as Nexavar) or placebo |

**NCT00791778** (*Continued*)

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|---|---|
| Outcomes | Primary:<br>• PFS, based on time to CT-documented relapse<br>Secondary:<br>• time to first pathologic CA125 serum levels<br>• OS<br>• ovarian cancer symptoms response<br>• general health status |
| Starting date | November 2008 |
| Contact information | Bayer Healthcare Pharmaceuticals Inc.<br>Email: medical.information@bayer.co.uk<br>Web: www.bayerscheringpharma.co.uk |
| Notes | Protocol online at: http://www.clinicaltrials.gov/show/NCT00791778 |

**NCT00866697**

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|---|---|
| Trial name or title | Efficacy and safety of pazopanib monotherapy after first line chemotherapy in ovarian, fallopian tube, or primary peritoneal cancer |
| Methods | Phase III, randomised, double-blind |
| Participants | Women ≥ 18 years old, with non-bulky FIGO Stage II-IV ovarian, fallopian tube or primary peritoneal cancer that has not progressed after completing first-line chemotherapy |
| Interventions | Randomisation to Ppazopanib monotherapy or placebo |
| Outcomes | Primary:<br>• PFS<br>Secondary:<br>• OS<br>• Safety and tolerability at 1 year<br>• 3-year PFS<br>• PFS by GCIG criteria<br>• QoL |
| Starting date | March 2009 |
| Contact information | US GSK Clinical Trials Call Center: 877-379-3718<br>Email: info@clinicaltrialsforgsk.com |
| Notes | Protocol online at: http://clinicaltrials.gov/show/NCT00866697<br>Extension trial in Asian women: NCT01227928 [see supplementary reference for this study] |

**NCT01015118**

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|---|---|
| Trial name or title | BIBF 1120 or placebo in combination with paclitaxel and carboplatin in first-line treatment of ovarian cancer |
| Methods | Phase III, randomised, double-blind, placebo-controlled |
| Participants | Women ≥ 18 years old, with advanced epithelial ovarian cancer, fallopian tube or primary peritoneal cancer |
| Interventions | Patients randomised to one of two arms, and followedup for 41 months<br>Arm I: paclitaxel and carboplatin chemotherapy, plus oral BIBF 1120<br>Arm II: paclitaxel and carboplatin chemotherapy, plus oral placebo |
| Outcomes | Primary:<br>• PFS<br>Secondary:<br>• PFS according to Response Evaluation Criteria In Solid Tumors 1.1 criteria<br>• OS<br>• Time to tumour marker progression<br>• Objective response<br>• Incidence and intensity of adverse events<br>• Changes in safety laboratory parameters |
| Starting date | November 2009 |
| Contact information | Boehringer Ingelheim Call Centre: 1-800 243-0127<br>Email: clintriage.rdg@boehringer-ingelheim.com |
| Notes | Protocol online at: http://www.clinicaltrials.gov/show/NCT01015118 |

**NCT01047891**

| | |
|---|---|
| Trial name or title | Efficacy and safety study of sorafenib with topotecan in patients with platinum-resistant recurrent ovarian cancer (TRIAS 2009) |
| Methods | Phase II, randomised, placebo-controlled, double-blind |
| Participants | Women ≥ 18 years old, with platinum-resistant recurrent ovarian cancer |
| Interventions | Randomisation to IV topotecan and oral sorafenib, or IV topotecan and oral placebo |
| Outcomes | Primary:<br>• PFS<br>Secondary:<br>• OS<br>• Response rate<br>• Duration of response<br>• Time to progression<br>• Safety and tolerability<br>• QoL |

**NCT01047891** (*Continued*)

| | |
|---|---|
| Starting date | January 2010 |
| Contact information | Jalid Sehouli, Professor<br>Tel: +49 (0) 30 450 564043<br>Email: sehouli@aol.com |
| Notes | Protocol online at: http://www.clinicaltrials.gov/show/NCT01047891 |

**NCT01081262**

| | |
|---|---|
| Trial name or title | Carboplatin and paclitaxel or oxaliplatin and capecitabine, with or without bevacizumab, as first-line therapy in treating patients with newly diagnosed stage II, stage III, stage IV, or recurrent stage I epithelial ovarian cancer or fallopian tube cancer |
| Methods | Phase III, randomised, open-label, multi-centre study |
| Participants | Women ≥ 18 years old, with newly-diagnosed stage II-IV or recurrent stage I mucinous epithelial ovarian or fallopian tube cancer |
| Interventions | Patients are first stratified according to disease status, then randomised to one of four treatment arms<br>Arm I: IV carboplatin and paclitaxel every 3 weeks for 6 courses<br>Arm II: single dose IV oxaliplatin and daily oral capecitabine for 2 weeks; repeat every 3 weeks for 6 courses<br>Arm III: as for arm I, plus bevacizumab, then continue bevacizumab every 3 weeks for another 12 courses<br>Arm IV: as for arm II, plus bevacizumab as for arm III |
| Outcomes | Primary Outcome:<br>• OS<br>Secondary Outcomes:<br>• PFS<br>• Response rate<br>• Toxicity<br>• Quality-of-life<br>• Financial costs vs clinical benefits |
| Starting date | January 2010 |
| Contact information | Principal Investigator: Martin E. Gore, MD. Royal Marsden NHS Foundation Trust<br>Principal Investigator: David M Gershenson, MD. M.D. Anderson Cancer Center |
| Notes | Protocol online at: http://www.clinicaltrials.gov/show/NCT01081262 |

**OCEANS: NCT00434642**

| | |
|---|---|
| Trial name or title | A study of carboplatin and gemcitabine plus bevacizumab in patients with ovary, peritoneal, or fallopian tube carcinoma (OCEANS) |
| Methods | Phase III, randomised, double-blind (subject, investigator), placebo-contolled, parallel assignment, multicentre 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:<br>• PFS<br>Secondary:<br>• Objective response and duration of response<br>• OS<br>• Incidence of gastrointestinal perforation (GIP)<br>• Characterisation of the safety of bevacizumab in combination with carboplatin and gemcitabine<br>• Incidence of all adverse events |
| Starting date | April 2007 |
| Contact information | Developing drug company: Roche/Genentech<br>Roche medical information contact: Dr Isabelle Widmer (isabelle.widmer@roche.com) |
| Notes | Protocol online at: http://clinicaltrials.gov/show/NCT00434642 |

**TRINOVA-1: NCT01204749**

| | |
|---|---|
| Trial name or title | 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 |
| Methods | Phase III, Randomised, double-blind, placebo-controlled, multicentre study |
| Participants | 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 | Randomisation to weekly IV infusions of either paclitaxel and placebo (control arm), or paclitaxel and AMG 386 |
| Outcomes | Primary:<br>• PFS<br>Secondary:<br>• Incidence of the occurrence of anti-AMG 386 antibody formation<br>• Patient-reported health related quality of life (HRQOL) and ovarian cancer related symptoms using the functional assessment of cancer therapy - ovary questionnaire (FACT-O) |

**TRINOVA-1: NCT01204749** (*Continued*)

| | |
|---|---|
| | • OS<br>• Objective Response Rate<br>• Duration of Response<br>• CA125 response rate per Gynecologic Cancer Intergroup (GCIG) and change in CA125<br>• Incidence of adverse events and significant laboratory abnormalities<br>• Pharmacokinetics of AMG 386 (Cmax and Cmin)<br>• Overall health status using EuroQOL (EQ5D) |
| Starting date | October 2010 |
| Contact information | MD, Study Director, Amgen<br>Amgen Call Center<br>tel: 866-572-6436 |
| Notes | Protocol online at: http://clinicaltrials.gov/show/NCT01204749 |

## DATA AND ANALYSES

**Comparison 1. Chemo + concurrent bevacizumab + maintenance placebo versus chemo + concurrent and maintenance placebo**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Overall survival | 1 | | Hazard Ratio (Random, 95% CI) | Subtotals only |
| 2 Progression-free survival | 1 | | Hazard Ratio (Random, 95% CI) | Subtotals only |
| 3 Grade ≥2 gastrointestinal adverse events | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 4 Grade ≥2 hypertension | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 5 Grade ≥3 proteinuria | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 6 Grade ≥2 pain | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 7 Grade ≥4 neutropenia | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 8 Febrile neutropenia | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 9 Venous thromboembolic event | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 10 Arterial thromboembolic event | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 11 Non-CNS bleeding (grade ≥3) | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |

**Comparison 2. Chemo + concurrent and maintenance bevacizumab versus chemo +/- placebo**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Overall survival | 2 | 2707 | Hazard Ratio (Random, 95% CI) | 0.87 [0.73, 1.03] |
| 1.1 Concurrent BEV (15 mg/kg) | 1 | 1209 | Hazard Ratio (Random, 95% CI) | 0.92 [0.73, 1.15] |
| 1.2 Concurrent BEV (7.5 mg/kg) | 1 | 1498 | Hazard Ratio (Random, 95% CI) | 0.81 [0.63, 1.04] |
| 2 Progression-free survival | 2 | 2707 | Hazard Ratio (Random, 95% CI) | 0.75 [0.68, 0.83] |
| 2.1 Concurrent BEV (15 mg/kg) | 1 | 1209 | Hazard Ratio (Random, 95% CI) | 0.72 [0.63, 0.82] |
| 2.2 Concurrent BEV (7.5 mg/kg) | 1 | 1498 | Hazard Ratio (Random, 95% CI) | 0.79 [0.68, 0.91] |
| 3 Severe gastrointestinal adverse events | 2 | 2407 | Risk Ratio (IV, Random, 95% CI) | 2.47 [1.08, 5.67] |
| 3.1 Grade ≥2 GI events | 1 | 909 | Risk Ratio (IV, Random, 95% CI) | 1.98 [0.67, 5.87] |
| 3.2 Grade ≥3 GI perforation | 1 | 1498 | Risk Ratio (IV, Random, 95% CI) | 3.37 [0.93, 12.19] |
| 4 Grade ≥2 hypertension | 2 | 2407 | Risk Ratio (IV, Random, 95% CI) | 5.13 [1.91, 13.82] |
| 5 Grade ≥3 proteinuria | 2 | 2407 | Risk Ratio (IV, Random, 95% CI) | 2.90 [0.84, 10.06] |
| 6 Grade ≥2 pain | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |
| 7 Severe neutropenia | 2 | 2407 | Risk Ratio (IV, Random, 95% CI) | 1.09 [0.99, 1.21] |
| 7.1 Grade ≥3 | 1 | 1498 | Risk Ratio (IV, Random, 95% CI) | 1.09 [0.86, 1.38] |
| 7.2 Grade ≥4 | 1 | 909 | Risk Ratio (IV, Random, 95% CI) | 1.10 [0.98, 1.23] |
| 8 Febrile neutropenia | 2 | 2407 | Risk Ratio (IV, Random, 95% CI) | 1.23 [0.76, 1.98] |

| | | | | |
|---|---|---|---|---|
| 8.1 All grades | 1 | 909 | Risk Ratio (IV, Random, 95% CI) | 1.17 [0.59, 2.34] |
| 8.2 Grade ≥3 | 1 | 1498 | Risk Ratio (IV, Random, 95% CI) | 1.28 [0.66, 2.50] |
| 9 Venous thromboembolic event | 2 | 2407 | Risk Ratio (IV, Random, 95% CI) | 1.64 [0.76, 3.56] |
| 9.1 All grades | 1 | 909 | Risk Ratio (IV, Random, 95% CI) | 1.13 [0.66, 1.93] |
| 9.2 Grade ≥3 | 1 | 1498 | Risk Ratio (IV, Random, 95% CI) | 2.49 [1.32, 4.70] |
| 10 Arterial thromboembolic event | 2 | 2407 | Risk Ratio (IV, Random, 95% CI) | 1.40 [0.50, 3.92] |
| 10.1 All grades | 1 | 909 | Risk Ratio (IV, Random, 95% CI) | 0.66 [0.15, 2.93] |
| 10.2 Grade ≥3 | 1 | 1498 | Risk Ratio (IV, Random, 95% CI) | 2.02 [0.95, 4.29] |
| 11 Grade ≥3 bleeding | 2 | 2407 | Risk Ratio (IV, Random, 95% CI) | 2.90 [1.10, 7.62] |
| 11.1 Non-CNS bleeding (grade ≥3) | 1 | 909 | Risk Ratio (IV, Random, 95% CI) | 2.15 [0.62, 7.47] |
| 11.2 Grade ≥3 bleeding | 1 | 1498 | Risk Ratio (IV, Random, 95% CI) | 4.55 [0.99, 20.98] |
| 12 Thrombocytopenia | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |

### Comparison 3. Chemo + AMG 386 at 10 mg/kg versus chemo + placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Overall survival | 1 | | Hazard Ratio (Random, 95% CI) | Subtotals only |
| 2 Progression-free survival | 1 | | Hazard Ratio (Random, 95% CI) | Subtotals only |

### Comparison 4. Chemo + AMG 386 at 3 mg/kg versus chemo + placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Overall survival | 1 | | Hazard Ratio (Random, 95% CI) | Subtotals only |
| 2 Progression-free survival | 1 | | Hazard Ratio (Random, 95% CI) | Subtotals only |

### Comparison 5. Continuous BIBF 1120 versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Progression-free survival | 1 | | Hazard Ratio (Random, 95% CI) | Subtotals only |
| 2 Severe gastrointestinal adverse events | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |

## Comparison 6. VEGF-Trap versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Overall survival | 1 | | Hazard Ratio (Random, 95% CI) | Subtotals only |
| 2 Fatal gastrointestinal events | 1 | | Risk Ratio (IV, Random, 95% CI) | Subtotals only |

### Analysis 1.1. Comparison 1 Chemo + concurrent bevacizumab + maintenance placebo versus chemo + concurrent and maintenance placebo, Outcome 1 Overall survival.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 1 Chemo + concurrent bevacizumab + maintenance placebo versus chemo + concurrent and maintenance placebo

Outcome: 1 Overall survival

| Study or subgroup | Chemo+concurrent Bev N | Chemo+placebo N | log [Hazard Ratio] (SE) | Hazard Ratio IV,Random,95% CI | Weight | Hazard Ratio IV,Random,95% CI |
|---|---|---|---|---|---|---|
| Burger 2010 (GOG-0218) | 607 | 601 | 0.04 (0.115) | | | 1.04 [ 0.83, 1.30 ] |
| **Subtotal (95% CI)** | **0** | **0** | | | | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: Z = 0.0 (P < 0.00001) | | | | | | |

### Analysis 1.2. Comparison 1 Chemo + concurrent bevacizumab + maintenance placebo versus chemo + concurrent and maintenance placebo, Outcome 2 Progression-free survival.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 1 Chemo + concurrent bevacizumab + maintenance placebo versus chemo + concurrent and maintenance placebo

Outcome: 2 Progression-free survival

| Study or subgroup | Chemo+concurrent Bev N | Chemo+placebo N | log [Hazard Ratio] (SE) | Hazard Ratio IV,Random,95% CI | Weight | Hazard Ratio IV,Random,95% CI |
|---|---|---|---|---|---|---|
| Burger 2010 (GOG-0218) | 607 | 601 | -0.097 (0.07) | | | 0.91 [ 0.79, 1.04 ] |
| **Subtotal (95% CI)** | **0** | **0** | | | | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: Z = 0.0 (P < 0.00001) | | | | | | |

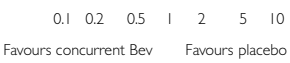

### Analysis 1.3. Comparison 1 Chemo + concurrent bevacizumab + maintenance placebo versus chemo + concurrent and maintenance placebo, Outcome 3 Grade ≥2 gastrointestinal adverse events.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 1 Chemo + concurrent bevacizumab + maintenance placebo versus chemo + concurrent and maintenance placebo

Outcome: 3 Grade ≥2 gastrointestinal adverse events

| Study or subgroup | Chemo+concurrent Bev n/N | Chemo+placebo n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| Burger 2010 (GOG-0218) | 17/607 | 4/301 | | | 2.11 [ 0.72, 6.21 ] |
| **Subtotal (95% CI)** | **0** | **0** | | | **0.0 [ 0.0, 0.0 ]** |
| Total events: 17 (Chemo+concurrent Bev), 4 (Chemo+placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.0 (P < 0.00001) | | | | | |

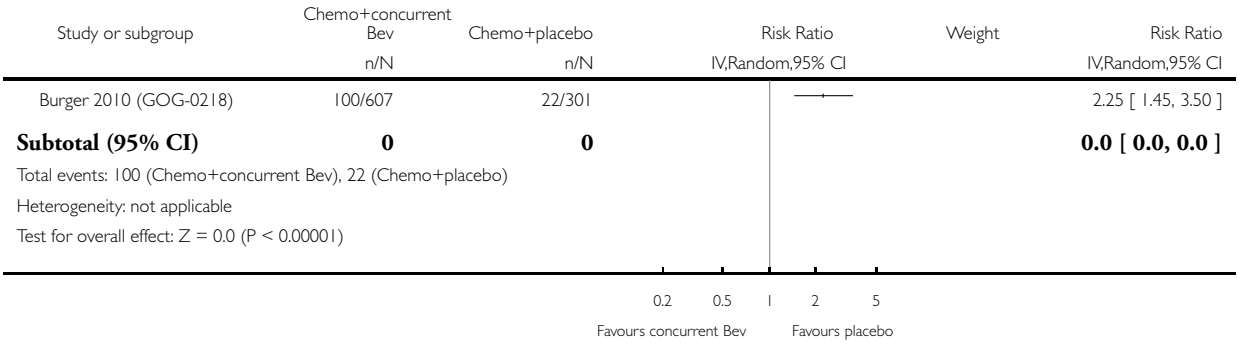


### Analysis 1.4. Comparison 1 Chemo + concurrent bevacizumab + maintenance placebo versus chemo + concurrent and maintenance placebo, Outcome 4 Grade ≥2 hypertension.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 1 Chemo + concurrent bevacizumab + maintenance placebo versus chemo + concurrent and maintenance placebo

Outcome: 4 Grade ≥2 hypertension

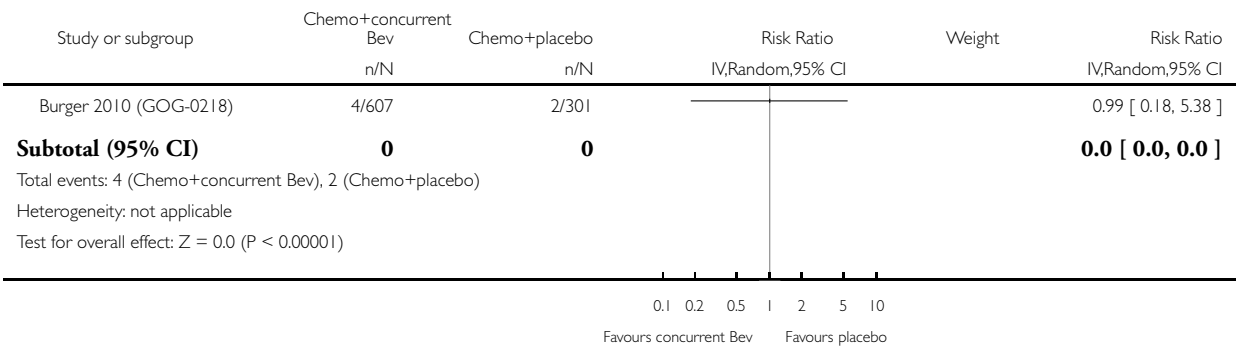



### Analysis 1.5. Comparison 1 Chemo + concurrent bevacizumab + maintenance placebo versus chemo + concurrent and maintenance placebo, Outcome 5 Grade ≥3 proteinuria.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 1 Chemo + concurrent bevacizumab + maintenance placebo versus chemo + concurrent and maintenance placebo

Outcome: 5 Grade ≥3 proteinuria



### Analysis 1.6. Comparison 1 Chemo + concurrent bevacizumab + maintenance placebo versus chemo + concurrent and maintenance placebo, Outcome 6 Grade ≥2 pain.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 1 Chemo + concurrent bevacizumab + maintenance placebo versus chemo + concurrent and maintenance placebo

Outcome: 6 Grade ≥2 pain

| Study or subgroup | Chemo+concurrent Bev n/N | Chemo+placebo n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| Burger 2010 (GOG-0218) | 252/607 | 125/301 | | | 1.00 [ 0.85, 1.18 ] |
| **Subtotal (95% CI)** | **0** | **0** | | | **0.0 [ 0.0, 0.0 ]** |
| Total events: 252 (Chemo+concurrent Bev), 125 (Chemo+placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.0 (P < 0.00001) | | | | | |


### Analysis 1.7. Comparison 1 Chemo + concurrent bevacizumab + maintenance placebo versus chemo + concurrent and maintenance placebo, Outcome 7 Grade ≥4 neutropenia.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 1 Chemo + concurrent bevacizumab + maintenance placebo versus chemo + concurrent and maintenance placebo

Outcome: 7 Grade ≥4 neutropenia

| Study or subgroup | Chemo+concurrent Bev n/N | Chemo+placebo n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| Burger 2010 (GOG-0218) | 384/607 | 174/301 | | | 1.09 [ 0.98, 1.23 ] |
| **Subtotal (95% CI)** | **0** | **0** | | | **0.0 [ 0.0, 0.0 ]** |
| Total events: 384 (Chemo+concurrent Bev), 174 (Chemo+placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.0 (P < 0.00001) | | | | | |

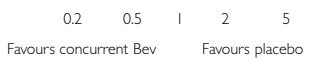
### Analysis 1.8. Comparison 1 Chemo + concurrent bevacizumab + maintenance placebo versus chemo + concurrent and maintenance placebo, Outcome 8 Febrile neutropenia.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 1 Chemo + concurrent bevacizumab + maintenance placebo versus chemo + concurrent and maintenance placebo

Outcome: 8 Febrile neutropenia

| Study or subgroup | Chemo+concurrent Bev n/N | Chemo+placebo n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| Burger 2010 (GOG-0218) | 30/607 | 11/301 | | | 1.35 [ 0.69, 2.66 ] |
| **Subtotal (95% CI)** | **0** | **0** | | | **0.0 [ 0.0, 0.0 ]** |
| Total events: 30 (Chemo+concurrent Bev), 11 (Chemo+placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.0 (P < 0.00001) | | | | | |




### Analysis 1.9. Comparison 1 Chemo + concurrent bevacizumab + maintenance placebo versus chemo + concurrent and maintenance placebo, Outcome 9 Venous thromboembolic event.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 1 Chemo + concurrent bevacizumab + maintenance placebo versus chemo + concurrent and maintenance placebo

Outcome: 9 Venous thromboembolic event

| Study or subgroup | Chemo+concurrent Bev n/N | Chemo+placebo n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| Burger 2010 (GOG-0218) | 32/607 | 18/301 | | | 0.88 [ 0.50, 1.54 ] |
| **Subtotal (95% CI)** | **0** | **0** | | | **0.0 [ 0.0, 0.0 ]** |
| Total events: 32 (Chemo+concurrent Bev), 18 (Chemo+placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.0 (P < 0.00001) | | | | | |

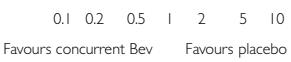
### Analysis 1.10. Comparison 1 Chemo + concurrent bevacizumab + maintenance placebo versus chemo + concurrent and maintenance placebo, Outcome 10 Arterial thromboembolic event.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 1 Chemo + concurrent bevacizumab + maintenance placebo versus chemo + concurrent and maintenance placebo

Outcome: 10 Arterial thromboembolic event

| Study or subgroup | Chemo+concurrent Bev n/N | Chemo+placebo n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| Burger 2010 (GOG-0218) | 4/607 | 3/301 | | | 0.66 [ 0.15, 2.94 ] |
| **Subtotal (95% CI)** | **0** | **0** | | | **0.0 [ 0.0, 0.0 ]** |
| Total events: 4 (Chemo+concurrent Bev), 3 (Chemo+placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.0 (P < 0.00001) | | | | | |




### Analysis 1.11. Comparison 1 Chemo + concurrent bevacizumab + maintenance placebo versus chemo + concurrent and maintenance placebo, Outcome 11 Non-CNS bleeding (grade ≥3).

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 1 Chemo + concurrent bevacizumab + maintenance placebo versus chemo + concurrent and maintenance placebo

Outcome: 11 Non-CNS bleeding (grade ≥3)

| Study or subgroup | Chemo+concurrent Bev n/N | Chemo+placebo n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| Burger 2010 (GOG-0218) | 8/607 | 3/301 | | | 1.32 [ 0.35, 4.95 ] |
| **Subtotal (95% CI)** | **0** | **0** | | | **0.0 [ 0.0, 0.0 ]** |
| Total events: 8 (Chemo+concurrent Bev), 3 (Chemo+placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.0 (P < 0.00001) | | | | | |

## Analysis 2.1. Comparison 2 Chemo + concurrent and maintenance bevacizumab versus chemo +/- placebo, Outcome 1 Overall survival.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 2 Chemo + concurrent and maintenance bevacizumab versus chemo +/- placebo

Outcome: 1 Overall survival

| Study or subgroup | Chemo+conc BEV+Maint BEV N | Chemo+placebo N | log [Hazard Ratio] (SE) | Hazard Ratio IV,Random,95% CI | Weight | Hazard Ratio IV,Random,95% CI |
|---|---|---|---|---|---|---|
| 1 Concurrent BEV (15 mg/kg) | | | | | | |
| Burger 2010 (GOG-0218) | 608 | 601 | -0.088 (0.117) | | 54.5 % | 0.92 [ 0.73, 1.15 ] |
| **Subtotal (95% CI)** | **608** | **601** | | | **54.5 %** | **0.92 [ 0.73, 1.15 ]** |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: Z = 0.75 (P = 0.45) | | | | | | |
| 2 Concurrent BEV (7.5 mg/kg) | | | | | | |
| Perren 2010 (ICON7) | 745 | 753 | -0.21 (0.128) | | 45.5 % | 0.81 [ 0.63, 1.04 ] |
| **Subtotal (95% CI)** | **745** | **753** | | | **45.5 %** | **0.81 [ 0.63, 1.04 ]** |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: Z = 1.64 (P = 0.10) | | | | | | |
| **Total (95% CI)** | **1353** | **1354** | | | **100.0 %** | **0.87 [ 0.73, 1.03 ]** |
| Heterogeneity: $Tau^2$ = 0.0; $Chi^2$ = 0.49, df = 1 (P = 0.48); $I^2$ =0.0% | | | | | | |
| Test for overall effect: Z = 1.66 (P = 0.097) | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.49, df = 1 (P = 0.48), $I^2$ =0.0% | | | | | | |

## Analysis 2.2. Comparison 2 Chemo + concurrent and maintenance bevacizumab versus chemo +/- placebo, Outcome 2 Progression-free survival.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 2 Chemo + concurrent and maintenance bevacizumab versus chemo +/- placebo

Outcome: 2 Progression-free survival

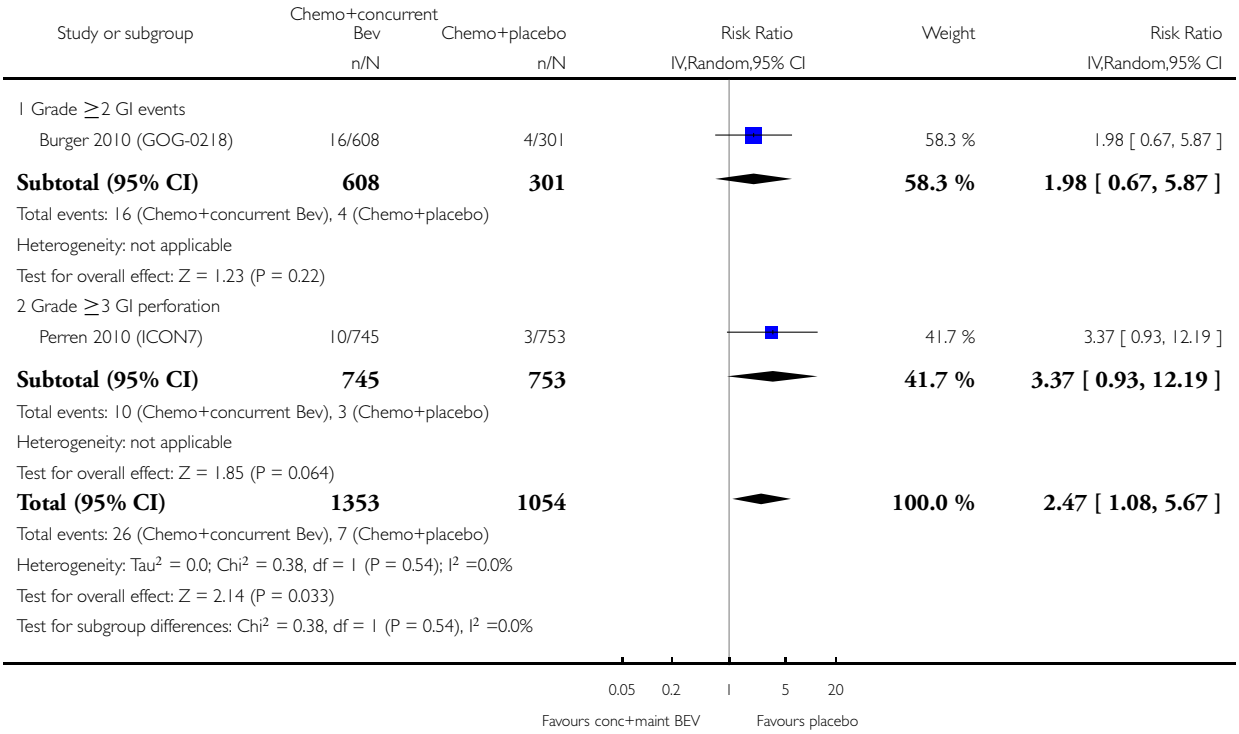
| Study or subgroup | Chemo+conc BEV+Maint BEV N | Chemo+placebo N | log [Hazard Ratio] (SE) | Hazard Ratio IV,Random,95% CI | Weight | Hazard Ratio IV,Random,95% CI |
|---|---|---|---|---|---|---|
| 1 Concurrent BEV (15 mg/kg) | | | | | | |
| Burger 2010 (GOG-0218) | 608 | 601 | -0.33 (0.07) | | 52.8 % | 0.72 [ 0.63, 0.82 ] |
| **Subtotal (95% CI)** | **608** | **601** | | | **52.8 %** | **0.72 [ 0.63, 0.82 ]** |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: Z = 4.71 (P < 0.00001) | | | | | | |
| 2 Concurrent BEV (7.5 mg/kg) | | | | | | |
| Perren 2010 (ICON7) | 745 | 753 | -0.24 (0.074) | | 47.2 % | 0.79 [ 0.68, 0.91 ] |
| **Subtotal (95% CI)** | **745** | **753** | | | **47.2 %** | **0.79 [ 0.68, 0.91 ]** |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: Z = 3.24 (P = 0.0012) | | | | | | |
| **Total (95% CI)** | **1353** | **1354** | | | **100.0 %** | **0.75 [ 0.68, 0.83 ]** |
| Heterogeneity: $Tau^2$ = 0.0; $Chi^2$ = 0.78, df = 1 (P = 0.38); $I^2$ =0.0% | | | | | | |
| Test for overall effect: Z = 5.65 (P < 0.00001) | | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.78, df = 1 (P = 0.38), $I^2$ =0.0% | | | | | | |

## Analysis 2.3. Comparison 2 Chemo + concurrent and maintenance bevacizumab versus chemo +/- placebo, Outcome 3 Severe gastrointestinal adverse events.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 2 Chemo + concurrent and maintenance bevacizumab versus chemo +/- placebo

Outcome: 3 Severe gastrointestinal adverse events

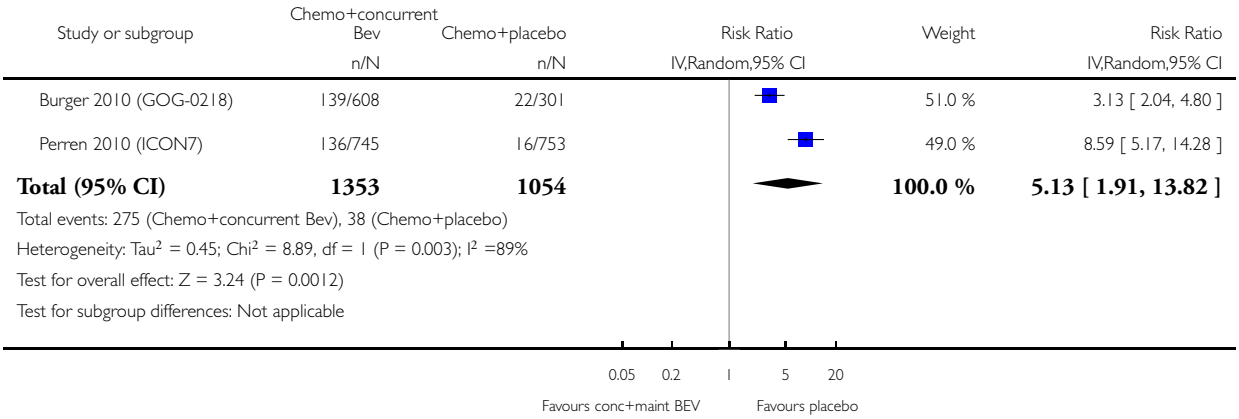


## Analysis 2.4. Comparison 2 Chemo + concurrent and maintenance bevacizumab versus chemo +/- placebo, Outcome 4 Grade ≥2 hypertension.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 2 Chemo + concurrent and maintenance bevacizumab versus chemo +/- placebo

Outcome: 4 Grade ≥2 hypertension

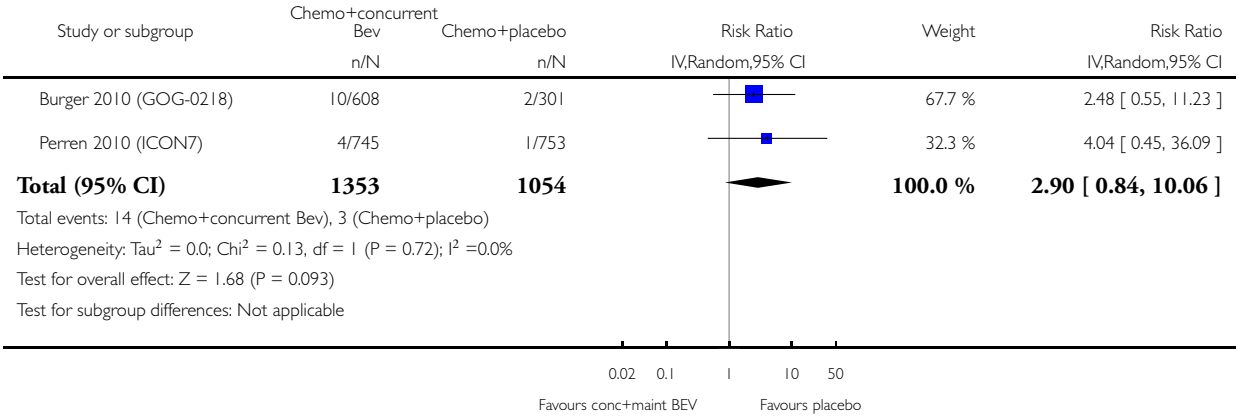


### Analysis 2.5. Comparison 2 Chemo + concurrent and maintenance bevacizumab versus chemo +/- placebo, Outcome 5 Grade ≥3 proteinuria.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 2 Chemo + concurrent and maintenance bevacizumab versus chemo +/- placebo

Outcome: 5 Grade ≥3 proteinuria

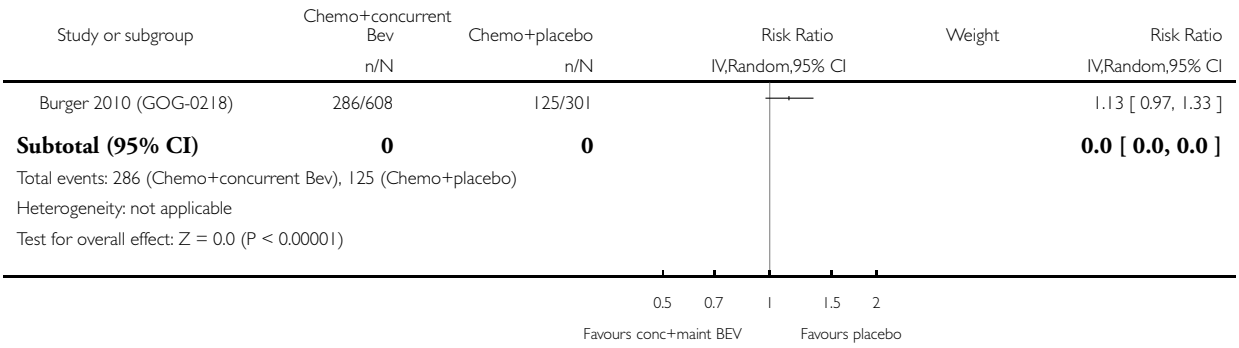



### Analysis 2.6. Comparison 2 Chemo + concurrent and maintenance bevacizumab versus chemo +/- placebo, Outcome 6 Grade ≥2 pain.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 2 Chemo + concurrent and maintenance bevacizumab versus chemo +/- placebo

Outcome: 6 Grade ≥2 pain



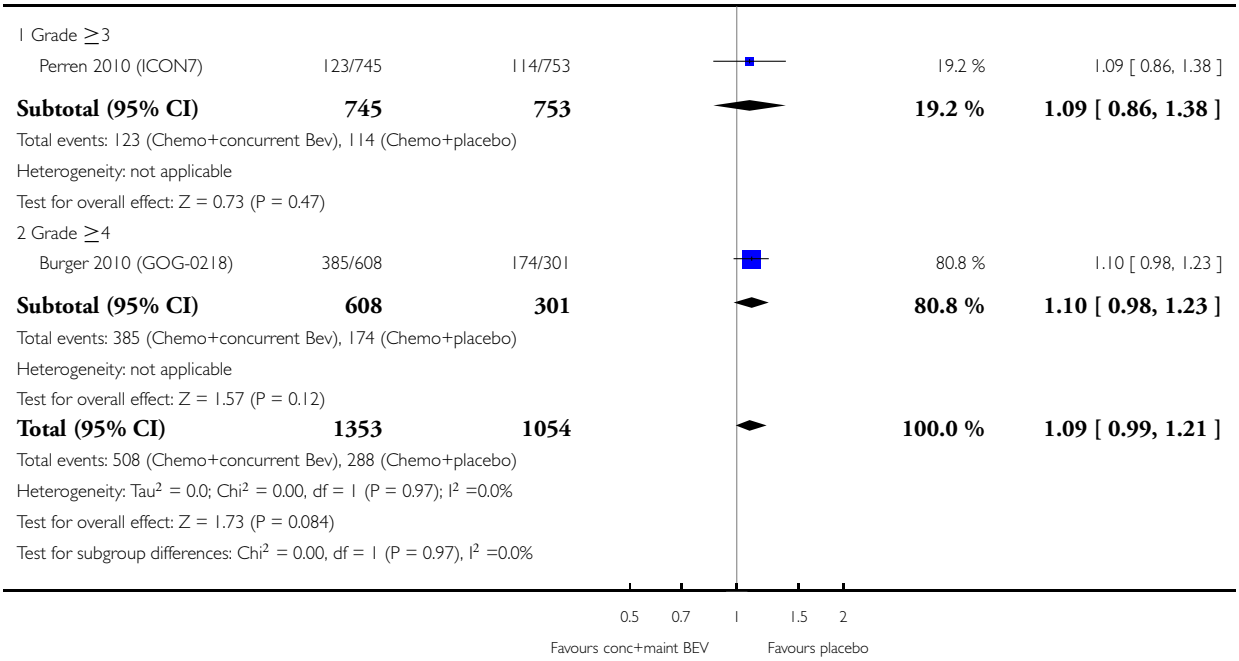
### Analysis 2.7. Comparison 2 Chemo + concurrent and maintenance bevacizumab versus chemo +/- placebo, Outcome 7 Severe neutropenia.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 2 Chemo + concurrent and maintenance bevacizumab versus chemo +/- placebo

Outcome: 7 Severe neutropenia

| Study or subgroup | Chemo+concurrent Bev n/N | Chemo+placebo n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| 1 Grade ≥3 | | | | | |
| Perren 2010 (ICON7) | 123/745 | 114/753 | | 19.2 % | 1.09 [ 0.86, 1.38 ] |
| **Subtotal (95% CI)** | **745** | **753** | | **19.2 %** | **1.09 [ 0.86, 1.38 ]** |
| Total events: 123 (Chemo+concurrent Bev), 114 (Chemo+placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.73 (P = 0.47) | | | | | |
| 2 Grade ≥4 | | | | | |
| Burger 2010 (GOG-0218) | 385/608 | 174/301 | | 80.8 % | 1.10 [ 0.98, 1.23 ] |
| **Subtotal (95% CI)** | **608** | **301** | | **80.8 %** | **1.10 [ 0.98, 1.23 ]** |
| Total events: 385 (Chemo+concurrent Bev), 174 (Chemo+placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.57 (P = 0.12) | | | | | |
| **Total (95% CI)** | **1353** | **1054** | | **100.0 %** | **1.09 [ 0.99, 1.21 ]** |
| Total events: 508 (Chemo+concurrent Bev), 288 (Chemo+placebo) | | | | | |
| Heterogeneity: $Tau^2$ = 0.0; $Chi^2$ = 0.00, df = 1 (P = 0.97); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 1.73 (P = 0.084) | | | | | |
| Test for subgroup differences: $Chi^2$ = 0.00, df = 1 (P = 0.97), $I^2$ =0.0% | | | | | |

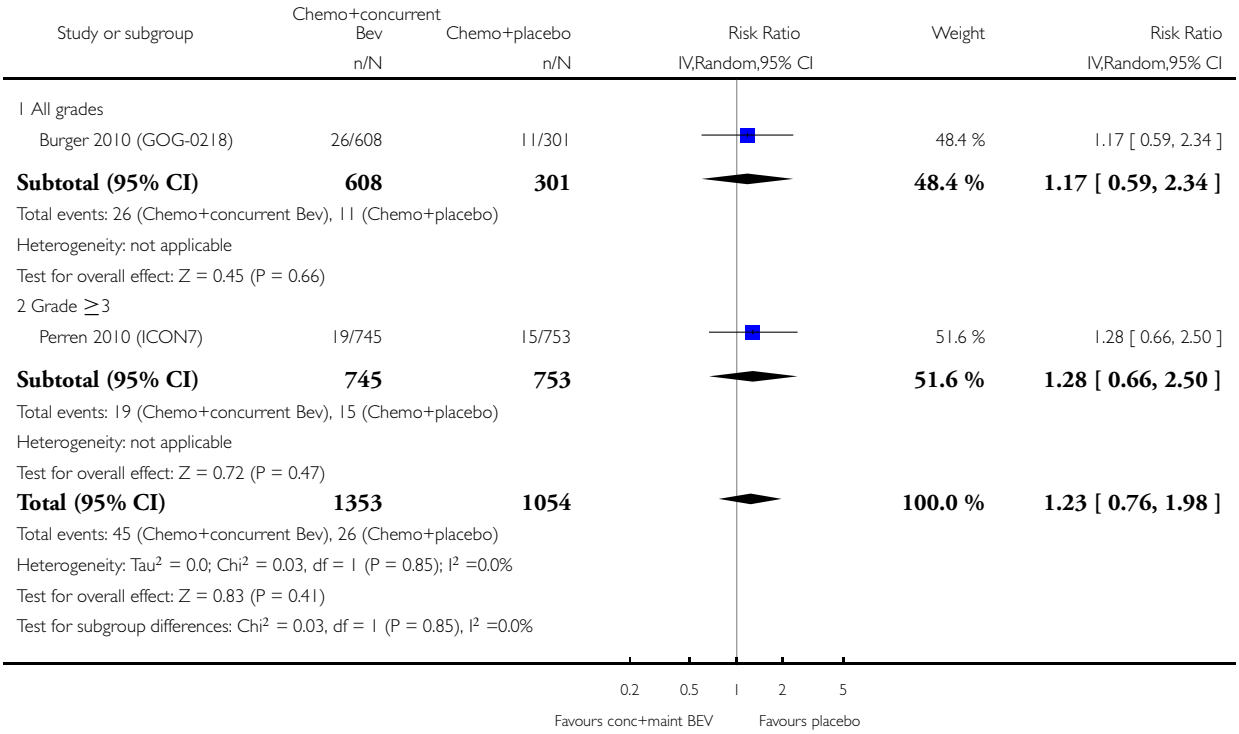


## Analysis 2.8. Comparison 2 Chemo + concurrent and maintenance bevacizumab versus chemo +/- placebo, Outcome 8 Febrile neutropenia.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 2 Chemo + concurrent and maintenance bevacizumab versus chemo +/- placebo

Outcome: 8 Febrile neutropenia

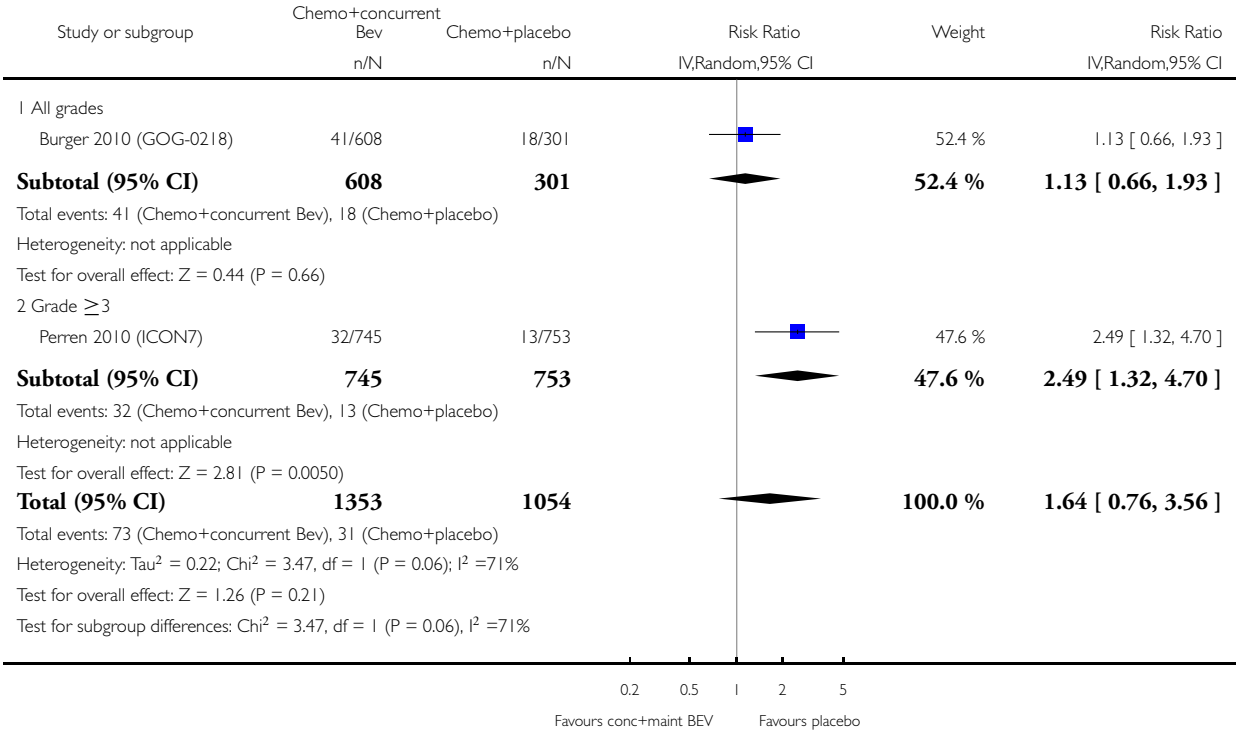


## Analysis 2.9. Comparison 2 Chemo + concurrent and maintenance bevacizumab versus chemo +/- placebo, Outcome 9 Venous thromboembolic event.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 2 Chemo + concurrent and maintenance bevacizumab versus chemo +/- placebo

Outcome: 9 Venous thromboembolic event

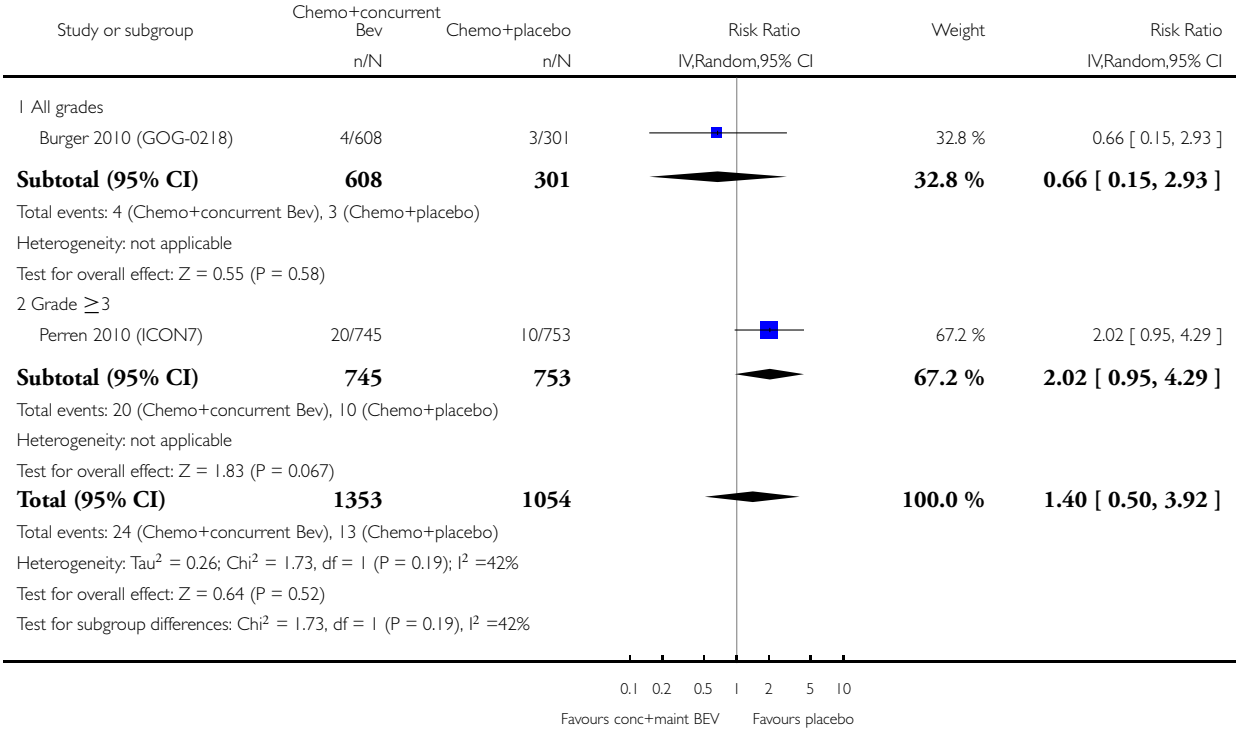


### Analysis 2.10. Comparison 2 Chemo + concurrent and maintenance bevacizumab versus chemo +/- placebo, Outcome 10 Arterial thromboembolic event.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 2 Chemo + concurrent and maintenance bevacizumab versus chemo +/- placebo

Outcome: 10 Arterial thromboembolic event

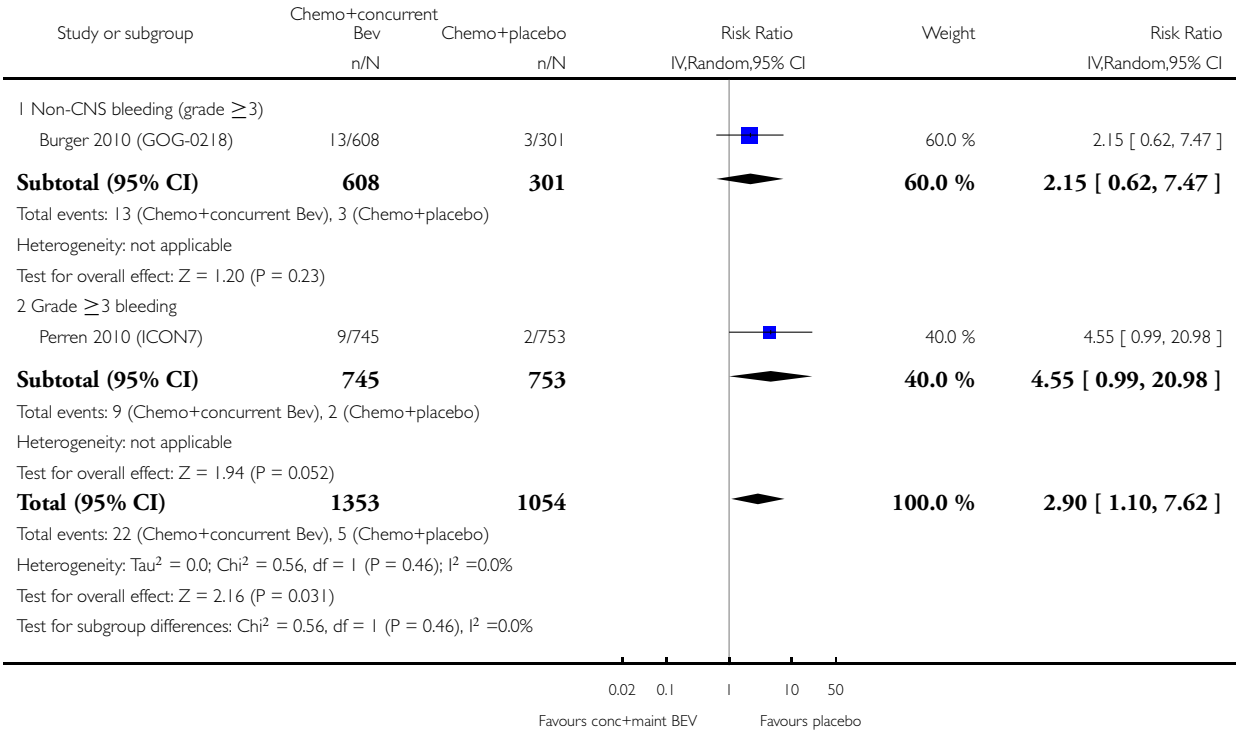


## Analysis 2.11. Comparison 2 Chemo + concurrent and maintenance bevacizumab versus chemo +/- placebo, Outcome 11 Grade ≥3 bleeding.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 2 Chemo + concurrent and maintenance bevacizumab versus chemo +/- placebo

Outcome: 11 Grade ≥3 bleeding



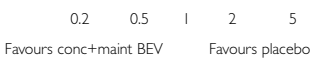
### Analysis 2.12. Comparison 2 Chemo + concurrent and maintenance bevacizumab versus chemo +/- placebo, Outcome 12 Thrombocytopenia.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 2 Chemo + concurrent and maintenance bevacizumab versus chemo +/- placebo

Outcome: 12 Thrombocytopenia

| Study or subgroup | Chemo+concurrent Bev n/N | Chemo+placebo n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| Perren 2010 (ICON7) | 26/745 | 15/753 | | | 1.75 [ 0.94, 3.28 ] |
| **Subtotal (95% CI)** | **0** | **0** | | | **0.0 [ 0.0, 0.0 ]** |
| Total events: 26 (Chemo+concurrent Bev), 15 (Chemo+placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.0 (P < 0.00001) | | | | | |




### Analysis 3.1. Comparison 3 Chemo + AMG 386 at 10 mg/kg versus chemo + placebo, Outcome 1 Overall survival.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 3 Chemo + AMG 386 at 10 mg/kg versus chemo + placebo

Outcome: 1 Overall survival

| Study or subgroup | Chemo+AMG at 10 mg/kg N | Chemo+ placebo N | log [Hazard Ratio] (SE) | Hazard Ratio IV,Random,95% CI | Weight | Hazard Ratio IV,Random,95% CI |
|---|---|---|---|---|---|---|
| Karlan 2010 | 53 | 55 | -0.51 (0.29) | | | 0.60 [ 0.34, 1.06 ] |
| **Subtotal (95% CI)** | **0** | **0** | | | | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: Z = 0.0 (P < 0.00001) | | | | | | |

### Analysis 3.2. Comparison 3 Chemo + AMG 386 at 10 mg/kg versus chemo + placebo, Outcome 2 Progression-free survival.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 3 Chemo + AMG 386 at 10 mg/kg versus chemo + placebo

Outcome: 2 Progression-free survival

| Study or subgroup | Chemo+AMG at 10 mg/kg N | Chemo+ placebo N | log [Hazard Ratio] (SE) | Hazard Ratio IV,Random,95% CI | Weight | Hazard Ratio IV,Random,95% CI |
|---|---|---|---|---|---|---|
| Karlan 2010 | 53 | 55 | -0.36 (0.23) | | | 0.70 [ 0.44, 1.10 ] |
| **Subtotal (95% CI)** | **0** | **0** | | | | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: Z = 0.0 (P < 0.00001) | | | | | | |


### Analysis 4.1. Comparison 4 Chemo + AMG 386 at 3 mg/kg versus chemo + placebo, Outcome 1 Overall survival.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 4 Chemo + AMG 386 at 3 mg/kg versus chemo + placebo

Outcome: 1 Overall survival

| Study or subgroup | Chemo+AMG at 3 mg/kg N | Chemo+placebo N | log [Hazard Ratio] (SE) | Hazard Ratio IV,Random,95% CI | Weight | Hazard Ratio IV,Random,95% CI |
|---|---|---|---|---|---|---|
| Karlan 2010 | 53 | 55 | -0.26 (0.27) | | | 0.77 [ 0.45, 1.31 ] |
| **Subtotal (95% CI)** | **0** | **0** | | | | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: Z = 0.0 (P < 0.00001) | | | | | | |

### Analysis 4.2. Comparison 4 Chemo + AMG 386 at 3 mg/kg versus chemo + placebo, Outcome 2 Progression-free survival.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 4 Chemo + AMG 386 at 3 mg/kg versus chemo + placebo

Outcome: 2 Progression-free survival

| Study or subgroup | Chemo+AMG at 3 mg/kg N | Chemo+placebo N | log [Hazard Ratio] (SE) | Hazard Ratio IV,Random,95% CI | Weight | Hazard Ratio IV,Random,95% CI |
|---|---|---|---|---|---|---|
| Karlan 2010 | 53 | 55 | -0.56 (0.24) | | | 0.57 [ 0.36, 0.91 ] |
| **Subtotal (95% CI)** | **0** | **0** | | | | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: Z = 0.0 (P < 0.000001) | | | | | | |


### Analysis 5.1. Comparison 5 Continuous BIBF 1120 versus placebo, Outcome 1 Progression-free survival.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 5 Continuous BIBF 1120 versus placebo

Outcome: 1 Progression-free survival

| Study or subgroup | Continuous BIBF 1120 N | Placebo N | log [Hazard Ratio] (SE) | Hazard Ratio IV,Random,95% CI | Weight | Hazard Ratio IV,Random,95% CI |
|---|---|---|---|---|---|---|
| Ledermann 2009 | 44 | 40 | -0.39 (0.243) | | | 0.68 [ 0.42, 1.09 ] |
| **Subtotal (95% CI)** | **0** | **0** | | | | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: Z = 0.0 (P < 0.00001) | | | | | | |

### Analysis 5.2. Comparison 5 Continuous BIBF 1120 versus placebo, Outcome 2 Severe gastrointestinal adverse events.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 5 Continuous BIBF 1120 versus placebo

Outcome: 2 Severe gastrointestinal adverse events

| Study or subgroup | Continuous BIBF 1120 n/N | Placebo n/N | Risk Ratio IV,Random,95% CI | Weight | Risk Ratio IV,Random,95% CI |
|---|---|---|---|---|---|
| Ledermann 2009 | 7/44 | 4/40 | | | 1.59 [ 0.50, 5.03 ] |
| **Subtotal (95% CI)** | **0** | **0** | | | **0.0 [ 0.0, 0.0 ]** |
| Total events: 7 (Continuous BIBF 1120), 4 (Placebo) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.0 (P < 0.00001) | | | | | |

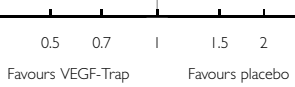

### Analysis 6.1. Comparison 6 VEGF-Trap versus placebo, Outcome 1 Overall survival.

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 6 VEGF-Trap versus placebo

Outcome: 1 Overall survival

| Study or subgroup | VEGF-Trap N | Placebo N | log [Hazard Ratio] (SE) | Hazard Ratio IV,Random,95% CI | Weight | Hazard Ratio IV,Random,95% CI |
|---|---|---|---|---|---|---|
| Vergote 2009 | 29 | 26 | 0.0227 (0.306) | | | 1.02 [ 0.56, 1.86 ] |
| **Subtotal (95% CI)** | **0** | **0** | | | | **0.0 [ 0.0, 0.0 ]** |
| Heterogeneity: not applicable | | | | | | |
| Test for overall effect: Z = 0.0 (P < 0.00001) | | | | | | |

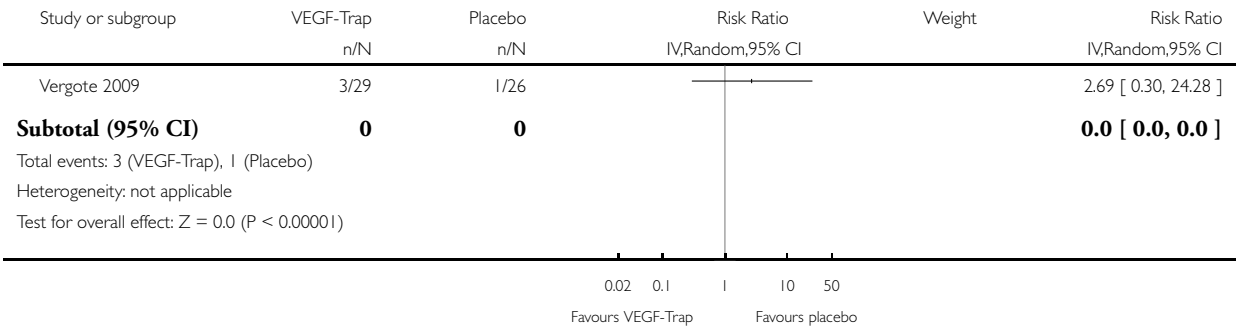


**Analysis 6.2. Comparison 6 VEGF-Trap versus placebo, Outcome 2 Fatal gastrointestinal events.**

Review: Angiogenesis inhibitors for the treatment of ovarian cancer

Comparison: 6 VEGF-Trap versus placebo

Outcome: 2 Fatal gastrointestinal events




# 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 OR #21 OR #22)
24. #3 and #23

## CONTRIBUTIONS OF AUTHORS

The protocol was written by JM and KG, with significant input from HD, AB and SN. SK and JM had the initial concept for the title and approved the final version of the protocol. KG, IM 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, IM, JM and AB wrote the review.

## DECLARATIONS OF INTEREST

None

## SOURCES OF SUPPORT


### Internal sources

- No sources of support supplied

### External sources

- NIHR CCRCD, UK.

JM is a Walport Clinical Lecturer, 50% academic component is funded by NIHR CCRCD

- Macmillan Cancer Supoort, UK.

JM is a subspecialist trainee in gynaecological oncology. This 50% clinical post is funded by a grant from Macmillan Cancer Support.

- Department of Health, UK.

NHS Cochrane Collaboration programme Grant Scheme CPG-506


## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

### How the intervention might work

In the Background section of the protocol, we wrote:
"AZD2171 (Recentin$^{TM}$ Astra Zeneca) is a small molecule inhibitor of VEGF-R that has demonstrated benefit in preclinical studies (Wedge 2005)."
AZD2171 has been more commonly referred to in the literature as "cediranib," and so this alternative name is also listed and used in the review.
Also in the Background section of the protocol, we wrote:
"Pazopanib is a potent selective receptor tyrosine kinase inhibitor of VEGF-R, PDGF-R (platelet derived growth factor receptor) and c-kit that blocks tumour growth and inhibits angiogenesis. It has shown biological activity in patients with CA125-positive recurrent ovarian cancer after primary platinum-based therapy and enrolment continues in this study (Friedlander 2007)."
The study described in Friedlander 2007 has now finished, and the full results have been published. The phrase "and enrolment continues in this study" has therefore been omitted in the review, and the reference has been updated to Friedlander 2010.
Also in the Background section of the protocol, we wrote:
"BIBF 1120 is an oral, small molecule, triple angiokinase inhibitor, targeting VEGF-R, FGF-R (fibroblast growth factor receptor) and PDGF-R. A recent phase II study has evaluated its use in maintenance of post-relapse remission in patients who responded to second, third or fourth line chemotherapy. Results from this study are expected later this year at ASCO 2009."
The results of this study have now been presented in conference/abstract form (Ledermann 2009), and are discussed in detail in the Included studies section). The phrase "Results from this study are expected later this year at ASCO 2009" has therefore been omitted in the review, and the updated reference inserted.
Also in the Background section of the protocol, we wrote, regarding sorafenib:
"Activity has been demonstrated against ovarian cancer in early clinical trials for pre-treated relapsed disease (Siu 2006) and its role in first-line treatment for ovarian cancer is under evaluation (NCT00390611 2006)."
A report of this still-ongoing trial has since appeared as a conference abstract, and so the reference has been updated accordingly, to Hainsworth 2010.
Also in the Background section of the protocol, we wrote:
"Another VEGF-R tyrosine kinase inhibitor, cediranib (AZD2171), is being trialed as a therapy in RCTs for relapsed ovarian cancer (ICON6 - 2007; ISRCTN68510403 - 2007)."

This sentence duplicated information and references given earlier in the same section, and so was omitted from the review.

### Quality of life (QoL)

QoL was not reported in any of the abstracts and data has not yet been made available, so the following sections in the protocol which discussed the handling of data for continuous outcomes were removed as they were unnecessary:

**"Data extraction and management**

- For continuous outcomes (e.g. QoL measures), we will extract the final value and standard deviation of the outcome of interest and the number of patients assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference between treatment arms and its standard error.

**Measures of treatment effect**

- For continuous outcomes, we will use the mean difference between treatment arms if all trials measured the outcome on the same scale, otherwise standardised mean differences will be used.

**Data synthesis**

If sufficient, clinically similar studies are available, their results will be pooled in meta-analyses.

- For continuous outcomes, the mean differences between the treatment arms at the end of follow-up will be pooled if all trials measured the outcome on the same scale, otherwise standardised mean differences will be pooled".

We identified only five included trials, therefore we were unable to assess reporting biases using funnel plots or adequately carry out sensitivity analyses. The following sections of the protocol were therefore removed:

**"Assessment of reporting biases**

Funnel plots corresponding to meta-analysis of the primary outcome will be examined to assess the potential for small study effects such as publication bias. If these plots suggest that treatment effects may not be sampled from a symmetric distribution, as assumed by the random-effects model, further meta-analyses will be performed using fixed-effect models.

**Sensitivity analysis**

Sensitivity analyses will be performed excluding (i) studies at high risk of bias and (ii) using unadjusted results".

We did not indirectly compare treatment groups so we removed reference to Bucher 1997 in the main text of the review:

**"Data synthesis**

If sufficient data are available, indirect comparisons, using the methods of Bucher 1997 will be used to compare competing interventions that have not been compared directly with each other."

## 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