NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)

Bevacizumab in combination with carboplatin and paclitaxel for the treatment of advanced ovarian cancer

August 2012

Contents

List of tables and figures

Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based when possible and clearly reference the relevant section of the submission. The summary should cover the following items.

This submission presents the efficacy and safety of bevacizumab (Avastin®), a recombinant humanised monoclonal antibody which inhibits VEGF-induced signalling, in combination with chemotherapy in the first-line treatment of advanced ovarian cancer. Primarily VEGF receptors are found on endothelial cells and bevacizumab inhibits VEGF-driven angiogenesis, to reduce vascularisation of tumours and thereby inhibit tumour growth. VEGF receptors have also been found on ovarian cancer cells, so inhibition of VEGF signalling may also have a direct anti-proliferative effect on ovarian tumours.

Bevacizumab is licensed throughout the world for use in metastatic colorectal cancer (mCRC) with fluoropyrimidine-based chemotherapy, advanced renal cell carcinoma (aRCC) with interferon alfa-2a, advanced non-small cell lung cancer (aNSCLC) in addition to platinum-based chemotherapy and in metastatic breast cancer (mBC) with paclitaxel or docetaxel (or with capecitabine in patients considered unsuitable for treatment with other chemotherapy including taxanes or anthracyclines). It is also licensed in numerous countries outside of the EU for the treatment of relapsed glioblastoma (GBM). Bevacizumab is available as a 25mg/ml solution for infusion. Two presentations are available, a 100mg vial (£242.66) and a 400mg vial (£924.40).

The recommended dose in advanced ovarian cancer is 15mg/kg every three weeks in addition to carboplatin and paclitaxel for up to 6 cycles, followed by continued use of Bevacizumab as a single agent until disease progression or for a maximum of 15 months or unacceptable toxicity, whichever occurs earlier.

Clinical summary

Ovarian cancer accounts for more deaths each year than all other gynaecological cancers combined. Because ovarian cancer tends to be asymptomatic or associated with vague, nonspecific symptoms, the majority of patients are diagnosed with advanced stage disease (FIGO stage III and IV), for which 5-year survival is only around 25%. Post debulking surgery, 6 cycles of combination chemotherapy with 3-weekly carboplatin and paclitaxel (CP) has been the international standard of care for many years. But although ovarian cancer is generally sensitive to chemotherapy, the majority of patients develop recurrence and die from their disease, with little improvement in survival with ovarian cancer over the past 2 decades. There is a clear unmet medical need to improve outcomes and this might be achieved by a therapy which not only prolonged time to recurrence, but also improved overall survival.

Data for this submission come from two randomised phase III studies which addressed the efficacy, safety and quality of life seen with bevacizumab in combination with CP chemotherapy, for first-line treatment of advanced ovarian cancer.

GOG-0218 was a double-blind placebo controlled study conducted in N.America and Asia, with bevacizumab at a dose of 15mg/kg q3w, for up to 15 months, in a population of Stage III and IV patients.

ICON7 an open label study, was conducted mainly in Europe, recruited 375 UK patients (representing 24.5% of the ITT population) and was run by the UK Medical Research Council (MRC). This study recruited patients with stage I and II, as well as stage III and IV disease and used bevacizumab at a dose of 7.5mg/kg q3w for up to 12 months. The MRC endorsed and published a subgroup analysis of ICON7, which reflects a ‘high risk’ subgroup of Stage III and IV patients with residual disease $\geq$1cm after debulking surgery, who fall within the bevacizumab licensed indication.

The license granted for bevacizumab in ovarian cancer reflected the dose and duration used in the GOG-218 study, due to the more robust study design and

a more complete dataset than that available for ICON7 at the time of licensing submission. However, ICON7 was considered by the EMA as supportive confirmation of GOG-218 and data from both studies are included in the Bevacizumab Summary of Product Characteristics. The ICON7 data have produced strong support from the UK clinical community for use of the 7.5mg/kg dose in ovarian cancer. As a result of this support, bevacizumab is available in all 10 English SHAs, via the Cancer Drug Fund 'fast-track' drug application process, for the treatment of ovarian cancer at a dose of 7.5mg/kg q3w. Because of this clinical support and current English usage, this submission covers both the licensed dose of 15mg/kg and the clinically preferred dose of 7.5mg/kg.

The submission addresses the efficacy, safety and quality of life shown with bevacizumab, in combination with and continued as maintenance therapy after carboplatin/paclitaxel (CP), for first-line treatment of advanced ovarian cancer. Both the GOG-0218 and the ICON7 studies met their primary endpoint of a significant improvement in progression free survival (PFS) with bevacizumab. In GOG-0218, the regulatory analysis (censored for progression by rising CA125 alone) showed that median PFS increased from 12.0 months with CP plus placebo, to 18.0 months with CP plus bevacizumab (HR 0.645, 95% CI 0.551-0.756; p<0.001). In ICON7, the pre-planned analysis of a similar study population ('high risk' patients with suboptimally debulked stage III and IV disease) showed that median PFS increased from 10.5 months with CP to 16.0 months with CP plus bevacizumab (HR 0.73, 95% CI 0.60-0.93; p=0.002). In an interim analysis, this 'high risk' population in ICON7 also showed an improvement in overall survival (OS) from a median of 28.8 months with CP to 36.6 months with CP plus bevacizumab (HR = 0.64, 95% CI 0.48 – 0.85; p=0.002). In the GOG-0218 study, up to 40% of placebo patients received bevacizumab post progression, which may have confounded OS. Even so, final OS results for GOG-0218 showed a median of 40.6 months with CP + placebo and 43.8 months with CP + bevacizumab (HR 0.88, 95% CI 0.75-1.04; p=0.0641). These improvements in therapeutic efficacy with bevacizumab were gained without a significant reduction in quality of life in either study due to the addition of a third agent to CP. The

adverse events seen in both studies were consistent with the known safety profile of bevacizumab and no new safety concerns were noted.

Economic summary

A cost utility analysis was conducted comparing bevacizumab in combination with carboplatin and paclitaxel against carboplatin and paclitaxel chemotherapy alone in ovarian cancer patients with advanced disease using patient-level data from the 2 key clinical trials in this indication; GOG-0218 and ICON7. The NICE reference case was followed throughout (including the utilisation of 3.5% p.a. non-differential discounting, half-cycle correction, NHS/PSS perspective, etc.).

Models for both studies were based on a 3-state semi-Markov model with health states consisting of PFS, Progression and Death, commonly used to model metastatic disease. The proportion of patients in each health state was derived from patient-level observations in GOG-0218 and ICON7 studies. Resource use in each health state was based on a previous appraisal in ovarian cancer (Papaioannou et al. 2010) and costs were taken from BNF63, PSSRU 2011 and NHS Reference Costs 2010/11 (Department of Health 2011;Joint Formulary Committee 2012;PSSRU 2011). Utilities of patients in PFS and PD health states were calculated from EQ-5D surveys of patients in the ICON7 trial and were assumed to include any dis-utility associated with adverse events experienced throughout the study.

The base case results of the economic evaluation of GOG-218 demonstrate that the addition of bevacizumab to standard chemotherapy provides an additional 0.228 years (0.188 QALYs) to patients with an expected survival of approximately 4 years. This benefit is achieved with an incremental cost of £27,000, resulting in an ICER of approximately £144,000 per QALY for bevacizumab at the licensed dose. However, where bevacizumab is available to suitable patients, clinicians have requested and administered a lower dose commensurate with the ICON7 study (7.5mg/kg). The base case results for a model based on this scenario demonstrates that bevacizumab provides an additional 0.743 years (0.561 QALYs) to patients with an expected survival of

approximately 3 years. This benefit is achieved with an incremental cost of almost £18,000, resulting in an ICER of approximately £31,600 per QALY for bevacizumab at the clinically relevant dose.

Table 1 Base-case cost-effectiveness results for GOG-0218 (ICON7)

	Bevacizumab + Chemotherapy	Chemotherapy
Technology acquisition cost	£26,588 (£16,877)	£228 (£215)
Other costs	£17,666 (£16964)	£16,938 (£15,896)
Total costs	£44,254 (£33,841)	£17,166 (£16,111)
Difference in total costs	N/A	£27,089 (£17,729)
LYG	4.212 (3.809)	3.985 (3.066)
LYG difference	N/A	0.228 (0.743)
QALYs	3.161 (2.839)	2.973 (2.278)
QALY difference	N/A	0.188 (0.561)
ICER	N/A	£144,066 (£31,592)

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR]), and a (draft) technical manual for devices should be provided (see section 10.1, appendix 1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Avastin (bevacizumab). Pharmaco-therapeutic group. Antineoplastic agents, monoclonal antibody ATC code: L01X C07, BNF 8.1.5.

1.2 What is the principal mechanism of action of the technology?

Bevacizumab is a humanised anti-vascular endothelial growth factor (VEGF) monoclonal antibody that inhibits VEGF-induced signalling in cells carrying VEGF receptors. Primarily VEGF receptors are found on endothelial cells and bevacizumab inhibits VEGF-driven angiogenesis, to reduce vascularisation of tumours and thereby inhibit tumour growth. VEGF receptors are also found on some ovarian cancer cells, so inhibition of VEGF signalling may also have a direct anti-proliferative effect on ovarian tumour cells.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

CHMP positive opinion was received 23rd September 2011, and bevacizumab was approved for advanced ovarian cancer (aOC) on the 19th of December 2011.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

A major issue discussed by the regulatory organisation is the population to be included in the indication, as the 2 Phase III studies, GOG-0218 and ICON7, included different patient groups. Agreed licensed indication is shown below.

A second issue centred on the criteria for assessing disease progression. In the GOG-0218 trial, disease progression could be demonstrated by an increase in CA-125 level alone, or by RECIST criteria or global clinical deterioration. The regulatory primary endpoint analysis within the GOG-0218 trial for PFS arose with censoring for CA-125-only progression events. However the ICON7 trial assessed disease progression only through RECIST criteria on radiological, clinical or symptomatic progression. The ICON7 data may be seen as more relevant to UK clinical practice, given the dominant role of RECIST clinical criteria, rather than CA-125, in determining progression in the UK.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

Avastin, in combination with carboplatin and paclitaxel is indicated for the front-line treatment of advanced (FIGO stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer. The recommended dose is 15mg/kg of body weight given every 3 weeks

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

No additional studies, over and above the 2 Phase III studies in this submission, are likely to provide additional evidence over the next 12 months.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Bevacizumab was launched in the UK in 2005, following the granting of its first licensed indication in metastatic colorectal cancer.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Bevacizumab is licensed throughout the world for use in metastatic colorectal cancer (mCRC), advanced renal cell carcinoma (aRCC), advanced non-small cell lung cancer (aNSCLC) and in metastatic breast cancer (mBC). It is also licensed in numerous countries outside of the EU for the treatment of relapsed glioblastoma (GBM).

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

An SMC submission for bevacizumab in this indication was made in June 2012 with final public guidance expected in October 2012.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 1 - Unit costs of technology being appraised

Pharmaceutical formulation	Avastin is available in two vial sizes. A 4ml vial containing 100mg of bevacizumab and a 16ml vial containing 400mg of bevacizumab.
Acquisition cost (excluding VAT)	100mg/4ml vial: £242.66 400mg/16ml vial: £924.40
Method of administration	Bevacizumab is administered by intravenous infusion
Doses	In aOC bevacizumab has been studied at doses of 7.5mg/kg (ICON7) and 15mg/kg (GOG-0218).
Dosing frequency	Bevacizumab has been administered in clinical trials every 21 days, until disease progression or toxicity for a maximum of 12 (ICON7) or 15 (GOG-0218) months
Average length of a course of treatment	The mean treatment duration in GOG-0218 was 13.7 cycles, while in ICON7, it was 13.4 cycles of bevacizumab
Average cost of a course of treatment	£36 078 (14 x £2 577) for 15mg/kg dosing; £16 338 (14 x £1 167) for 7.5mg/kg, both based on a patient weight of 65kg.
Anticipated average interval between courses of treatments	An aOC patient will receive only one course of treatment with bevacizumab.
Anticipated number of repeat courses of treatments	An aOC patient will receive only one course of treatment with bevacizumab.
Dose adjustments	The dose of bevacizumab is not reduced or escalated. In cases of serious bevacizumab-related toxicity, bevacizumab may be either temporarily or permanently discontinued

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide

details of the anticipated unit cost, including the range of possible unit costs.

N/A

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

No additional tests are required to select patients for the administration of bevacizumab and no additional tests are required prior to the administration of bevacizumab. Treatment with bevacizumab should continue until disease progression, which will be determined in the usual manner for advanced ovarian cancer patients. A small amount of additional resource will be required for the administration of bevacizumab alongside the patient's routine cytotoxic chemotherapy.

There will be minimal additional monitoring to that required for a patient's chemotherapy, to detect the most common side effects of bevacizumab.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

The introduction of bevacizumab into the care pathway warrants minimal additional monitoring above and beyond current clinical practice in first line advanced ovarian cancer.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Up to 6 x 3-weekly cycles of intravenous carboplatin and paclitaxel will be administered at the start of a course of treatment with bevacizumab.

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

The technology will be used for the most common group of ovarian cancers that arise in the epithelium, namely epithelial ovarian cancer (EOC), fallopian tube cancer (FTC) and primary peritoneal cancer (PPC). These diseases are histologically equivalent and the recommendation of FIGO (International Federation of Gynaecology and Obstetrics) is that treatment for PPC and FTC follows the guidance for EOC (Benedet et al. 2000). Throughout this document the term ovarian cancer is used to refer to all three diseases.

Ovarian cancer is one of the most common gynaecological cancers in Europe and the United States. The incidence of ovarian cancer varies by geographic region, with the highest rates observed in North America, Europe, and other developed countries (Holschneider & Berek 2000). Ovarian cancer is the fifth leading cause of cancer death in women (Colombo et al. 2010).

In 2008 around 5,300 new cases of ovarian cancer were diagnosed in England (Cancer Research UK 2011a), making it the second most common gynaecological cancer and the fifth most common cancer in women. There were around 3,546 deaths from ovarian cancer in England in 2008. The majority (80%) of cases occur in women over 50 years of age and approximately 50% of new patients are over 65 years old. Survival for ovarian cancer has improved over the last 35 years, but long-term rates are still low. For women diagnosed in England during 2003-07, the one- and five-year age-standardised relative survival rates are 72.3% and 42.9% (Cancer Research UK 2011a;Kitchener 2008).

Although mortality from the disease has fallen in recent years, survival rates for ovarian cancer in the UK are significantly worse than those observed in

other countries, including Australia, Canada, Norway, and Sweden (Berrino et al. 2007;Cancer Research UK 2011a;Coleman et al. 2011;Sant et al. 2009;Thomson & Forman 2009). Differences in data quality and coding practices across Europe may contribute to some of the variation, but the consistently lower levels for the UK suggest real differences in survival. It has been estimated that if survival from ovarian cancer in Britain equalled the best in Europe, almost 2,400 deaths could be avoided within five years of diagnosis (Abdel-Rahman et al. 2009).

Course of disease and factors influencing survival

Because the disease tends to be asymptomatic in early stages, or associated with vague, nonspecific symptoms, the majority of patients are diagnosed with advanced stage disease (FIGO stage III and IV). Current therapies prove effective for patients with early stage disease (FIGO stage I/II) where 5-year survival rates range from 73% to 93%. Their usefulness, however, is limited for patients with advanced stage disease where the 5-year survival is only about 30% (Guarneri et al. 2010;Surveilance Epidemiology and End Results 2010). Disease stage at diagnosis and the amount of residual disease after surgical debulking have the greatest influence on both progression free survival (PFS) and overall survival (OS). Thus patients with no visible residual disease post surgery have longer PFS and OS than those with >1mm residuals, who in turn fare better than patients with >1cm residual disease (du Bois et al. 2009;Heintz et al. 2006). However, even amongst patients with Stage III and IV tumours, whose median OS may be only 2-3 years, between 10 and 20% of patients survive for as long as ten years (du Bois et al. 2009) ,demonstrating the immense variability of the disease.

Notwithstanding this small proportion of long-term survivors, for the majority of patients with advanced disease, cure is not possible but prolongation of survival and delay in first recurrence is considered clinically meaningful and important.

VEGF, ovarian cancer and angiogenesis

The process of angiogenesis provides the new vessels to nourish growth in all tissues. Angiogenesis in solid tumours stimulates the production of new vessels to provide the nutrients and oxygen essential for growth beyond a volume of 1 mm^3 (Bergers & Benjamin 2003). Vascular endothelial growth factor (VEGF) is the most potent and specific promoter of angiogenesis known and is a key regulator of new vessel formation during embryogenesis, skeletal growth and female reproductive functions (Ferrara, Gerber, & LeCouter 2003). In non-neoplastic tissues, recurrent VEGF-mediated angiogenesis and vascular regression is unique to the ovulatory cycle. New vessel generation and regulation is essential both for the cycle and for pregnancy. VEGF expression is highly regulated throughout the ovulatory cycle, with peak VEGF production occurring after the mid-cycle peak of leuteinising hormone (LH) and follicle stimulating hormone (FSH). Post-menopause, the continuous high LH and FSH levels give rise to increased VEGF expression (Ramakrishnan et al. 2005).

VEGF binds to its receptors on quiescent endothelial cells to begin the signalling cascade which initiates new blood vessel formation (Itakura et al. 2000). VEGF not only has mitogenic effects on vascular endothelial cells, it also stimulates capillary formation and increases vascular permeability (Liu et al. 2002).

VEGF is also implicated in pathological angiogenesis, for example in tumours. Newly formed tumour vessels are markedly dependent on VEGF which is upregulated in many tumours (Ferrara & Davis-Smyth 1997). Ovarian tumours are highly vascularised and the microvascular density and biological aggressiveness of ovarian cancers appear to be correlated (Alvarez et al. 1999). VEGF overexpression has been correlated with malignant progression and a worse overall prognosis and also with the development of ascites, due to effects on vascular permeability. In ovarian carcinomas, a direct relationship has been demonstrated between increased expression of biomarkers for angiogenesis such as VEGF and VEGF-R and tumour behaviour (Cooper et al. 2002;Paley et al. 1997).

Initially VEGF receptors were thought only to be expressed on endothelial cells, however it has also been demonstrated that some ovarian cancer cells express VEGF-R1 (flt-1) and VEGF-R2 (KDR), possibly leading to direct stimulation of ovarian tumour growth by VEGF and potentially a direct anti-tumour effect of anti-VEGF therapy (Boocock et al. 1995). These findings suggest an important role for inhibition of the VEGF pathway in the treatment of patients with ovarian carcinomas.

Clinical need for improved therapeutic efficacy

The ICON5/GOG-0182 study was designed to evaluate four different, emerging regimens with promising new cytotoxic agents compared to combination carboplatin and paclitaxel alone. This large trial in over 4000 ovarian cancer patients clearly demonstrated that none of the regimens with additional cytotoxic agents demonstrated an improvement over a combination of carboplatin and paclitaxel alone (Bookman et al. 2009). This study is emblematic of how difficult it is to improve treatment for patients with ovarian cancer and over the past two decades, there have been only modest improvements in 5-year overall survival. The last new drug to be approved for first line ovarian cancer was paclitaxel, launched in the EU in 1994. Increasing the benefit of first-line treatment of advanced ovarian cancer, by extending progression-free survival, should significantly improve the therapeutic outcome for patients and may even extend overall survival. This is particularly important in patients with poor prognosis factors such as FIGO stage III and IV and residual disease after initial surgery, which represent a large unmet clinical need in society.

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

The annual incidence for the licensed population (Stage IIIB, IIIC and IV ovarian cancer) in England and Wales is 4,408. This is calculated from the total population (Office of National Statistics 2011a;Office of National Statistics 2011b) and the age-standardised incidence rate for ovarian cancer (Cancer Research UK 2011b). These give a total annual incidence of 6,905 and of these 82% of cases are calculated to be Stage IIIB to IV. From the licensed population, about 10% will be unsuitable for chemotherapy, about 10% entered into clinical studies and about 4% will have contraindications to bevacizumab, so a total of about 4,400 patients should be eligible for bevacizumab therapy.

The proportion of Stage IIIB-IV patients with suboptimal debulking in the two Phase III clinical studies in this submission was 66% and 42%. This suggests that the eligible numbers for the high-risk (suboptimally debulked) population in England and Wales is between 1,800 and 2,900.

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

Because the disease tends to be asymptomatic in early stages, or associated with vague, nonspecific symptoms, the majority of patients are diagnosed with advanced stage disease (FIGO stage III and IV). Current therapies prove effective for patients with early stage disease (FIGO stage I/II) where 5-year survival rates range from 73% to 93%. Their usefulness, however, is limited for patients with advanced stage disease where the 5-year survival is only about 30% (Guarneri et al. 2010;Surveilance Epidemiology and End Results 2010).

For patients with advanced stage disease, cure is not possible in the majority of cases, but prolongation of survival can be achieved and delay in first recurrence is considered clinically meaningful.

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

Technology Appraisal No. 91 (TA91), May 2005, 'Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for the treatment of advanced ovarian cancer' (Review of TA 28, TA 45 and TA 55 [for relapsed disease only]). Review date: November 2012

Technology Appraisal No. 55 (TA55), January 2003, 'Review of the clinical effectiveness and cost effectiveness of paclitaxel for ovarian cancer'. Review date: on static list

Technology Appraisal No. 222 (TA222), April 2011, 'Trabectedin for the treatment of relapsed ovarian cancer'. Review date: Not applicable

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

After initial surgical diagnosis, staging and cytoreduction, the standard primary systemic chemotherapy for women with advanced ovarian cancer is a platinum and taxane combination (du Bois et al. 2003;McGuire & Markman 2003), usually carboplatin and paclitaxel. Although most patients (70% to 80%) initially respond to first-line chemotherapy, most responders eventually relapse (55% to 75% within 2 years) (NICE 2003) and women ultimately die of their disease, underlining the need to improve front line therapy.

Therapy with platinum compounds has long been recognised as the most effective treatment for ovarian cancer and NICE TA55 recommends that paclitaxel in combination with a platinum-based compound (cisplatin or carboplatin) or platinum-based therapy alone are offered as alternatives for first-line chemotherapy (usually following surgery) in the treatment of ovarian cancer. It is estimated that 75% of women with ovarian cancer currently receive a paclitaxel/platinum combination as first-line therapy (Muggia 2009;NICE 2003).

After achieving a response with first-line therapy, a majority of patients relapse with recurrent disease within 2 years. The timing of this relapse determines the therapy for recurrent disease; relapse more than 6 months after previous therapy suggests the disease is platinum sensitive and such patients receive further platinum therapy. Patients relapsing during or up to 6 months after platinum therapy are regarded as platinum resistant and their subsequent therapeutic options are very limited. In the third and subsequent lines of therapy, the treatment options are equally limited for both platinum-sensitive and platinum–resistant patients, with the majority of patients ultimately developing platinum-resistant disease (Markman & Bookman 2000;Modesitt & Jazaeri 2007). A significant aim of first-line therapy is to extend the recurrence-free interval to beyond 6 months for as many patients as possible, in order that they may continue to receive platinum-based therapy.

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

The choice of platinum agent for front-line therapy is a potential issue. However, three trials have investigated the equivalence of carboplatin and cisplatin in combination with paclitaxel in the first-line setting and have demonstrated similar outcomes for the two drugs (du Bois 2001;Neijt et al. 2000;Ozols et al. 2003). Overall carboplatin is associated with significantly lower neurotoxicity and renal toxicity and the combination of carboplatin and paclitaxel infused over 3 hours can be given as an out-patient schedule.

Potentially improved outcomes have also been reported with two modified regimens of paclitaxel:

- Dose-dense or weekly paclitaxel (Katsumata N, Yasuda M, & Isonishi S 2012;Katsumata et al. 2009):

Although a dose-dense i.e. weekly paclitaxel regimen showed improvement in PFS and survival compared to a conventional regimen of paclitaxel and carboplatin given every 3 weeks, there was greater haematological toxicity in the dose-dense treatment group than in the conventional treatment group, which resulted in more delays and dose modifications. The optimum dose and

schedule of dose-dense paclitaxel and carboplatin have not yet been established.

Further clarity may be provided by the results of three ongoing studies of carboplatin plus dose-dense or conventional paclitaxel (GOG-262, ICON8 and OCTAVIA), two of which include concomitant use of bevacizumab (Gonzalez-Martin A et al. 2012;Medical Research Council 2011;Seamon, Richardson, & Copeland 2012). While results are anticipated in the near future, any change to the optimal dosing regimen of paclitaxel would be covered within the scope of the bevacizumab licensed indication.

- Intraperitoneal paclitaxel (Armstrong et al. 2006):

Difficulties in the administration of intraperitoneal chemotherapy, increased toxicity and reduced patient quality of life during treatment have, so far, limited its adoption into standard practice and NICE guideline CG122 on the management of ovarian cancer does not recommend intraperitoneal chemotherapy to women with ovarian cancer except as part of a clinical trial (NICE 2011).

It is also worth noting that bevacizumab (at the 7.5mg/kg dosing schedule) is currently on lists of 'approved' drugs in all 10 SHAs in England with access to the Cancer Drugs Fund, for front-line advanced ovarian cancer patients with residual disease following debulking surgery. Although exact numbers of patients treated in this way are not available, it is indicative of significant clinical interest in the availability of this treatment option.

2.7 Please identify the main comparator(s) and justify their selection.

3-weekly combination therapy with carboplatin plus paclitaxel is the main comparator. This is the internationally recognised standard therapy for first-line treatment of advanced ovarian cancer.

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Anti-hypertensive agents, such as ACE inhibitors or calcium channel blockers, may be required for hypertension management.

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Bevacizumab is intravenously administered in a hospital setting every 21 days. This administration requirement equates to a cost of £271 per cycle (NHS Reference costs 2009/2010 (SB13Z): Deliver more complex Parenteral Chemotherapy at first attendance (Daycase)). In addition to this delivery cost bevacizumab will require pharmacy preparation of infusion every 21 days. The only additional monitoring requirements associated with bevacizumab beyond those currently in place for first line advanced ovarian cancer treatment are blood pressure monitoring and assessment of proteinuria – these may be part of general clinical practice.

2.10 Does the technology require additional infrastructure to be put in place?

N/A

3 Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

3.1 Identification of equality issues

3.1.1 **Please let us know if you think that this appraisal:**

- **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;**
- **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology**
- **could lead to recommendations that have any adverse impact on people with a particular disability or disabilities**

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

To Roche's knowledge there are no such issues.

3.1.2 **How has the analysis addressed these issues?**

N/A

4 Innovation

4.1.1 **Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the**

technology is a ‘step-change’ in the management of the condition.

Yes, as shown in Section 2.1, many publications link the induction and growth of ovarian cancers with high levels of VEGF and the expression of VEGF receptors on ovarian cancer cells suggests that VEGF inhibitors may directly inhibit tumour cell growth as well as inhibiting tumour angiogenesis. Bevacizumab is the first licensed anti-VEGF targeted therapy in ovarian cancer. Its mode of action is targeted directly against one of the drivers of the tumour (VEGF) and its exceptional single-agent activity on overall response rates and PFS, in heavily pre-treated patients(Burger et al. 2007;Cannistra et al. 2007;Smerdel et al. 2010) emphasises the importance of targeting VEGF in ovarian cancer therapy. Its adverse event profile, unlike that of cytotoxic agents, allows it to be combined with cytotoxic chemotherapies without providing an intolerable additional burden of toxicity. This direct targeted therapeutic activity, with a different toxicity profile from previous agents, provides an innovative step change in the management of ovarian cancer.

4.1.2 **Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.**

N/A

4.1.3 **Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.**

N/A

5 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

Table 2 - Statement of the decision problem

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from the scope**
Population	Women with newly diagnosed, stage III or IV ovarian cancer who have not received prior chemotherapy	The submission will present data from GOG-0218 ITT population as the base case.	NA
Intervention	Bevacizumab in combination with paclitaxel and carboplatin	As per scope	NA
Comparator(s)	Platinum-based chemotherapy (cisplatin or carboplatin with or without paclitaxel), without bevacizumab	The submission will focus on carboplatin with paclitaxel as the base case chemotherapy option.	Both clinical trials for bevacizumab in this setting used carboplatin with paclitaxel as the comparator chemotherapy regimen.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related	As per scope	NA

	quality of life		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per scope	NA
Subgroups to be considered		1. MRC-defined 'High risk' subgroup. These are patients with stage IIIB-IV disease with suboptimal debulking surgery. 2. An expanded 'High risk' subgroup which includes	1. This pre-planned subgroup analysis was designed to reflect recruitment criteria in GOG-0218. 2. This subgroup includes patients on whom debulking surgery was not performed and is

		the MRC-defined patients listed in no. 1.as well as inoperable patients excluded from the MRC analysis	more closely aligned with stratified groups in ICON7.
Special considerations, including issues related to equity or equality	None	As per scope	NA

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	**Reference case**	**Section in 'Guide to the methods of technology appraisal'**
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12
HRQL, health-related quality of life; NHS, National Health Service; PSS, personal social services; QALY(s), quality-adjusted life year(s)		

6 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

6.1 Identification of studies

Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in Section 9.2, Appendix 2.

Searches used index and text words which included bevacizumab and ovarian cancer as descriptors. The search was restricted to include only documents that were written in English relating to humans, females, clinical trials or non-interventional studies, and to exclude reviews wherever possible. The search was further restricted manually according to inclusion/exclusion criteria in Section 9.2.6

Full details of the searches conducted and terms used are provided in Section 9.2. Details of the search outputs/records obtained and reasons for exclusion/inclusion of records are also provided in an embedded document in Section 9.2.7

6.2 Study selection

6.2.1 **Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.**

Table B1 Eligibility criteria used in search strategy

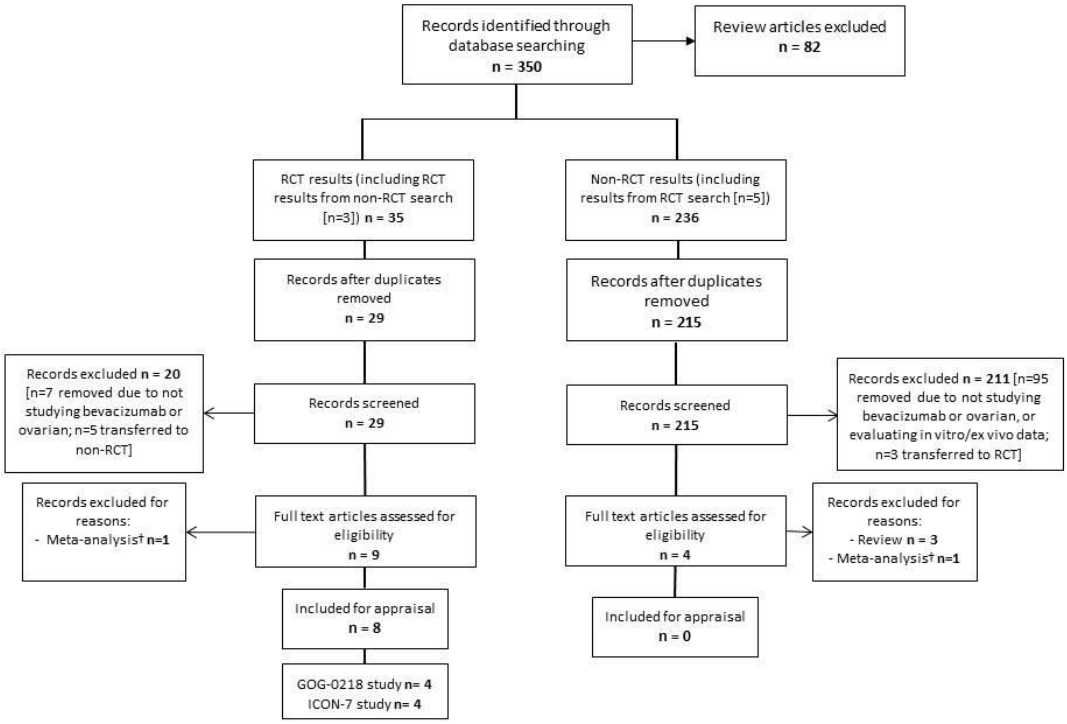
	Clinical effectiveness
Inclusion criteria	Population Interventions Outcomes Study design Language restrictions
Exclusion criteria	Population Interventions Outcomes Study design Language restrictions

See Section 9.2.6

6.2.2 **A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.**

See Figure 1 below.

Figure 1 - Systematic review flow diagram



6.2.3 **When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.**

The references relevant to the specific studies are listed under the study heading in section 6.2.4.

Complete list of relevant RCTs

6.2.4 **Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group.**

Table 3 - list of relevant RCTs

	Intervention	Comparator	Population	Primary study
GOG-0218	Carboplatin (AUC6) and paclitaxel (175mg/m^2) (q3w 6 cycles) with concurrent bevacizumab (15mg/kg) (q3w for 5 cycles), followed by extended bevacizumab (15mg/kg q3w for a further 16 cycles) (n=623)	Carboplatin (AUC6) and paclitaxel (175mg/m^2) (q3w 6 cycles) with concurrent bevacizumab (15mg/kg) (q3w for 5 cycles), followed by placebo (q3w for 16 cycles) (n=625) and: Carboplatin (AUC6) and paclitaxel (175mg/m^2) (q3w 6 cycles) and placebo (q3w for 5 cycles), followed by placebo (q3w for 16 cycles) (n=625)	n=1873 (ITT) Epithelial ovarian cancer, primary peritoneal cancer and fallopian tube cancer with stage III optimal (macroscopic), stage III suboptimal or stage IV disease	Burger et al. NEJM 2011;365:2473-83
ICON7 (BO17707)	Carboplatin (AUC5 or 6) and paclitaxel (175mg/m^2) with concurrent bevacizumab (7.5mg/kg) (q3w for 6 cycles), followed by extended bevacizumab (7.5mg/kg q3w for 12 cycles) (n=764)	Carboplatin (AUC5 or 6) and paclitaxel (175mg/m^2) (q3w for 6 cycles) (n=764)	n=1528 (ITT) Epithelial ovarian carcinoma, primary peritoneal carcinoma or fallopian tube carcinoma with high risk early stage (FIGO stage I/IIA clear cell or grade 3 carcinoma) or advance stage (FIGO stage IIB-IV, all grades and all histological subtypes) disease	Perren et al. NEJM 365;2484-96

GOG-0218

The GOG-0218 trial was an international, double blind, phase III, randomised, placebo-controlled trial that evaluated the efficacy, safety and QoL of patients with advanced ovarian cancer who receive bevacizumab in combination with carboplatin and paclitaxel, compared to carboplatin and paclitaxel alone. It was published in the New England Journal of Medicine in December 2011:

Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med. 2011 Dec 29;365(26):2473-83

The following abstracts have also been published:

Burger, R. A., Brady, M. F., Bookman, M. A., Walker, J. L., Homesley, H. D., Fowler, J., Monk, B. J., Greer, B. E., Boente, M., & Liang, S. X. 2010, "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): A Gynecologic Oncology Group study", ASCO Meeting Abstracts, vol. 28, no. 18_suppl, p. LBA1.

Burger RA, Brady MF, Bookman MA, Monk BJ, Walker JL, Homesley HD., Fowler J., Greer BE., Boente M., Liang SX 2010, “Safety and subgroup efficacy analyses in GOG-0218, a phase III trial of bevacizumab in the primary treatment of advanced epithelial ovarian cancer, primary cancer, or fallopian tube cancer: a Gynecologic Oncology Group Study”. ESMO abstract #978PD

Monk BJ, Huang, H., Burger RA., Mannel RL., Homesley HD, Fowler J., Greer, BE., Boente M., Liang SX. and Wenzel L. 2011, Quality of live outcomes of randomized, placebo controlled trial of bevacizumab in the front line treatment of ovarian cancer: a Gynecologic Oncology Group Study. ECCO/ESMO. Abstract 23LA.

ICON7

The ICON7 trial was an international, open-labelled, placebo controlled, phase III trial investigating the effect of bevacizumab in combination carboplatin and paclitaxel compared to carboplatin and paclitaxel alone in patients with new

diagnosed ovarian cancer. It was published in the New England Journal of Medicine in December 2011:

Perren TJ, Swart AM, Pfisterer J,et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med. 2011 Dec 29;365(26):2484-96. Erratum in: N Engl J Med. 2012 Jan 19;366(3):284

The following abstracts have also been published:

Perren T, Swart, A, Pfisterer J, et al. “ICON7: a phase 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).” ESMO 2010; abstract LBA4

Kristensen, G., Perren, T., Qian, W., Pfisterer, J., Ledermann, J. A., Joly, F., Carey, M. S., Beale, P. J., Cervantes, A., Oza, A. M. GCIG 2011, "Result of interim analysis of overall survival in the GCIG ICON7 phase III randomized trial of bevacizumab in women with newly diagnosed ovarian cancer", *ASCO Meeting Abstracts*, vol. 29, no. 18_suppl, p. LBA5006.

Stark D, Nakivell M, Hipert F, Elit L, Brown J, Lanceley A, Valikova G, Oza, A, Swart AM, Perren T, 2011 “Quality of life data in the ICON7 GCIC phase III randomised clinical trial”. ECCO/ESMO. Abstract 22LBA.

6.2.5 **Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.**

GOG-0218 and ICON7 are the only studies that compare the intervention with appropriate comparators.

6.2.6 **When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no**

access to the level of trial data required, this should be indicated.

All publications highlighted above were included in this assessment.

List of relevant non-RCTs

6.2.7 **Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.**

No relevant non-RCTs were found.

6.3 Summary of methodology of relevant RCTs

6.3.1 **As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.**

Methods

Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments.

Table 4 - comparative summary of the methodology of RCTs

	GOG-0218	ICON7
Location	336 investigative sites in Canada, Japan, South Korea and the USA. This trial was conducted by the Gynaecologic Oncology Group (GOG).	263 investigative sites in 8 European countries (inc. UK, Germany, France, Norway, Denmark, Spain) and 3 non-European countries (Canada, Australia and New Zealand). This trial was conducted by the Gynaecologic Cancer InterGroup (GCI) and sponsored by the MRC, UK.
Design	Phase III, randomised, three-armed, double blind, placebo-controlled, superiority trial. See Figure 2 for full study schema.	Phase III, randomised, two-armed, open label, controlled, superiority trial. See Figure 3 for full study schema.
Duration of study	October 2005 to February 2010 (data un-blinded to sponsor)	December 2006 to February 2010 (first patient randomised to clinical data cut-off)
Method of randomisation	1873 patients were randomised in a 1:1:1 ratio to one of three treatment arms. Randomisation was implemented by the GOG Coordinating Center using a dynamic allocation procedure. The two stratification factors for randomisation were initial GOG performance status (0 vs. 1 or 2) and disease stage. Disease stage included the following levels: Macroscopic optimally debulked (FIGO Stage III with maximum diameters of all gross residual disease ≤ 1 cm) Suboptimally debulked (FIGO Stage III with maximum diameter of any gross residual disease > 1 cm) FIGO Stage IV	1528 patients were randomised in a 1:1 ratio to one of two treatment arms. Stratification arose for the following factors using stratified block randomisation: FIGO stage (category 1: stage I-III with residual disease ≤ 1 cm, category 2: Stage I-III with residual disease > 1 cm, category 3: FIGO stage IV and inoperable FIGO stage III) Intent to start chemotherapy ≤ 4 weeks following surgery versus intent to start chemotherapy > 4 weeks after surgery GCIG group. The randomisation system limited the proportion of FIGO stage I and IIa patients enrolled by investigators in any individual country or group to a maximum of 10% of the total patients enrolled by that country or group (based on estimated accrual).
Method of blinding (care provider, patient	GOG-0218 was a double-blind trial conducted by GOG. Thus, investigators, patients and research personnel did	ICON7 was an open-label study conducted by GCI and sponsored by the MRC. Therefore, once patients were

	GOG-0218	ICON7
and outcome assessor)	not know the treatment received by patients. The Sponsor (Genentech) had no access to unblinded trial data during the conduct of the trial. Genentech remained blinded to the results until 22 February 2010. Study treatments were unblinded to all patients as of 25 February 2010. Placebo infusions were no longer to be administered after this date. Patients in the CPB15+ arm were given the option of receiving open-label bevacizumab on study, with continued safety data collection.	randomised to an arm, both the patient and investigator were aware of the treatment assigned. The MRC reviewed tumour response assessment data listings produced by Covance (the contracted company monitoring investigative sites) on a regular basis and in a blinded manner to ensure data was validated as required by data management, and to add a data quality control component. Roche had no direct access to the data throughout the conduct of the study and were distanced from processes of data generation.
Intervention(s) (n =) and comparator(s) (n =)	GOG-0218 was a three armed trial: CPP: Carboplatin (AUC6) and paclitaxel (175mg/m2) (q3w for 6 cycles), and placebo (q3w for 5 cycles), followed by placebo (q3w for 16 cycles) (n=625). vs. CPB15: Carboplatin (AUC6) and paclitaxel (175mg/m2) (q3w for 6 cycles) with concurrent IV bevacizumab (15mg/kg) (q3w for 5 cycles), followed by placebo (q3w for 16 cycles) (n=625) vs. CPB15+: Carboplatin (AUC6) and paclitaxel (175mg/m2) (q3w for 6 cycles) with concurrent bevacizumab (15mg/kg) (q3w for 5 cycles), followed by extended bevacizumab (15mg/kg q3w for 16 cycles) (n=623).	ICON7 was a two armed trial: CP: Carboplatin (AUC5 or 6) and paclitaxel (175mg/m2) (q3w for 6 cycles) (n=764). vs. CPB7.5+: Carboplatin (AUC5 or 6) and paclitaxel (175mg/m2) with concurrent bevacizumab (7.5mg/kg) (q3w for 6 cycles), followed by extended bevacizumab (7.5mg/kg q3w for 12 cycles) (n=764). Patients received treatment until disease progression, unacceptable toxicity or completion of 6 cycles of treatment in the CP arm, or completion of 18 cycles of treatment in the CPB7.5+ arm, whichever came first. All drugs were administered intravenously. Cross-over was not permitted.

	GOG-0218	ICON7
	Patients received treatment until disease progression, unacceptable toxicity or completion of 22 cycles of treatment, whichever came first. All drugs (placebo and active compounds) were administered intravenously. Patients in the placebo arm (CPP) were permitted to cross-over to receive bevacizumab in subsequent lines of treatment, if recommended by their treating physician.	
Primary outcomes (including scoring methods and timings of assessments)	The primary efficacy outcome measure was PFS based on investigator assessment. The primary objective of the study was to determine if the addition of bevacizumab to standard chemotherapy (carboplatin and paclitaxel) for 5 cycles followed by maintenance bevacizumab for 16 cycles increases PFS when compared to 6 cycles of standard therapy alone in women with newly diagnosed Stage III (with any gross residual disease) and Stage IV, epithelial ovarian, primary peritoneal, or fallopian tube cancer. The primary objective also determined whether the addition of bevacizumab to standard chemotherapy increases the duration of PFS when compared to 6 cycles of standard therapy alone in the same patient population. PFS was defined as the period from randomisation until disease progression or death from any cause, whichever occurred first. Primary efficacy outcomes compared the CPB15 arm versus the CPP arm and the CPB15+ arm versus the CPP arm. Comparisons of CPB15 versus CPB15+ only arose if both bevacizumab containing treatment arms	The primary efficacy outcome measure was PFS based on investigator assessment. The objective of the study was to determine whether the addition of bevacizumab to standard chemotherapy improves PFS when compared to standard chemotherapy alone in women with high risk early stage or advance stage epithelial carcinoma, primary peritoneal carcinoma or fallopian tube carcinoma. Tumour assessments were made using RECIST criteria based on CT (or MRI) scans at baseline (post-operative), at 3 and 6 cycles of chemotherapy, after approx. 9 and 12 months after start of chemotherapy and periodically thereafter as clinically indicated. Progression based on CA-125 criteria alone was verified with a CT scan. Patients were clinically assessed and CA-125 measured at baseline within a 7 day period prior to first cycle of trial treatment and at the start of every chemotherapy cycle and then six weekly during the first year of the trial. In the second and third year of the trial patients were assessed and CA-125 measured every three months. In the fourth and fifth year patients were clinically assessed and CA-125 measured every six months. Thereafter,

	GOG-0218	ICON7
	were significantly different to the placebo arm. Progression could be based on global clinical deterioration, CA125 progression and RECIST criteria only. CA125 progression increase was greater than or equal to twice the nadir or upper limit of normal. Radiographic tumour assessments were performed at baseline and subsequently: after Cycle 3 of CP, after Cycle 6 of CP, after completion of CP chemotherapy, and during treatment with bevacizumab /placebo at Cycle 10, Cycle 14, Cycle 18, Cycle 22. Tumour assessments will arise after completion of all protocol therapy: every 3 months for 2 years, then every 6 months for 3 years, then annually. Radiographic imaging could be performed at any time if clinical or laboratory findings indicated the possibility of progressive disease. When disease progression was defined using CA-125 criteria alone, sites were encouraged to obtain imaging, within 2 weeks that such progression was documented. Suspected progression based solely on developing or worsening ascites or pleural effusions must have been verified cytologically. The ITT population was the primary population for the efficacy analyses.	assessments were yearly. Progression based on CA-125 criteria alone was always verified with a CT scan. The ITT population was the primary population for the efficacy analyses.
Secondary outcomes (including scoring methods and timings of assessments)	The secondary efficacy outcome measures were overall survival (OS) and objective response rate (ORR). Sensitivity analysis of PFS was a secondary outcome and included an IRC review and PFS which was not censored for CA-125 progression.	The secondary efficacy outcomes were overall survival, objective response rate (ORR), duration of response and biological Progression-Free Interval (PFIBIO). Sensitivity analysis of PFS included worst case analysis and time to censoring analysis.

	GOG-0218	ICON7
	The safety outcome measures were the frequency and severity of adverse events (AEs). AEs of special interest to bevacizumab were recorded. Secondary safety analysis assessed the extent of AEs during concomitant bevacizumab therapy with chemotherapy and AEs during bevacizumab maintenance therapy AE forms were completed after each cycle during the treatment phase of the trial. Thereafter, patients were monitored for delayed toxicity every 3 months for 2 years and then every 6 months for 3 years, and then annually during the post-treatment period. The safety-evaluable population included all randomised patients who received at least one full or partial dose of any study treatment during Cycles 2 or beyond. Patients who did not receive any of their assigned study treatment were not included in these analyses. The proportion of patients experiencing at least one adverse event was reported by toxicity term and by treatment arm. Quality of life was measured using the FACT-O TOI questionnaire, the Ovarian Cancer Subscale measure and abdominal discomfort score. The FACT-O measure is a self-administered questionnaire, consisting of three modules: a 7-item physical well-being (PWB) module, a 7-item functional well-being (FWB) module, and a 14-item “additional concerns” module, for a total of 28 items. The “additional concerns” module consists of a 12-item ovarian cancer subscale (OCS) and two items for abdominal discomfort. The principal outcome measure is the TOI, which consists of PWB, FWB, OCS scores.	The safety outcome measures recorded the frequency and severity of adverse events. AEs of special interest to bevacizumab were recorded. Other secondary outcomes were quality of Life assessments (using EORTC QLQ-C30, EORTC QLQ-OV28 and EuroQoL EQ-5D questionnaires) and cost effectiveness assessments. The first QoL assessment was completed during the screening visit, then at the onset of every chemotherapy cycle, every 6 weeks until the end of the first year and then every 3 months until progression or to the end of year 2. HRQoL was also measured on day 1 of the first cycle of chemotherapy at first relapse, and in the cohort at three years from randomisation. For further detailed scoring assessments and analysis timings see section 5.3.8.

	GOG-0218	ICON7
	For further detailed scoring assessments and analysis timings see section 5.3.8.	
Duration of follow-up	All patients who discontinue or complete study treatment will be followed for survival every 3 months when the patient is <2 years in the post-treatment period and every 6 months when the patient is 2-5 years in the post-treatment period. The protocol contains no specific requirement regarding the frequency of survival follow-up when the patient is >5 years in the post-treatment period. It is GOG standard procedure to follow patients annually after the patient has completed 5 years of follow-up.	Follow up prior to disease progression arises every three months during years 2 and 3, every six months during years 4 and 5 and then yearly. Follow up after disease progression was every six months during the first five year, and then yearly.

Figure 2 - Study schema for GOG-0218

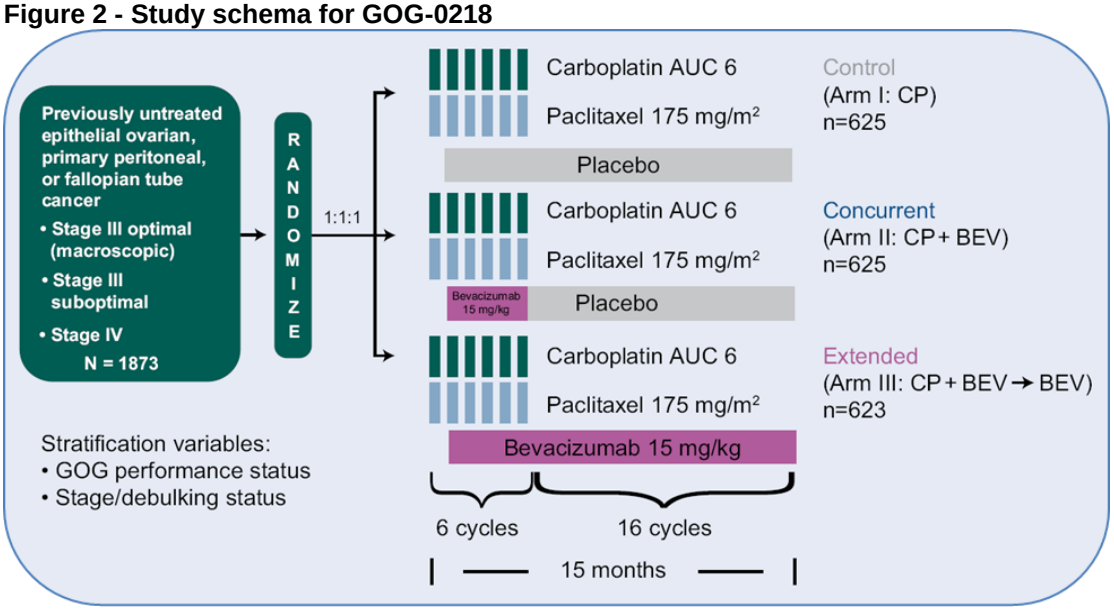
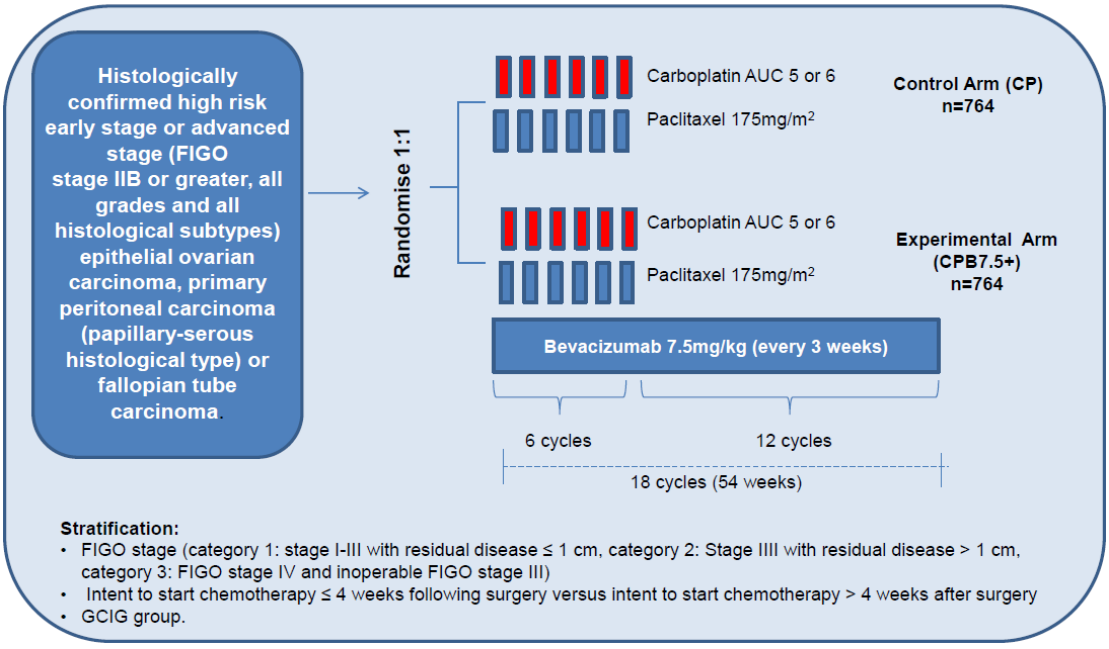


Figure 3 - Study schema for ICON7



Summary of similarities and differences between GOG-0218 and ICON7 trials:

- Both trials were superiority trials investigating the PFS benefit with bevacizumab and standard chemotherapy (carboplatin and paclitaxel), compared to standard chemotherapy alone.
- Both trials investigated women with epithelial ovarian carcinoma, primary peritoneal carcinoma or fallopian tube carcinoma.
- GOG-0218 was a double-blind, placebo-controlled study, whereas ICON7 was an open-labelled study.
- The ICON7 trial was a European study, with 48 centres in the UK, whereas GOG-0218 was primarily based in US/Canada and Asia.
- The bevacizumab dose and duration of the trials was different: GOG-0218 used bevacizumab 15mg/kg for a total of up to 15 months, compared to the ICON7 trial that used bevacizumab 7.5mg/kg for a total of up to 12 months. Both trials administered bevacizumab once every three weeks.
- The eligibility criteria for GOG-0218 only permitted the inclusion of patients with stage III and IV disease, whereas, ICON7 included patients with a wider range of disease stages (stages I-IV). However, in the ICON7 study, pre-planned OS and PFS subgroup analysis was performed, investigating a similar patient population to those in the GOG-0218 study.
- The classification of PFS in the GOG-0218 and ICON7 was different, with GOG-0218 using CA-125 criteria alone, as well as RECIST and global deterioration criteria to determine PFS, whereas the ICON7 trial only used RECIST and clinical /symptomatic progression. However, the Regulatory primary efficacy analysis (PFS) of the GOG-0218 trial determined progression with CA-125 alone progression events censored.
- Stratification variables between trials were different. In the GOG-0218 trial patients were stratified according to GOG performance status and disease stage. The disease stage included the following levels: Macroscopic optimally debulked (FIGO Stage III

with maximum diameters of all gross residual disease ≤ 1 cm), Sub-optimally debulked (FIGO Stage III with maximum diameter of any gross residual disease > 1 cm) and FIGO Stage IV. In the ICON7 trial patients were also stratified according to stage and residual disease,Stratum 1: stage I-III with residual disease ≤ 1 cm, Stratum 2: Stage I-III with residual disease > 1 cm, Stratum 3: FIGO stage IV and inoperable FIGO stage III.

- Cross-over post progression was permitted in the GOG-0218 trial, whereas it was not allowed in the ICON7 trial.

Participants

6.3.2 **Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT, Highlight any differences between the trials.**

Table 5 - Eligibility criteria in the GOG-0218 and ICON7 trials

	GOG-0218	ICON7
Inclusion criteria	Histological diagnosis of epithelial ovarian cancer, primary peritoneal cancer or fallopian tube carcinoma. GOG performance status of 0, 1, or 2. Adequate renal and hepatic function Motor /sensory neuropathy grade ≤1. Adequate blood coagulation parameters and haematological function. Study entry between 1 and 12 weeks after initial surgery. Patients with measurable and non-measurable disease. Patients in this trial may have received oestrogen with or without progestin replacement therapy. Entry to trial 1-12 weeks after debulking surgery Over 18 years of age.	Histologically confirmed high risk early stage (FIGO stage I or IIA clear cell or Grade 3 carcinoma) or advanced stage (FIGO stage IIB or greater, all grades and all histological subtypes) epithelial ovarian carcinoma, primary peritoneal carcinoma (papillary-serous histological type) or fallopian tube carcinoma. Patients should have already undergone surgical debulking. Patients with stage III and IV disease in whom initial surgical debulking was not appropriate were eligible, providing they had a histological diagnosis and debulking surgery prior to disease progression was not forseenECOG performance status 0, 1 or 2. Life expectancy >12 weeks Adequate bone marrow function and coagulation parameters. Urine dipstick for proteinuria < 2+. Adequate liver and renal function Over 18 yrs of age. Signed informed consent and ability to comply with the protocol.

Exclusion criteria	Current diagnosis of borderline epithelial ovarian tumour or recurrent invasive epithelial ovarian, primary endometrial cancer, primary peritoneal, or fallopian tube cancer treated with surgery only. Prior radiotherapy or chemotherapy for any abdominal or pelvic tumour. Prior targeted therapy or hormonal therapy for epithelial ovarian, fallopian tube, or peritoneal primary cancer. Prior bevacizumab treatment. Other invasive malignancies Serious non-healing wound or active bleeding conditions that carried high risk of bleeding. CNS disease, including primary brain tumour. Significant cardiovascular disease, including: uncontrolled hypertension, myocardial infarction or unstable angina. Serious cardiac arrhythmia requiring medication, or history of cerebro-vascular accident (CVA) within 6 months Clinically significant proteinuria. Invasive procedures such as major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to the trial initiation. GI obstruction that required parenteral hydration and/or nutrition	Non-epithelial ovarian cancer, including malignant mixed Mullerian tumors, or borderline tumours. Planned intraperitoneal chemotherapy or prior systemic anti-cancer therapy for ovarian cancer. Non-healing wound, traumatic injury, surgery within 4 weeks prior start of trial or planned surgery during the 58 week period from the start of study treatment Uncontrolled hypertension, previous CVA, Transient Ischaemic Attack (TIA) or Sub-Arachnoid Haemorrhage (SAH) within 6 months prior to randomisation Any previous radiotherapy to the abdomen or pelvis History/evidence of brain metastases or spinal cord compression Treatment with other investigational agents or previous exposure to mouse CA-125 antibody Patients with synchronous primary endometrial carcinoma, or a history of primary endometrial cancer. Malignancies other than ovarian cancer within last 5 yrs History or evidence of thrombotic or haemorrhagic disorders Clinically significant CV disease: myocardial infarction, unstable angina, CHF, poorly controlled cardiac arrhythmia, grade ≥ 3 peripheral vascular disease. Current or recent use of full-dose anticoagulants, thrombolytic agents or chronic use of aspirin. Pre-existing sensory or motor neuropathy ≥ Grade 2
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee		

For both the ICON7 and GOG-0218 studies, the exclusion criteria were consistent with the contraindications listed on the bevacizumab Summary of Product Characteristics.

Summary of similarities and differences between the GOG-0218 and ICON7 inclusion/exclusion criteria:

- Both GOG-0218 and ICON7 trials investigated adult patients with epithelial ovarian cancer, primary peritoneal carcinoma or fallopian tube cancer.
- Patients were to have no previous chemotherapy treatment for ovarian cancer, thus trials investigated the effects of first-line therapy. All patients in the trials had an initial GOG performance status of 0-2 and the intention was that all patients should have prior debulking surgery. However, in ICON7 inoperable patients could be included if debulking surgery was not planned prior to progression.
- The key difference between the inclusion/exclusion criteria of the trials was the stage of disease. In GOG-0218 trial, only advanced patients with stage III (macroscopic optimal and suboptimal) and IV disease were included, whereas in the ICON7 trial patients with a wider range of disease stages (stages I-IV) were included. The ICON7 trial permitted patients who had stage I-IIA disease (with either grade 3 disease or clear cell histology) and patients who had IIB to IV disease (all grades and histological subtypes).
- The criteria describing stage III optimal debulking was different between the GOG-0218 and ICON7 trial. In the GOG-0218 trial, patients with stage III optimally debulked disease had macroscopic residuals (tumour visible to the naked eye), whereas in the ICON7 trial, optimally debulked patients could have either macroscopic or microscopic (not visible to naked eye) residual disease.

6.3.3 **Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.**

GOG-0218

Table 6 shows the baseline characteristics for patients in each arm of the GOG-0218 trial. Overall, baseline disease characteristics were balanced across the three treatment arms. The majority of patients (92.8%) had a baseline performance status of either 0 or 1. Approximately one-third of patients (n = 639; 34.1%) had Stage III macroscopic optimally debulked disease, 751 patients (40.1%) had Stage III suboptimally debulked disease, and 483 patients (25.8%) had Stage IV disease.

Baseline performance status and disease stage were stratification factors used in the randomisation and were well balanced across the three treatment arms. To be eligible, patients with Stage III optimally debulked disease should have macroscopic (visible or palpable) residual disease after surgery. However, 106 patients (5.7% overall; 27 patients in the CPP arm, 40 in the CPB15 arm, and 39 in the CPB15+ arm) had no macroscopic residual disease at study entry

The primary site of cancer in the majority of patients (1558 patients; 83.2%) was the ovary, followed by the peritoneum (279 patients; 14.9%) and the fallopian tube (36 patients; 1.9%).

The majority of patients (1591 patients; 84.9%) had serous adenocarcinoma. Smaller numbers of patients had histologic types associated with worse prognosis; specifically, 4.2% and 1.7% of patients had clear cell and mucinous adenocarcinoma, respectively; the percentages were comparable across the treatment arms. There were 73 patients (3.9%) who had more than one histologic type, mostly a combination of serous and endometrioid adenocarcinomas. The majority of patients (1359 patients; 72.6%) had ascites prior to initial staging surgery. Approximately two-thirds of patients (1192

patients; 63.6%) had measurable disease at baseline. At study entry, most patients (1768 patients; 94.4%) had elevated CA-125 (greater than the ULN).

Table 6 - Baseline characteristics of participants in the GOG-0218 trial

GOG-0218	CPP (n = 625)	CPB15 (n = 625)	CPB15+ (n = 623)	All Patients (n = 1873)
Age in years				
Mean (SD)	58.9 (10.8)	59.8 (10.3)	59.0 (10.6)	59.2 (10.6)
Median	60.0	60.0	59.0	60.0
Range	24-85	23-87	22-89	22-89
GOG performance status				
0	311 (49.8%)	314 (50.2%)	307 (49.3%)	932 (49.8%)
1	272 (43.5%)	270 (43.2%)	264 (42.4%)	806 (43.0%)
2	42 (6.7%)	41 (6.6%)	52 (8.3%)	135 (7.2%)
Primary Site of cancer				
Ovary	515 (82.4%)	512 (81.9%)	531 (85.2%)	1558 (83.2%)
Fallopian tube	8 (1.3%)	17 (2.7%)	11 (1.8%)	36 (1.9%)
Peritoneum	102 (16.3%)	96 (15.4%)	81 (13.0%)	279 (14.9%)
Disease stage				
Stage III optimally debulked (macroscopic)	219 (35.0%)	204 (32.6%)	216 (34.7%)	639 (34.1%)
Stage III suboptimally debulked	253 (40.5%)	256 (41.0%)	242 (38.8%)	751 (40.1%)
Stage IV	153 (24.5%)	165 (26.4%)	165 (26.5%)	483 (25.8%)
Histologic type of epithelial OCa				
Serous	530 (84.8%)	528 (84.5%)	533 (85.6%)	1591 (84.9%)
Clear cell	20 (3.2%)	34 (5.4%)	25 (4.0%)	79 (4.2%)
Endometrioid	35 (5.6%)	30 (4.8%)	30 (4.8%)	95 (5.1%)
Mucinous	11 (1.8%)	10 (1.6%)	10 (1.6%)	31 (1.7%)
Mixed epithelial	18 (2.9%)	9 (1.4%)	17 (2.7%)	44 (2.3%)
Adenocarcinoma, unspecified	17 (2.7%)	18 (2.9%)	20 (3.2%)	55 (2.9%)
Other	25 (4.0%)	24 (3.8%)	19 (3.0%)	68 (3.6%)
Size of residual disease				
0 cm or microscopic optimally debulked disease	27 (4.3%)	40 (6.4%)	39 (6.3%)	106 (5.7%)
> 0 cm and ≤ 1 cm	261 (41.8%)	247 (39.5%)	253 (40.6%)	761 (40.6%)
> 1 cm	337 (53.9%)	338 (54.1%)	331 (53.1%)	1006 (53.7%)
Ascites prior to initial staging				
Yes	454 (72.6%)	460 (73.6%)	445 (71.4%)	1359 (72.6%)

GOG-0218	CPP (n = 625)	CPB15 (n = 625)	CPB15+ (n = 623)	All Patients (n = 1873)
No	154 (24.6%)	141 (22.6%)	165 (26.5%)	460 (24.6%)
Unknown	17 (2.7%)	24 (3.8%)	13 (2.1%)	54 (2.9%)
Baseline CA-125				
Normal	35 (5.6%)	39 (6.2%)	31 (5.0%)	105 (5.6%)
Elevatedb	590 (94.4%)	586 (93.8%)	592 (95.0%)	1768 (94.4%)

ULN = upper limit of normal. [a] Patients could be counted in more than one category for several variables. [b] Elevated indicates that CA-125 was greater than the ULN.

ICON7

Baseline ovarian tumour characteristics were well balanced between treatment arms (Table 7).

The majority of patients had epithelial ovarian cancer (CP: 87%; CPB7.5+: 88%) followed by primary peritoneal cancer (7% in both CP and CPB7.5+ arms) and fallopian tube cancer (4% in both CP and CPB7.5+ arms) or a mixture of the three sources (2% in both CP and CPB7.5+ arms). Most patients had an ECOG performance of 1-2 (both arms: 93%).

The most common histological subtype of epithelial ovarian cancer was serous carcinoma (69% in both CP and CPB7.5+ arms arm) followed by clear cell (CP: 8%; CPB7.5+: 9%), endometroid (CP: 7%; CPB7.5+: 8%), mucinous (2% in both CP and CPB7.5+ arms arm) other histological subtypes (7% in both CP and CPB7.5+ arms) or a mixture of subtypes (CP: 6%; CPB7.5+: 5%).

The majority of the patients in each treatment arm (CP: 74%; CPB7.5+: 71%) had poorly differentiated (Grade 3) primary tumours at baseline, followed by moderately differentiated primary tumours (CP: 19%; CPB7.5+: 23%) and well differentiated primary tumours at baseline (CP:7%; CPB7.5+: 5%).

The FIGO stages were well balanced between the treatment arms. The most common staging was stage III (68% in both CP and CPB7.5+ arms) followed by stage IV (CP: 13%; CPB7.5+: 14%), stage II (CP: 10%; CPB7.5+: 11%) and stage I (CP: 8%; CPB7.5+: 7%). 98% of patients had debulking surgery and 74% of the patients in each arm were ‘optimally’ debulked, with $\leq$ 1 cm

residual disease. Of the three stratification groups, the 1st (FIGO I-III and residual disease≤1cm was the largest, with 66 & 68% of patients in the two study arms. 18-20% of patients were in stratification group 2 (FIGO I-III and residual disease > 1cm) and the third group (inoperable Stage III or Stage IV) had only 14% of the patients. The group of patients defined as closest to the GOG-218 population (FIGO IV and FIGO III with >1cm residual disease; the High Risk of Progression group) made up 30-31% of the total study population.

Table 7 - Baseline characteristics of participants in the ICON7 trial

ICON7	**CP (n = 764)**	**CPB7.5+ (n = 764)**
Age in years		
Mean (SD)	56.7 (10.61)	56.5 (10.42)
SEM	0.38	0.38
Median (min-max)	57 (18-81)	57 (24-82)
Age category (< 65 vs ≥ 65)		
< 65	571 (75%)	576 (75%)
≥ 65	193 (25%)	188 (25%)
Performance status (ECOG)	**(n=762)**	**(n=753)**
0	333 (44%)	307 (41%)
1	375 (49%)	391 (52%)
2	54 (7%)	55 (7%)
Primary site of Cancer*		
Ovary (epithelial)	667 (87%)	673 (88%)
Fallopian tube	29 (4%)	27 (4%)
Primary peritoneal	56 (8%)	50 (7%)
Ovary (epithelial) /other tube	12 (1%)	14 (1%)
Histology type of Epithelial Ovarian Cancer*		
Serous	529 (69%)	525 (69%)
Mucinous	15 (2%)	19 (2%)
Endometriod	57 (7%)	60 (8%)
Clear cell	60 (8%)	67 (9%)
Other	55 (7%)	53 (7%)
Mixed	48 (6%)	40 (5%)
Degree of differentiation	(n=754)	(n=754)
Grade I	56 (7%)	41 (5%)
Grade II	142 (19%)	175 (23%)
Grade III	556 (74%)	538 (71%)
FIGO staging		
I	65 (8%)	54 (7%)
II	80 (10%)	83 (11%)
IIIA	32 (4%)	22 (3%)
IIIB	44 (6%)	45 (6%)

ICON7	CP (n = 764)	CPB7.5+ (n = 764)
IIIC	432 (57%)	438 (57%)
III	14 (2%)	18 (2%)
IV	97 (12%)	104 (14%)
FIGO stage and surgery – n (%) (stratification factor)		
FIGO I-III & residuals <1cm	508 (66)	518 (68)
FIGO I-III & residuals >1cm	150 (20)	140 (18)
FIGO III inoperable & IV	106 (14)	106(14)
High risk of progression – n (%) (FIGO stage IV with resection or FIGO stage III and >1 cm residual disease		
No	530 (69)	533 (70)
Yes	234 (31)	231 (30)

***More than one category is possible**

Summary of similarities and differences between the baseline characteristics of the GOG-0218 and ICON7 trials

- Patients were of similar median age (GOG-0218: 59 years, ICON7: 57 years) and performance status (PS 0-1: 93%) in the bevacizumab-containing arms of the GOG-0218 and ICON7 trials. There were more patients in the bevacizumab-treated arm of the ICON7 trial (n=764) compared to the GOG-0218 trial (CPB15+ arm, n=623).
- In both trials, the majority of cancers were epithelial in origin (83% in the GOG-0218 trial, and 87% in the ICON7 trial) followed by primary peritoneal and fallopian tube carcinoma. There were marginally more patients with primary peritoneal cancer in the GOG-0218 trial (14.9%) compared to the ICON7 trial (7%).
- The main histological type in both trials was serous carcinoma, more patients had serous carcinoma in the GOG-0218 trial (84.9%) compared to the ICON7 trial (69%). Clear cell carcinoma, which is linked to a poor prognosis, arose in 4.2% of patients in the GOG-0218 trial and 8-9% of patients in the ICON7 trial, the level of mucinous carcinoma was similar between trials.

- The patient population in these two studies are therefore broadly comparable for the above factors. However, there are differences between the trials in disease Stage and residual disease post-surgery. All patients in the GOG-0218 trial had stage III and IV disease, while only 81% of ICON7 patients had stage III or IV disease. Resected Stage IV patients and Stage III with >1cm residuals made up 54% of the population in the GOG-218 study, but only 31% of the ICON7 study population (the pre-planned 'high risk' subgroup). Finally, the two recruitment strata of ICON7 which covered the patient with most residual disease, that is stratum 2 (FIGO I-III and residuals >1cm) and stratum 3 (FIGO III inoperable and IV) comprised 32 and 34% of the population in the two study arms.

Outcomes

6.3.4 **Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.**

Table 8 - Primary and secondary outcomes of the RCTs

	GOG-0218	ICON7
Primary outcome	**Progression free survival** The primary outcome of the GOG-0218 trial was PFS determined by investigator assessment. PFS was the period from randomisation until disease progression or death from any cause. Disease progression was assessed by international criteria proposed by the RECIST Committee (Therasse P 2000), global clinical deterioration or CA-125. CA125 progression increase was greater than or equal to twice the nadir or upper limit of normal. For the primary Regulatory efficacy analysis of PFS, progression was based on global clinical deterioration and RECIST criteria only. PFS for any patient who progressed solely on the basis of rising serum CA-125 levels was censored at the time of last radiographic assessment during which the patient was known to be progression free. The primary efficacy analysis arose in the intent-to-treat (ITT) population, defined as all patients randomised to study treatment, irrespective of whether the assigned treatment was actually received.	**Progression free survival** The primary efficacy outcome measure was PFS based on investigator assessment. PFS was defined as the time from randomisation to the time of first documented disease progression or death, whichever occurred first. Disease progression was based on RECIST, clinical or symptomatic progression. CA-125 measurements alone were not used to determine disease progression. The ITT population was the primary population for the efficacy analyses.
Secondary outcomes	**Overall survival** Interim OS analysis was performed at primary PFS analysis, when 23.7% of patients had died. Final OS analysis was conducted based on a data cut-off of August 26th 2011, when 46.9% of patients had died. OS was defined as the time from randomisation to death from any cause. OS for patients who had not died (or were not known to have died or were lost to follow-up) at the time of analysis were censored at the date the patient was	**Overall survival** Current data for OS are immature, with final analysis due in 2013. The duration of OS was defined as the time from randomisation to death from any cause. Patients for whom no death was captured on the clinical database were censored at the last time they were known to be alive. Analysis arose from patients in the ITT population.

	GOG-0218	ICON7
	last known to be alive. If the initial primary analysis of PFS was positive at the interim or final analysis, OS would be compared between the CPP vs CPB15 arms, and the CPP versus CPB15+ arms using a stratified log-rank test. The stratification factors would consist of the two factors used for patient randomisation: GOG performance status and disease stage. **ORR** Objective response was defined as the occurrence of a complete or partial best overall response (according to the modified RECIST), confirmed by the investigator ≥ 4 weeks after the criteria for response were first met. An independent review of ORR was performed as well as investigator assessed analysis.	**ORR** Patients were classified as responders if their best overall response was either confirmed complete response or confirmed partial response (according to modified RECIST). Patients without any assessments were regarded as non-responders. **Duration of response** Duration of response was defined as the time when response (CR or PR) was first documented to disease progression or death (whichever occurs first). **Biological Progression Free Interval:** Biological progression free interval was defined as the time from randomisation to the time of first documented disease progression by CA-125.
Sensitivity analysis of PFS (secondary analysis)	Sensitivity analysis arose to test the robustness of the primary efficacy endpoint, PFS: **IRC** An independent review committee determined radiologically confirmed PFS based on tumour assessments and response evaluation for progression events. **Uncensored data** A sensitivity analysis of PFS comparing CPP and CPB15+ in which progression according CA125 results was allowed. **Worst-case analyses** Worst case analyses of PFS accounted for early	Sensitivity analysis arose to test the robustness of the primary efficacy endpoint, PFS: **Time to censoring analysis** A Kaplan-Meier plot of the time to censoring in the different treatment arms was generated to investigate differences in follow-up time. **Missing assessments analysis** A sensitivity analysis was performed investigating the effect of missing assessments followed by an assessment of PD/recurrence. **Worst case analysis** The effect of incomplete tumour assessment follow-up information was assessed.

	GOG-0218	ICON7
	discontinuation. These analyses were performed in patients who missed two or more tumour assessments prior to the data cutoff, and were assumed to have progressed on the date of first missed assessment.	
Exploratory analysis (secondary analysis)	**Subgroups analysis** Exploratory analysis of PFS and OS arose by assessing subgroup data. The following subgroups were analysed: site of primary disease, stage of disease, histologic cell type, grade, age, race, GOG performance status, baseline SLD (sum of longest diameter), baseline CA-125 levels.	**Subgroup analysis** Exploratory analysis of PFS and OS arose by assessing subgroup data. The following subgroups were analysed: age, race, ECOG PS, origin of cancer, degree of differentiation, histology, intent to start chemotherapy following surgery, pre-treatment CA-125 value, GCIG group, FIGO stage, maximum diameter of residual tumour, subgroup with high risk of progression (FIGO IV resected plus FIGO III with >1cm residual after debulking surgery)
Safety analysis	For all safety analyses, patients were grouped according to the treatment to which they were randomised. Investigators reported events using the NCI CTCAE term, and events were graded according to the NCI CTCAE, v3.0. The incidence of adverse events and adverse events of special interest was reported. Adverse events of special interest to bevacizumab treatment included ATE, VTE, hypertension, GI perforation, abscesses and fistulae, bleeding (CNS, non-CNS), proteinuria, wound-healing complications /dehiscence, congestive heart failure (CHF) or left ventricular systolic dysfunction, neutropenia, febrile neutropenia, and RPLS.	The intensity of adverse events was graded using CTCAE v3.0. The relationship of the adverse event to the treatment was also assessed. AEs occurring at any time from the first drug intake on study day 1 (defined as the first day any component of the study treatment regimen received) until the day of the safety follow-up visit (between weeks 56 and 58) were to be recorded in both treatment arms. Adverse events of special interest to bevacizumab included hypertension, proteinuria, GI perforation, wound healing complications, thromboembolic events, venous thrombosis, arterial thrombosis, bleeding, mucocutaneous bleeding, tumour associated haemorrhage, CNS bleeding, congestive heart failure, abscesses and fistulae, reversible Posterior Leukoencephalopathy Syndrome (RPLS), neutropenia, febrile neutropenia.

	GOG-0218	ICON7
Patient reported outcomes (secondary outcome)	The objectives of the health-related quality of life (HRQoL) analysis were to assess the impact of bevacizumab treatment on HRQoL from a patients' perspective. The key measures were the Functional Assessment of Cancer Therapy–Ovarian (FACT-O TOI), Ovarian Cancer Subscale, and abdominal discomfort score (ADS).	HRQoL was assessed using three questionnaires devised by The European Organisation for the Research and Treatment of Cancer (EORTC) and by the EuroQoL (EQ) groups: The first was the EORTC QLQ-C30 quality of life questionnaire (version 3.0) assessed the QoL of cancer patients participating in international cancer trials. The second was the EORTC QLQ-OV28 module, which is designed for ovarian cancer patients with local or advanced disease. It consists of 28 items assessing abdominal/GI symptoms, peripheral neuropathy, other side effects, hormonal symptoms, body image, attitudes to disease/treatment and sexuality. The third was the EQ-5D module which measures health status and provides a generic measure of health.

Reliability/validity/ current use in clinical practice

PFS

PFS is a valid endpoint for both the GOG-0218 and ICON7 trials. As both studies investigated the efficacy of first line treatment, PFS is a reasonable measurement of disease progression as it reflects the true measure of front-line therapy and is not confounded by cross-over or post-study therapies. PFS is an accepted primary endpoint in oncology for most regulatory authorities, including the European Medicines Agency (EMA), and is also accepted as an endpoint for front-line therapy for ovarian cancer by international groups involved in clinical research, such as the Gynecologic Cancer InterGroup (GCIG).

Both studies used the ITT population in the assessment of PFS – this reduced bias arising from an imbalance between treatment arms in the number of patients failing to complete treatment.

The RECIST criteria are the standard method of classifying tumour response. For the primary Regulatory analysis of the GOG-0218 trial, progression based on CA-125 criteria alone was censored. Serum levels of CA-125, a tumour-associated glycoprotein antigen, are elevated in 80% of patients with epithelial ovarian, primary peritoneal, and fallopian tube cancer. CA-125 is often monitored on a frequent basis to verify response to therapy, presence of residual disease, and as early evidence of recurrence. However, CA-125 is not entirely tumour specific and can be elevated in a variety of benign conditions. In addition, levels of CA-125 can be discordant with tumour response, both as false–positive and false–negative trends.

Nonetheless, because imaging modalities can be relatively insensitive in detecting disease progression, it has been standard practice for patients and physicians to interpret a progressive rise in CA-125 levels post-therapy as evidence of recurrent or progressive disease and make therapeutic decisions solely on the basis of CA-125. This has complicated the assessment of PFS in prior trials, as patients have received new therapy prior to clinical documentation of progressive disease on the basis of physical examination or

radiographic findings. The publication and presentation at ASCO of the early vs late treatment MRC OV05/EORTC 55955 trial, which assessed the use of the CA-125 marker for progression in ovarian cancer (Rustin et al. 2011) will have probably decreased any use CA-125 alone as a marker for further treatment in UK clinical practice as no survival benefit was demonstrated for early treatment based on CA-125.

Retrospective analyses of patients with ovarian cancer who received bevacizumab treatment have suggested that determining progression on CA-125 levels may be unreliable, as bevacizumab may have a direct effect on CA-125 levels (O'Cearbhaill RE 2010;Olson C 2010;Therasse P 2000). It was therefore reasonable to censor for CA-125 progression in the GOG-0218 study.

The independent review committee's assessment of PFS was added to provide additional, unbiased support for the primary endpoint of investigator-assessed PFS. The review of imaging-based evaluation was by radiologists in a blinded fashion.

OS

OS is often regarded as a meaningful standard for determining the efficacy of potential life-extending drugs, it is however, difficult to reliably and ethically determine. In first-line trials, OS results may be confounded as patients may go on to receive several years' worth of additional life prolonging treatments. The GOG-0218 trial protocol did not exclude the control arm patients from crossing over to receive treatment with bevacizumab after leaving the trial. In the US, where much of the GOG-0218 trial was undertaken, approximately 30-40% of patients receive bevacizumab for relapsed ovarian cancer and the most recent data cut suggests that 40% of the CPP patients in this study have now received bevacizumab in their subsequent therapy. Unlike the GOG-0218 trial, in the open label ICON7 trial patients were not allowed to cross over to receive subsequent lines of bevacizumab treatment, so this may increase the validity of using OS data from the ICON7 trial.

Objective response rate

ORR was defined according to the RECIST criteria, which are the standard criteria for accessing ORR. Objective response is important to patients, as shrinkage of their lesions correlates with an improved quality of life and patient well-being (Baum et al. 1980;Coates A 1987).

Patient reported outcomes

The self-reporting FACT-O and EORTC QLQ-OV28, EORTC QLQ-C30 and EQ-5D questionnaires are all appropriate for the use in oncology clinical trials, as well as in clinical practice. All questionnaires analysed a variety of QoL variables, including QoL specifically associated with ovarian cancer and treatment of the disease.

Safety

The NCI CTCAE (v3.0) criteria was used to analyse safety, this version is the current, standard assessment of safety. Adverse events of special interest of bevacizumab were also collected. The safety analysis included all patients who received any amount of protocol treatment, and patients were grouped according to the treatment they actually received. The incidence of grade 3-5 adverse events were collected and were summarised by treatment arm and grade according to NCI CTCAE terminology.

Statistical analysis and definition of study groups

6.3.5 **State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.**

GOG-0218

Analysis Population

Primary efficacy analysis was undertaken in the intent-to-treat (ITT) population, defined as all patients randomised to study treatment, irrespective of whether the assigned treatment was actually received. For all efficacy analyses, patients were grouped according to the treatment they were assigned to at randomisation.

The primary safety population consisted of patients who had received at least Cycle 2 of study treatment or beyond. The primary safety population was used for the analyses of adverse events that occurred from the start of Cycle 2 and within 30 days of the last dose of any study treatment. The primary safety population was defined in this manner because the study drug (bevacizumab/placebo) was not started until Cycle 2 of treatment. A separate exploratory-safety population consisted of patients who received at least one cycle of any study treatment. This population was used for the summary of adverse events occurring before Cycle 2 of treatment (chemotherapy-only phase).

Sample Size and Power

The study protocol specified the enrolment of 1800 patients, based on 90% power to detect a PFS hazard ratio of ≤0.77. A total of 1873 patients were randomised to the study and comprised the intent-to-treat population.

The final analysis of the initial primary efficacy endpoint of PFS was to be taken after the 375th event is observed among patients randomised to the CPP arm. If PFS results between CPP vs CPB15 arm, and CPP vs CBP15+ arm was significantly different, late primary analysis would arise, which assesses the PFS difference between the CPB15 and CPB15+ arm. This would arise when a total of 710 events are observed among patients randomised to CPB15 or CPB15+ arm.

The analysis for the overall survival was to occur at either the interim or final PFS analysis. If either experimental regimen decreased the risk of death by

23% compared with the control arm (i.e. the median OS extended from 34 to 44 months), and assuming that OS events were anticipated from 90% of patients enrolled (i.e. 10% cure rate), then GOG design provided approximately 50% and 65% power to correctly identify the regimen as superior to standard therapy at the interim and the final PFS analysis, respectively. The power calculations were based on approximately 290 OS events from an experimental arm and the standard therapy arm at the interim PFS, and approximately 400 OS events at the final PFS analysis.

Primary efficacy analysis

Hypotheses

The primary efficacy analysis investigated whether there was a significant increase in PFS in patients treated with CPB15 compared to CPP, and CPB15+ compared to CPP. This analysis was referred to as the “initial primary” analysis. If both CPB15 and CPB15+ were statistically superior to CPP with respect to PFS, a PFS comparison between the two bevacizumab-containing regimens would be performed (CPB15 vs. CPB15+). This analysis would be termed the “late primary” analysis.

The null hypotheses for Initial Primary Comparisons was as follows:

$H01: \Delta 01 = \lambda CP / \lambda CPB15 \leq 1$

$H02: \Delta 02 = \lambda CP/\lambda CPB15+ \leq 1$

These were assessed separately, where λ was the PFS event rate for the indicated treatment.

Null hypotheses for Late Primary Comparisons:

$H01: \Delta 01 = \lambda\ CPB15/\ \lambda CPB15+ \leq 1$

Where the λ represents the hazard of progression conditional on having been progression free to Cycle 7.

Statistical Analysis

The overall type I error rate for the primary endpoint of PFS was controlled at a one-sided α=0.025 (for both primary and late analysis).

As the two initial primary efficacy analyses were comparisons against a common control arm, a Dunnett procedure was used (Dunnett CW 1955) to take into account the correlation between test statistics. With an assumed correlation of 0.50, a one-sided α = 0.0135 was allocated for each comparison: CPB15 versus CPP and CPB15 + versus CPP.

PFS was formally compared in the initial and late primary comparisons using a one-sided p-value from a stratified log-rank test. The stratification factors consisted of the two factors used for patient randomisation, initial GOG performance status (0 vs. 1 or 2) and disease stage. Disease stage included the following levels:

- Macroscopic optimally debulked (FIGO stage III with maximum diameters of all gross residual disease ≤1cm)
- Suboptimally debulked (FIGO stage III with maximum diameter of any gross residual disease >1cm)
- FIGO stage IV

Results from an unstratified log-rank test were also presented. Kaplan−Meier methodology was used to estimate median PFS for each treatment arm.

Because the χ^2 statistic underlying the log-rank test automatically produces a two-sided test, testing at a one-sided significance level (per protocol) was achieved by dividing the (two-sided) log-rank test p-value by two and verifying that the treatment effect favoured the experimental arm. This verification was made by comparing the estimated hazard ratio to one, whereby the hazard ratio was estimated by a stratified Cox proportional hazard model with stratification factors as used for patient randomisation (GOG performance status and disease stage) and a model parameter corresponding to treatment group. For simplicity, this procedure was referred to as a “one-sided log-rank test” and the resulting p-value as a “one-sided p-value” from a log-rank test.

The presentation of results show PFS in each of the three treatment arms. However, for exploratory subgroup analysis, the CPB15 and CPB15+ arms

were combined. This was allowed as the CPB15 and CPB15+ arms had identical regimens until Cycle 7 (Week 19), PFS events that occurred prior to Cycle 7 were informative for both efficacy comparisons. This pooling of PFS events was used for the log-rank tests and the Cox model.

Secondary efficacy analysis

OS

OS was defined as the time from randomisation to death from any cause. All reported deaths were included in this analysis. OS for patients who had not died (or were not known to have died or were lost to follow-up) at the time of analysis were censored at the date the patient was last known to be alive.

OS was compared between each experimental arm and standard therapy using a stratified log-rank test. The stratification factors consist of the two stratification factors (initial GOG performance status (0 vs. 1 or 2) and disease stage, see above for more details). Results from an unstratified log-rank test were also presented. Kaplan−Meier methodology would be used to estimate median survival time for each treatment arm.

A hierarchical procedure was used to simultaneously control the type I error for all secondary analyses. The type I error rate for the two OS comparisons was simultaneously controlled at a one-sided $\alpha = 0.025$ level using a Dunnett procedure. If either comparison produced a one-sided p-value ≤ 0.0135, then it would be concluded that the corresponding bevacizumab-containing regimen (CPB15 or CPB15+) prolonged OS compared with standard therapy alone in the patient population.

ORR

Objective response was defined as the occurrence of a complete or partial best overall response (CR or PR; according to the modified RECIST), confirmed by repeat assessment performed by the investigator ≥ 4 weeks after the criteria for response were first met. Randomised patients who did not meet this criterion, including patients for whom post-baseline tumour

assessments were not performed, were considered non-responders in the analysis of objective response.

ORR based on the investigator assessment, was analysed in the CPB15 versus CPP arm and the CPB15+ versus CPP arm. ORRs were formally compared between arms using the Cochran−Mantel−Haenszel test, with GOG performance status and disease stage as stratification factors. For each treatment arm, estimates of the ORR and its 95% confidence interval (CI) were determined; the 95% CI was constructed using the normal approximation to the binomial distribution. Analysis of ORR arose in patients who had measureable disease at baseline, rather than the ITT population.

Safety

The primary safety population included all randomised patients who received at least one full or partial dose of any study treatment during Cycle 2 or beyond (1816 patients). Safety was assessed through summaries of adverse events from the GOG-0218 Toxicity and Follow-Up CRFs and in the NCI AdEERS database. Investigators reported events using the NCI CTCAE term, and events were graded according to the NCI CTCAE, v3.0. Genentech coded the NCI CTCAE data into the Medical Dictionary for Regulatory Activities (MedDRA), v13.0.

The primary analysis of AEs investigated events from cycle 2 of the study. Three secondary safety analyses were performed. These analyses differed according to the time period during which the adverse events occurred:

• S1 analysis: Cycle 2 to before Cycle 7

• S2 analysis: Cycle 7 to the end of follow-up

• S3 analysis: prior to Cycle 2.

Quality of life

Overall FACT-O TOI scores were calculated from the three subscales collected (physical well-being, functional well-being, and ovarian cancer subscale) as per the algorithm suggested by the Functional Assessment of

Chronic Illness Therapy (FACIT) organization. The ovarian cancer subscale score is calculated from the first 11 items only (i.e., excluding item BMT7 which inquires about the patient's concern regarding the ability to have children). If at least 50% of the items in a subscale are missing at a time point for a patient, the subscale score will not be derived. If at least one subscale score cannot be derived, the overall FACT-O TOI will be missing at that time point for the patient. If fewer than 50% of the items in a subscale are missing at a time point for a patient, a subscale score will be imputed. The overall FACT-O TOI is derived from the imputed subscale(s).

Each patient was asked to complete the FACT-O TOI questionnaire at the following time-points during their participation in the study:

- Timepoint 1: pre-treatment, baseline (prior to Cycle 1)
- Timepoint 2: midpoint of scheduled chemotherapy phase (prior to Cycle 4, 9 weeks after starting treatment)
- Timepoint 3: end of scheduled chemotherapy phase and start of maintenance phase (prior to Cycle 7, 18 weeks after starting treatment)
- Timepoint 4: approximate midpoint of scheduled bevacizumab/placebo only maintenance phase (prior to Cycle 13, 36 weeks after starting treatment)
- Timepoint 5: end of scheduled bevacizumab/placebo only maintenance phase (prior to Cycle 21, 60 weeks after starting treatment)
- Timepoint 6: follow-up (6 months after scheduled end of study treatment, 84 weeks after starting treatment)

Descriptive Summaries

Descriptive statistics of the overall FACT-O TOI score changes from baseline score will be provided. Specifically:

For changes at Timepoint 2 and Timepoint 3 from baseline, the statistics will be provided for arm CP as one group, arms CTB5 and CTB+ as the other group. This is because up to Cycle 7 (Timepoint 3), arms CTB5 and CTB+ have identical treatment regimens.

For changes at Timepoint 4, Timepoint 5, and Timepoint 6 from baseline, the statistics will be provided for each arm. Graphical display of the mean score change from baseline over time by treatment arm will also be provided.

c. Hypothesis Testing and Method

Following the protocol specifications with modifications, three hypotheses regarding whether FACT-O TOI scores reported by patients during the treatment period over time are independent of treatment received will be tested. Each hypothesis is tested at a two-sided 0.05 α level and is assessed using a mixed effect model with treatment group, time and the interaction between treatment group, and time as fixed effects, adjusting for pretreatment TOI score and age as covariates.

The first hypothesis test will compare TOI scores for patients from CP and CPB15 arms. An appropriate interaction contrast will be defined to take into account only variation at Timepoint 2 and Timepoint 3. In addition, since the treatment regimen in the CPB15+ arm prior to Cycle 7 is identical to that of the CPB15 arm, the appropriate interaction contrast will defined so that score data prior to Cycle 7 for patients on the CPB15+ arm are consider similar to those from patients on the CPB15 arm and they are different from scores from patients on the CP arm (i.e., contrasting CPB15 and CPB15+ against CP).

The second hypothesis test will compare TOI scores for patients from CP and CPB15+ Timepoint 2 to Timepoint 5 will be included in the formation of the interaction contrast between treatment and time.

The third hypothesis test will compare TOI scores for patients from CPB15 and CPB15+. An appropriate interaction contrast will be defined to take into account only variation at Timepoint 4 and Timepoint 5.

Ovarian Cancer Subscale

Descriptive statistics (mean, median, standard deviation, min and max) of the ovarian subscale score changes from baseline score will be provided. Graphical display of the mean ovarian subscale score change from baseline over time by treatment arm will also be provided.

In addition, graphical display of the mean abdominal discomfort score (sum of 4 items collected on the QoL CRF: GP4, O3, SP1, and SP2) change from baseline will also be provided.

ICON7

Analysis Population

The ITT population was defined as all patients randomised to the study regardless of whether they actually received any dose of study medication. The treatment group was assigned as randomised. The ITT population was the primary population for the efficacy analyses.

The safety population was defined as all patients randomised and exposed to study treatment. Patients were assigned to treatment groups based on the treatment they actually received. Patients who received one or more doses of bevacizumab were assigned to the bevacizumab treatment group even if this administration was given in error.

Patients who were randomised to bevacizumab but did not receive bevacizumab were included in the non-bevacizumab arm.

Sample Size and Power

The data cutoff date for the initial primary comparison of PFS was based on the number of events in the control arm as determined by the MRC/GOG. Specifically, if an initial primary comparison crossed the efficacy boundary at the interim analysis or information (75% information), the data cutoff date was the date of the 281st PFS event in the control arm CP. If an initial primary comparison crossed the efficacy boundary at full information, the data cutoff date was the date of the 375th PFS event in the control arm CP.

With 1444 patients randomised at a steady rate over 24 months with an additional 12 months follow-up after the last patient randomised, the trial had 93% power (two-sided test, significance level of 5%) to show a 28% change in PFS from a median value of 18 months in the control arm to 23 months in the bevacizumab arm i.e. a Hazard Ratio (HR) of 0.78.

It was expected that 788 PFS events would have to occur at this point. To achieve 90% power (two-sided test, significance level of 5%) 684 events were required. To allow for non-compliance of the order of 5%, 1520 patients were enrolled, 760 in each treatment arm.

The trial was powered to detect an improvement in overall survival. A total of 715 deaths were required in the two treatment arms in order to demonstrate a 19% improvement in OS from a median value of 43 months in the control arm to 53 months in the bevacizumab arm i.e. a HR of 0.81 with 80% power at a significance level of 5% (two-sided test). With a sample size of 1444 patients, it was expected that 715 events would have had to arise in 36 months, approx. 24 months after the final analysis of the PFS endpoint.

Primary efficacy analysis

Hypotheses

The primary outcome measure was to determine whether the addition of bevacizumab to standard chemotherapy (CPB7.5+) significantly improves PFS when compared to standard chemotherapy alone (CP).

Statistical Analysis

The primary statistical analysis performed in this trial was a non-stratified two-sided log-rank test, at an α-level of 5%.The stratified analysis served as a sensitivity analysis to check the robustness of these results.

For the stratified analyses, the stratification variables used for randomisation were included in the model regardless of their actual prognostic value, unless the factors were included for logistical reasons only. Stratification factors were the following:

- FIGO Stage (I-III with residual disease ≤ 1 cm, I-III with residual disease > 1 cm, IV and inoperable III)
- Intent to start of chemotherapy following surgery (≤ 4, > 4 weeks)

Censoring arose in patients without disease progression at the date of last tumour assessment by CT scan or date of last clinical follow-up visit, whenever occurred last.

Secondary endpoints

OS

The trial was powered to detect an improvement in median overall survival. Duration of overall survival was defined as the time from randomisation to death from any cause.

Patients for whom no death was captured on the clinical database were censored at the last time they were known to be alive.

Kaplan-Meier curves were created and estimates were provided. OS was compared the experimental arm and standard therapy using a log-rank test.

ORR

Differences between Objective Response Rates (measured by RECIST) of the two arms were calculated using Chi-square test with Schouten correction to test for treatment differences between the bevacizumab and the control arm. Two-sided 95% Pearson-Clopper confidence intervals for response rates were calculated. ORR was analysed in patients with measureable disease at baseline, rather than the ITT population.

Duration of response

For Duration of Response of the “Responders”, “RECIST Responders” and “CA-125 Responders”, however, no formal hypothesis testing was performed as this analysis was based on a non-randomised subset of patients. Hazard ratios and confidence intervals were calculated.

Biological PFS

The biological PFS was measured by Kaplan-Meier curves. Estimates were provided and the log-rank tests were used in an exploratory manner to assess the differences between the bevacizumab arm and the control arm.

Quality of Life

Summary statistics for the assessment scores from the three quality of life questionnaires EORTC-QLQ-C30, EORTC-QLQ-OV28 and EuroQol EQ-5D were presented for the two treatment groups at each scheduled visit, together with the change from baseline. Plots of mean values and standard error of the mean values by treatment group over time and the change from baseline were depicted for each scale or item from the three quality of life questionnaires.

Safety

AEs were coded by MedDRA. Adverse Events and laboratory parameters were graded according to NCI-CTC AE v3.0. Summaries of AE severity, seriousness and relationship to study treatment were assessed. Separate summaries of adverse events leading to death, premature withdrawal from study treatment and study treatment dose modification or interruption were also performed.

6.3.6 **Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.**

GOG-0218

Exploratory analysis of PFS and OS was calculated in various subgroups. Analysis compared PFS and OS in the CPP arm versus the CPB15 arm and the CPP arm versus the CPB15+ arm. The subgroups investigated were:

- Site of primary disease (ovarian vs extra-ovarian)
- Stage of disease (III-optimal vs III-suboptimal vs IV)
- Histologic cell type (mucinous or clear cell vs other cell types)
- Grade (1 and 2 vs 3)
- Age (<40 vs 40-65 vs > 65 years)
- Race (white vs non-white)
- GOG-0218 performance status (0 vs 1-2)
- Baseline SLD (≤ SLD vs >SLD)
- Baseline CA-125 levels (normal vs abnormal).

Median PFS was estimated using the Kaplan-Meier method. The HR relative to the CPP arm and 95% CI for the HR were estimated using Cox regression. Analysis was censored for CA-125 progression and NPT and was determined by investigators. Analyses were carried out on the ITT population.

ICON7

Planned exploratory analyses (subgroup analyses and Cox regression) on PFS were performed in order to assess the influence of prognostic factors that were expected to have an impact on the efficacy endpoints.

PFS was assessed in the following subgroups:

- • Age (< 65, ≥ 65 years)
- • Race (White, Other)
- • ECOG PS (0, 1, 2)
- • Origin of cancer (epithelial ovarian, Fallopian tube and primary peritoneal,
- combination of the three)
- • Degree of differentiation (grade 1, 2, 3)
- • Histology (serous, mucinous, endometroid, clear cell, other, mixed)
- • Intent to start chemotherapy following surgery (≤ 4, >4 weeks)
- • Pre-treatment CA-125 value (≥ 2 x ULN, < 2 x ULN)
- • GCIG group
- • FIGO stage (I, II, III and IV)
- • Maximum diameter of residual tumour (> 1 cm, ≤ 1 cm and microscopic residual disease, no debulking surgery)

FIGO stage (I, II, III and IV) and maximum diameter of residual tumour (> 1 cm, ≤ 1 cm and microscopic residual disease, no debulking surgery) were separated and displayed in more detail.. A pre-planned subgroup analysis of patients was also performed in ICON7 to assess the PFS and OS of patients in a population that was most like the GOG-0218 trial; the ‘High risk’ subgroup of FIGO stage III sub-optimally debulked and stage IV.

The estimated hazard ratio for PFS for CP vs CPP7.5+ was calculated by the Cox regression model including only treatment as a factor, the corresponding two-sided 95% confidence interval was also calculated. These subgroup analyses were carried out on the ITT and PP (per-protocol) populations.

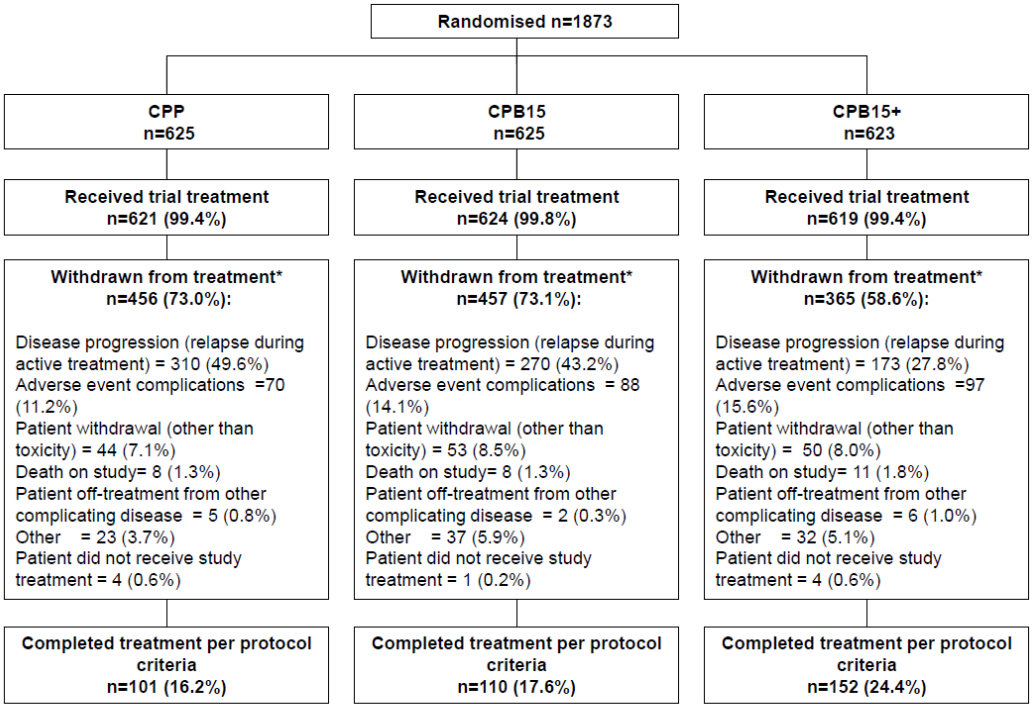
Participant flow

6.3.7 **Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.**

GOG-0218

The protocol specified the enrolment of 1800 patients who had not previously received treatment for epithelial ovarian, fallopian tube or primary peritoneal cancer. Of the 1873 randomised patients, 9 patients (4 in the CPP arm, 1 in the CPB15 arm, and 4 in the CPB15+ arm) did not receive any study treatment (Figure 4). Among patients who received any component of study treatment, a higher percentage of patients in the CPB15+ arm completed study treatment as planned per protocol (22 cycles of study treatment). Specifically, 24.4% of patients in the CPB15+ arm completed study treatment compared with 16.2% and 17.6% of patients in the CPP and CPB15 arms, respectively. At the time of safety data cut-off (5 February 2010), more patients were not known to have discontinued study treatment in the CPB15+ arm than in the CPP and CPB15 arms (102 patients in the CPB15+ arm, 57 patients in the CPB15 arm, and 64 patients in the CPP arm).

Figure 4 - CONSORT flow diagram of patients in the GOG-0218 study



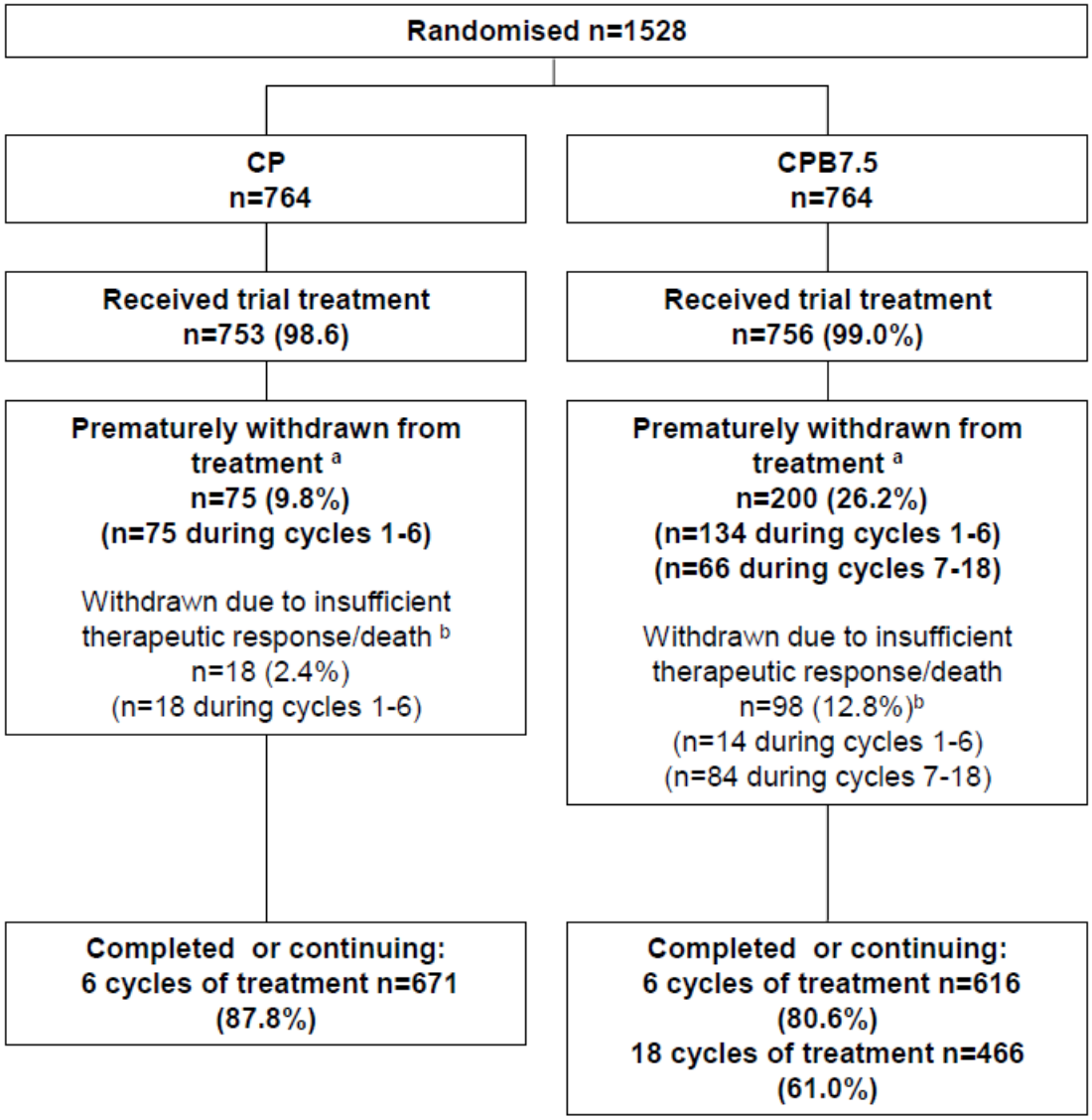
* Disease progression or relapse during active treatment, adverse event, patient withdrawal or refusal for reason other than toxicity, death on study, patients off treatment for other complicating disease, other.

ICON7

A total of 1528 patients were randomised to one of the two treatment arms – carboplatin (AUC 5 or 6) and paclitaxel (175 mg/m2) q3w (CP) or carboplatin (AUC 5 or 6) and paclitaxel (175 mg/m2) plus bevacizumab (7.5 mg/kg) q3w (CPB7.5+) (Figure 5). 764 patients were randomised to each of the two treatment arms. Of the 764 patients randomised to each of the treatment arms, 11 in the CP arm and 8 in the CPB7.5+ arm did not receive any study treatment.

Sixteen patients in the CP arm (2.1%) and 97 patients in the CPB7.5+ arm (12.7%) discontinued at least one component of study treatment due to insufficient therapeutic response. This large difference was attributed to 84 patients in the CPB7.5+ arm discontinuing bevacizumab during the period from Cycle 7-18 when bevacizumab was administered alone. For the period when chemotherapy was administered fewer patients (13) in the CPB7.5+ arm discontinued at least one component of study treatment due to insufficient therapeutic response or death compared to the CP arm.

Figure 5 - CONSORT flow diagram of patients in the ICON7 study



a Withdrawn from at least one treatment component due to AE. b Two patients in the CP arm and one patient in the CPB7.5+ arm had death as the reason for withdrawal on the CRF.

6.4 Critical appraisal of relevant RCTs

6.4.1 **The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria**

for assessment of risk of bias in RCTs, but the list is not exhaustive.

- **Was the method used to generate random allocations adequate?**
- **Was the allocation adequately concealed?**
- **Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?**
- **Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?**
- **Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?**
- **Is there any evidence to suggest that the authors measured more outcomes than they reported?**
- **Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?**

6.4.2 **Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.**

6.4.3 **If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.**

Table 9 - Quality assessment results for RCTs

	GOG-0218	ICON7
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	No
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	No
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

6.5 Results of the relevant RCTs

6.5.1 **Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. If there is more than one RCT, tabulate the responses.**

6.5.2 **The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.**

6.5.3 **For each outcome for each included RCT, the following information should be provided.**

- **The unit of measurement.**
- **The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-**

event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.

- **A 95% confidence interval.**
- **Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. State the results in absolute numbers when feasible.**
- **When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.**
- **Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.**
- **Discuss and justify definitions of any clinically important differences.**
- **Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.**

6.5.3.1 GOG-0218: Progression Free Survival

Final analysis of PFS arose with a cut-off date of 29th September 2010. In the primary Regulatory efficacy analysis with CA-125 and NPT censored, there was a significant improvement in the median PFS of 6 months in the CPB15+ arm compared to the CPP arm (CPP: 12 months, CPB15+: 18 months, HR: 0.645, 95% CI: 0.551 - 0.756, p<0.001) (Table 1). The stratified analysis yielded a hazard ratio of 0.645 favouring the CPB15+arm and demonstrating a 35.5% decrease in risk of disease progression or death. Thus, the null hypothesis of no difference in PFS between the CPP arm and the CPB15+ arm was rejected. The Kaplan-Meier plot showed separation of the curves in favour of the CPB15+ after 4 months, the separation was maximal after the end of bevacizumab therapy (15 months) and was then maintained up to 24 months.

There was a 0.7 month increase in the median PFS in the CPB15 arm compared to the control arm (CPP: 12 months, CPB15: 12.7 months) (Table 10). The stratified analysis yielded a hazard ratio of 0.84 (95% CI: 0.71, 0.99) favouring the CPB15 arm; the one-sided log-rank p-value of 0.0204 which does not cross the p-value boundary of 0.0116 to declare statistical significance. Thus, the null hypothesis of no difference in PFS between the CPP arm and the CPB15 arm was accepted.

Results from the GOG-0218 trial show that concurrent bevacizumab and chemotherapy for 5 cycles followed by maintenance bevacizumab for a further 16 cycles provides an improved efficacy benefit compared to chemotherapy and placebo or chemotherapy and bevacizumab for 6 cycles in women with advanced ovarian cancer.

Table 10 - Investigator assessment of PFS[1] in the GOG-0218 study (ITT population)

	CPP (n= 625)	CPB15 (n= 625)	CPB15+ (n=623)
Number of events[2]	277	258	207
Median PFS (months)	12.0	12.7	18.0
Stratified hazard ratio (95% CI)[3]		0.84 (0.71-0.99)	0.645 (0.551, 0.756)
p –value[3,4]		0.204	< 0.001

[1] Primary PFS analysis, censored for CA-125 progressions and non-protocol therapy prior to disease progression) [2] 375 events in the control arm defined the data cutoff date, although these events arose, they are not reported here because of censoring for CA125 progression and NPT therapy. [3] Relative to the control arm; One-sided log-rank p-value [4] Subject to a p-value boundary of 0.0116.

6.5.3.2 GOG-0218: Sensitivity Analysis of PFS

Independent review committee (IRC) analysis of PFS

Results of the PFS comparisons between the CPP arm and CPB15+ arm derived from the independent review of tumour scans were consistent with the results of the primary Regulatory PFS analysis (Table 11). 91% of patients participated in the IRC analysis. According to the IRC assessment the PFS was significantly improved by a median of 6 months in the CPB15+ arm compared to the CPP arm (CPP: 13.1 months, CPB15+: 19.1 months, HR= 0.62, 95% CI = 0.50-0.77, p<0.0001). The HR was 0.62, indicating a 38%

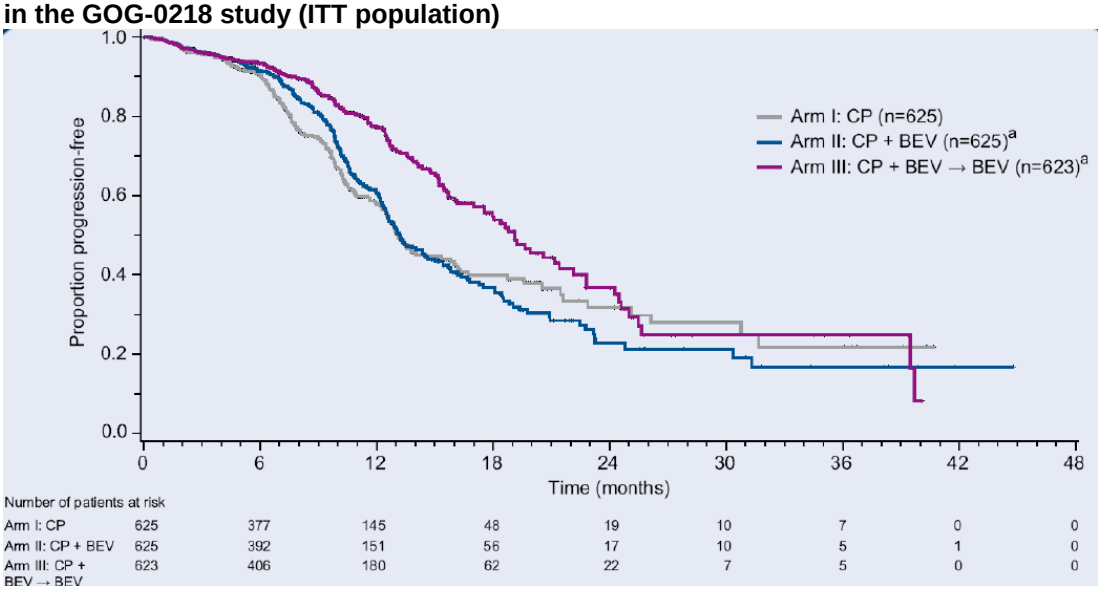
decrease in the risk of disease progression or death (p<0.0001). This result was similar to the investigator assessed results, and as expected of a double blind trial, indicates little investigator bias in the determination of disease progression. As per the investigator assessment, the Kaplan-Meier plot showed separation of the curves in favour of the CPB15+ after 4 months, which was maintained for up to 24 months (Figure 6).

Table 11 - Independent review committee assessment of PFS[1] in the GOG-0218 study (ITT population)

	CPP (n= 625)	CPB15 (n= 625)	CPB15+ (n=623)
Number of events	203	240	177
Median PFS (months)	13.1	13.2	19.1
Stratified hazard ratio (95% CI)[2]		0.93 (0.76, 1.13)	0.62 (0.50, 0.77)
p –value[2]		0.2220	< 0.0001

[1] PFS analysis, censored for CA-125 progressions and non-protocol therapy prior to disease progression) [2] Relative to the control arm; One-sided log-rank p-value

Figure 6 - Kaplan-Meier plot of the independent review committee's assessment of PFS in the GOG-0218 study (ITT population)



[a]Events prior to cycle 7 from the concurrent CP + BEV and CP + BEV → BEV arms (Arms II and III) were pooled for analysis. [b]Censored for non-protocol therapy and CA-125

GOG analysis of PFS (without censoring for CA-125 progression or NPT)

A GOG protocol-specified analysis of PFS was undertaken without censoring CA-125 progression or use of NPT prior to progression. These results were consistent with the censored analysis (HR= 0.71, 95% CI: 0.61- 0.83) (Table 12). However, estimates of median PFS for the CPP and CPB15+ arms (10.3 and 14.1 months, respectively) were shorter than the median values derived from the primary analysis censored for CA-125 (CPP arm: 12.0 months; CPB15+ arm: 18.0 months). There was a non-significant increase in the median PFS in the CPB15 arm compared to the CPP arm (CPP= 10.3 months, CPB15= 11.2 months, HR= 0.908, 95% CI: 0.795-1.040, p= 0.16, p-value boundary < 0.0116).

The results of an updated PFS analysis, as of August 26th 2011, were consistent with those from the original analysis, showing a hazard ratio of 0.770 (95% CI: 0.681-0.870) for CPB15+ versus CPP.

Table 12 - Investigator assessed PFS (without censoring for CA-125 progression or NPT prior to disease progression) in the GOG-0218 study (ITT population)[1]

	CPP (n= 625)	CPB15 (n= 625)	CPB15+ (n= 623)
Median PFS (months)	10.3	11.2	14.1
Hazard ratio (95% CI)[1]		0.908 (0.795,1.040)	0.717 (0.625, 0.824)
p –value[2]		0.0.16	< 0.0001

[1] Analysis with a data cut of 25th February 2010. [2] Relative to the control arm; One-sided log-rank p-value.

6.5.3.3 GOG-0218: Exploratory PFS

Subgroup analyses

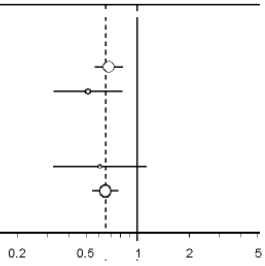
PFS was determined in various subgroups using baseline risk factors. Results of PFS in the CPP arm versus the CPB15+ arm with pooled CPB15 events can be found in Table 13.

PFS subgroup data were consistent with the primary PFS results in the CPP and CPB15+ arms. All subgroups of patients examined exhibited a hazard ratio less than 1 (favouring CPB15+, compared to CPP) and were close to the stratified hazard ratio of 0.62 reported in the primary analysis of PFS in the ITT population of the study. The difference in the median PFS between the

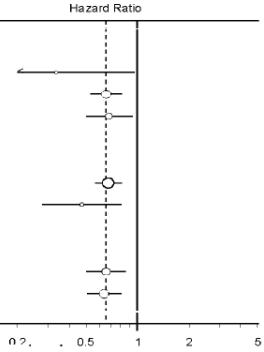
CPB15+ and CPP arms in the various subgroups was also close to the 6 month benefit reported in the primary analysis of PFS (Table 10). These results demonstrate robustness in the statistically significant benefit of the primary analysis of PFS comparing the long-duration bevacizumab arm and the control arm.

Table 13 - Investigator assessed PFS in the CPP vs CPB15+ arms of the study. (ITT population). Data from the CPB arm of the trial was pooled with the CPB15 arm.

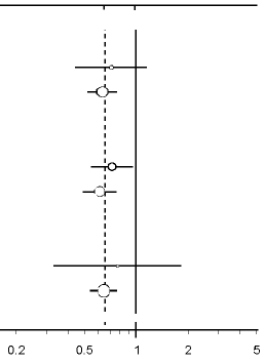
Baseline Characteristic	Total n	Total events	CPP (n=625) # of events	CPP (n=625) Median (month)	CPB15+ (n=1248) # of events	CPB15+ (n=1248) Median (month)	Hazard Ratio	(95% CI)
Primary Site								
Ovary	1558	446	230	12.1	216	18.2	0.68	(0.57 - 0.82)
Non-Ovary	315	79	47	9.7	32	16.7	0.52	(0.33 - 0.81)
Histologic Cell Type								
Mucinous or Clear Cell	109	40	18	5.8	22	9.3	0.60	(0.32 - 1.13)
All Others	1764	485	259	12.1	226	18.6	0.65	(0.54 - 0.78)



Baseline Characteristic	Total n	Total events	CPP (n=625) # of events	CPP (n=625) Median (month)	CPB15+ (n=1248) # of events	CPB15+ (n=1248) Median (month)	Hazard Ratio	(95% CI)
Age (yr)								
< 40	63	17	12	12.4	5	NE	0.34	(0.12 - 0.96)
40-65	1287	343	176	12.3	167	18.2	0.66	(0.53 - 0.82)
> 65	523	165	89	10.4	76	17.5	0.69	(0.50 - 0.93)
Race								
White	1630	468	246	12.1	222	17.9	0.68	(0.57 - 0.81)
Non-White	243	57	31	11.7	26	19.7	0.47	(0.28 - 0.80)
Baseline GOG Performance Status								
0	932	218	118	13.4	100	19.7	0.65	(0.50 - 0.86)
1 or 2	941	307	159	10.2	148	15.7	0.64	(0.51 - 0.80)



Baseline Characteristic	Total n	Total events	CPP (n=625) # of events	CPP (n=625) Median (month)	CPB15+ (n=1248) # of events	CPB15+ (n=1248) Median (month)	Hazard Ratio	(95% CI)
Histologic Tumor Grade								
<=2	285	69	38	14.0	31	20.6	0.71	(0.44 - 1.15)
3	1403	400	215	11.0	185	17.9	0.63	(0.52 - 0.77)
Baseline SLD								
<= Observed Median SLD	904	198	101	15.0	97	19.7	0.72	(0.55 - 0.96)
> Observed Median SLD	895	303	163	9.7	140	15.4	0.61	(0.49 - 0.77)
Baseline CA-125								
Normal	105	22	12	17.0	10	20.6	0.77	(0.33 - 1.81)
Abnormal	1768	503	265	11.3	238	17.9	0.65	(0.54 - 0.77)



Subgroup analysis by disease stage and debulking status from the GOG-0218 trial are presented in Table 14. There was a significant increase in PFS for all disease stages assessed with bevacizumab and chemotherapy, compared to chemotherapy alone. The Hazard Ratios in Table 14 suggest that this benefit

was at least as large in the optimally debulked Stage III patients (with macroscopic residuals <1cm) as in the Stage III suboptimally debulked and Stage IV patients. Overall, the subgroup analyses of PFS indicate that the benefit observed in the overall study population was maintained consistently across the subgroups, including poor risk and stratification factor subgroups.

Table 14 - PFS[1] Results by Disease Stage and Debulking Status from Study GOG-0218

Randomised patients stage III optimally debulked disease [2,3]			
	CPP (n = 219)	**CPB15 (n = 204)**	**CPB15+ (n = 216)**
Median PFS (months)	12.4	14.3	17.5
Hazard ratio (95% CI)[4]		0.81 (0.62, 1.05)	0.66 (0.50, 0.86)
Randomised patients with stage III suboptimally debulked disease[3]			
	CPP (n = 253)	**CPB15 (n = 256)**	**CPB15+ (n = 242)**
Median PFS (months)	10.1	10.9	13.9
Hazard ratio (95% CI)[4]		0.93 (0.77, 1.14)	0.78 (0.63, 0.96)
Randomised patients with stage IV disease			
	CPP (n = 153)	**CPB15 (n = 165)**	**CPB15+ (n = 165)**
Median PFS (months)	9.5	10.4	12.8
Hazard Ratio (95% CI)[4]		0.90 (0.70, 1.16)	0.64 (0.49, 0.82)

[1] Investigator assessed GOG protocol-specified PFS analysis (neither censored for CA-125 progressions nor censored for NPT prior to disease progression) with data cut-off date of 25 February, 2010 [2]With gross residual disease. [3] 3.7% of the overall randomized patient population had Stage IIIB disease rRelative to the control arm.

6.5.3.4 GOG-0218: Overall Survival

ITT analysis of OS

The final OS analysis presented here was calculated when 46.9% of patients had died. A non-significant increase in median OS of 3.2 months was observed in the CPB15+ arm compared to the CPP arm (CPP: 40.6 months; CPB15+ months: 43.8 months) (Table 15). The stratified analysis yielded a hazard ratio of 0.88, favouring the CPB15+ arm (95% CI: 0.75, 1.04). However, the one-sided log-rank p-value was 0.0641, indicating no difference in OS between the CPB15+ arm and the CPP arm.

Table 15 - OS in the GOG-0218 study (ITT population)

	CPP (n= 625)	CPB15 (n= 625)	CPB15+ (n= 623)
Median OS (months)	40.6	38.8	43.8
Hazard Ratio (95% CI)		1.07 (0.91,1.25)	0.88 (0.75,1.04)
One-sided log-rank p-value[1]		0.2197	0.0641

[1]**Subject to a p-value boundary of 0.0116.**

6.5.3.5 GOG-0218: Objective Response Rate

The ORR, according to the investigator assessment, was 63.4% in patients in the CPP arm compared to 66% in the CPB15+ arm, this increase of 2.6% was not significant (p=0.204). A significant increase in the ORR was however observed in the IRC analysis; where the ORR was 68.8% in the CPP arm and 77.4% in the CPB15+ arm (p<0.0012) (Table 16).

Table 16 - Investigator and IRC assessed objective response rate in the GOG-0218 study (patients with measureable disease at baseline)

Investigator Assessment			
	CPP (n= 396)	**CPB15 (n= 393)**	**CPB15+ (n=403)**
% patients with objective response	63.4	66.2	66.0
p –value[1]		0.2341	0.2041
Best confirmed response			
Complete response	63 (15.9)	68 (17.3)	68 (16.9%)
Partial response	188 (47.5%)	192 (48.9%)	198 (49.1%)
Stable disease	117 (29.5%)	108 (27.5%)	99 (24.6%)
Progressive disease	17 (4.3%)	10 (2.5%)	16 (4.0%)
Unable to evaluate	11 (2.8%)	15 (3.8%)	22 (5.5%)
IRC Assessment			
	CPP (n= 474)	**CPB15 (n=460)**	**CPB15+ (n=499)**
% patients with objective response	68.8	75.4	77.4
p –value[1]		0.0106	0.0012

[1] **Relative to control arm; one-sided log rank p-value**

6.5.3.6 GOG-0218: Quality of life

The instrument used in this study to assess the HRQoL was the self-administered FACT-O, which consists of three subscales: PWB (7 items),

FWB (7 items), and the ovarian cancer subscale (OCS; the first 12 items indicated as “additional concerns”). The principal measure is the TOI, which is a score derived from combining PWB, FWB, and OCS. The MID (minimally important difference) for the TOI score is 5 points and for the OCS is 3 points. In addition, there is the ADS, consisting of two items from the OCS and two more items from the additional concerns module.

The FACT-O TOI score, its subscales, as well as the ADS were all converted to have one directional interpretation: a higher score means better HRQoL.

FACT-O TOI

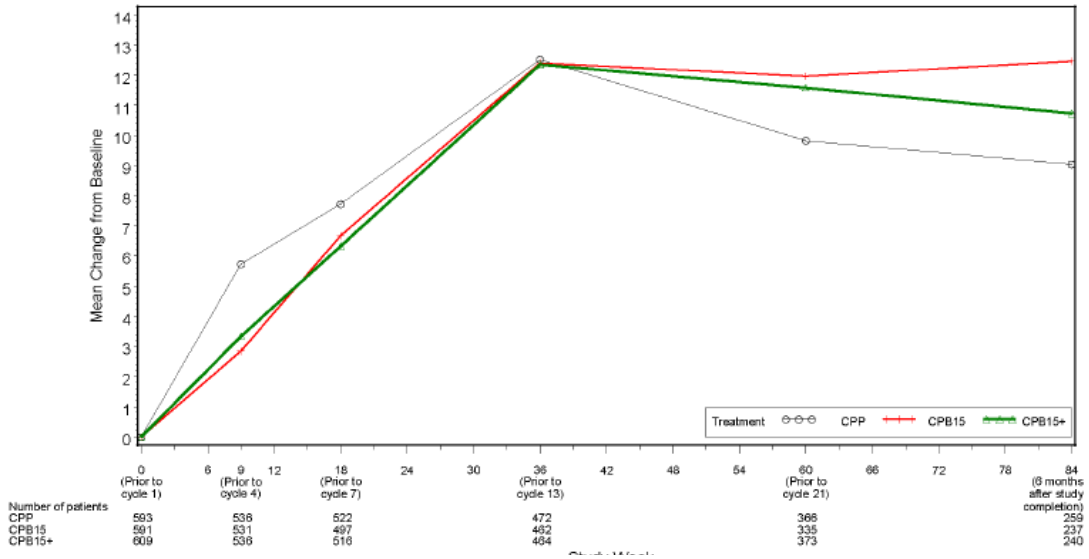
Each patient was asked to complete the FACT-O TOI questionnaire at the following timepoints during their participation in the study (see section 5.3.6 for further details on timepoints):

Based on the guidance of the MID for FACT-O TOI, an improvement of at least 5 points is considered clinically meaningful (Cella DF 1993). At Timepoint 2, the mean improvement of 5.7 points (median of 6 points) in TOI score over baseline for patients in the CPP arm was clinically meaningful, while the mean improvement of 3.1 points (median of 2 points) in the CPB15/CPB15+ arm was not clinically meaningful. At Timepoint 3 the mean improvements of 7.7 points in the CPP arm and 6.5 points in the CPB15 and CPB15+ arms were both clinically meaningful. However, the difference between the arms was not clinically meaningful. At Timepoint 4 the mean changes from baseline were similar in three arms: 12.5 points for the CPP arm, 12.4 points for the CPB15 arm, and 12.4 points for the CPB15+ arm. At Timepoint 5, the mean changes from baseline were greater for patients in the active arms compared with those in the control arm: 9.8 points for the CPP arm, 12.0 points for the CPB15 arm, and 11.6 points for the CPB15+ arm). However, the differences between the arms were not clinically meaningful (Figure 7).

During the chemotherapy phase, mean FACT-O TOI scores were slightly lower in the CPB15 and CPB15+ arms than in the CPP arm, although these differences were not significant. Similarly, there was no significant difference

between the CPB15/CPB15+ arms and CPP arm during the maintenance phase.

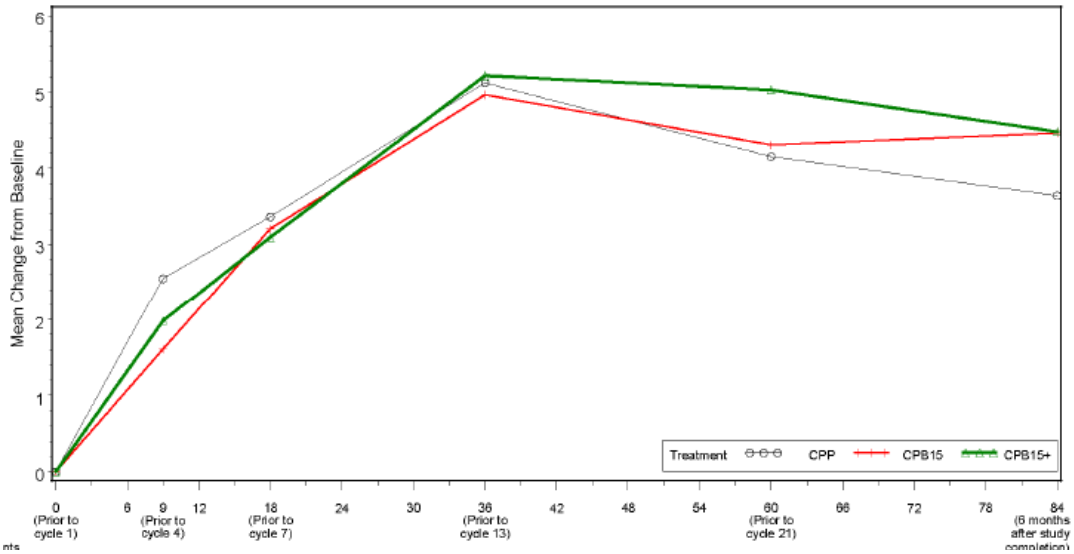
Figure 7 - Mean change from baseline in overall FACT-O TOI scores over time:



Ovarian Cancer Subscale (OCS)

Similar to the FACT-O TOI score, the OCS score was summarised by timepoint (see section 5.3.6 for timings). The mean improvement at Timepoint 3 (18 weeks after Cycle 1, prior to Cycle 7) exceeded the MID in both the control arm CPP and the combined active arms CPB15/CPB15+ (Figure 8). However, the difference between the arms was not clinically meaningful. The improvement in ovarian subscale scores from baseline at Timepoints 4 and beyond was clinically meaningful in all treatment arms. However, the differences between the arms were not clinically different.

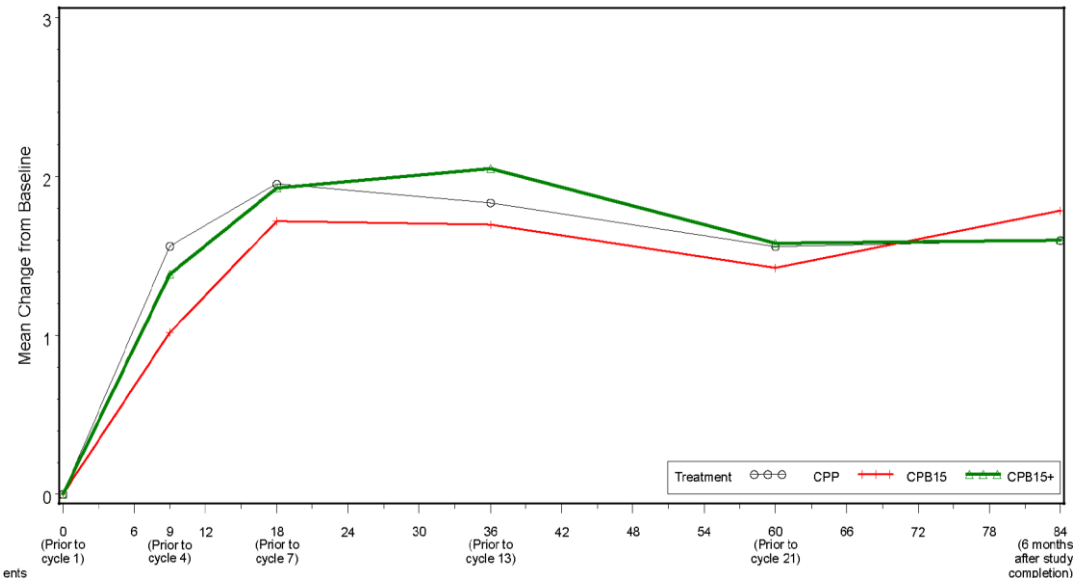
Figure 8 - Mean change from baseline in ovarian cancer subscale scores over time: randomised patients



Abdominal discomfort score

The ADS is a measure of pain and abdominal symptoms from the four items of the additional concerns module (I have pain, I have cramps in my stomach area, I have pain in my stomach area, and stomach pain interferes with my daily functioning). A higher score indicates better QoL (less pain for disturbances from the abdominal pain and other symptoms). There was a general positive trend in the mean score and the median score at all timepoints, indicating that patients in all three arms improved over baseline; however, there is not a clear trend to indicate whether patients in a specific treatment arm improved more than patients in another treatment arm (Figure 9).

Figure 9 - Mean Change from Baseline in abdominal discomfort score: randomised Patients



In conclusion, bevacizumab-containing therapy produced some statistically significant QoL disruptions during chemotherapy; however, these differences were small and not clinically significant.

6.5.3.7 GOG-0218 Summary

Patients with advanced ovarian cancer who received front-line therapy with bevacizumab in combination with chemotherapy (paclitaxel and carboplatin), followed by continued use of bevacizumab alone for a total duration of up to 21 cycles, had a statistically significant and clinically meaningful improvement in PFS compared with patients who received chemotherapy plus placebo.

The hazard ratio was 0.645 (95%CI: 0.551, 0.756), which corresponds to a 35.5% reduction in the risk of progression or death. There was a 6.0 month gain in median PFS (18.0 months in the CPB15+arm compared with 12.0 months in the CPP arm)

Patients who received bevacizumab in combination with chemotherapy without continued bevacizumab maintenance therapy had a smaller PFS benefit. The benefit observed for PFS in the CPB15+ arm was further supported by a series of subgroup and sensitivity analyses, including the IRC-assessed PFS which all demonstrate the robustness of the primary investigator-assessed analysis.

Subgroup analysis of a) stage III optimally debulked, b) stage III suboptimally debulked and c) stage IV disease patients demonstrated that the benefit of bevacizumab therapy was seen across all the patients recruited to the study, including those with (macroscopic) optimally debulked disease.

At the time of final analysis, 46.9% of patients had died across the three treatment arms. There were numerically fewer deaths and longer overall survival in the CPB15+ arm compared to the CPP arm, resulting in a hazard ratio of 0.88 for OS. These results did not achieve statistical significance, as the upper limit of the 95% confidence interval overlapped the significance threshold. However, substantial post-progression cross-over of placebo patients to receive bevacizumab may have confounded these data.

ICON7

6.5.3.8 ICON7 progression free survival

Primary PFS endpoint

At the time of the data cut-off (28th February 2010) for analyses of PFS, 759 progression events had occurred. ICON7 met the primary endpoint of the study by demonstrating a statistically significant improvement in PFS when bevacizumab was used in combination with standard chemotherapy followed by bevacizumab maintenance treatment in patients with ovarian epithelial cancer, fallopian tube carcinoma and primary peritoneal carcinoma. At the updated PFS analysis (30th November 2010) the risk of disease progression or death was decreased by 13% for patients in the CPB7.5+ arm compared to the CP arm (HR 0.87, CI: 0.75-0.98, p = 0.04, log-rank test) (Table 17). The median PFS duration was 17.4 months with CP and 19.8 months with CPB7.5+.

Table 17 - Investigator assessment of the PFS in the ICON7 trial (ITT population)[1]

	CP (n= 764)	CPB7.5+ (n=764)
Median PFS (months) (updated)	17.4	19.8
Hazard ratio (95% CI)		0.87 (0.77 – 0.99)
p –value		0.04

[1] **Updated PFS analysis with additional 9 months analysis (data cutoff 30 November 2010)**

6.5.3.9 ICON7: Exploratory PFS analyses

Subgroup analysis

A pre-planned subgroup analysis of PFS in patients who were FIGO stage III sub-optimally debulked and stage IV debulked (the groups of patients who most closely resemble those in the GOG-0218 trial) was performed. There was a significant median PFS increase of 5.4 months in this 'high risk' group of FIGO stage III suboptimally debulked and resected FIGO stage IV patients who were in the CPB7.5+ arm compared to the CP arm (CP: 10.5 months, CPB7.5+: 15.9 months, p<0.001, HR = 0.68, 95% CI: 0.55-0.85) (Figure 10). The updated analysis supported this significant increase (Table 18).

Figure 10 - A Kaplan-Meier plot to show the PFS of FIGO stage III suboptimal and FIGO stage IV patients with debulking in the ICON7 trial (ITT analysis)

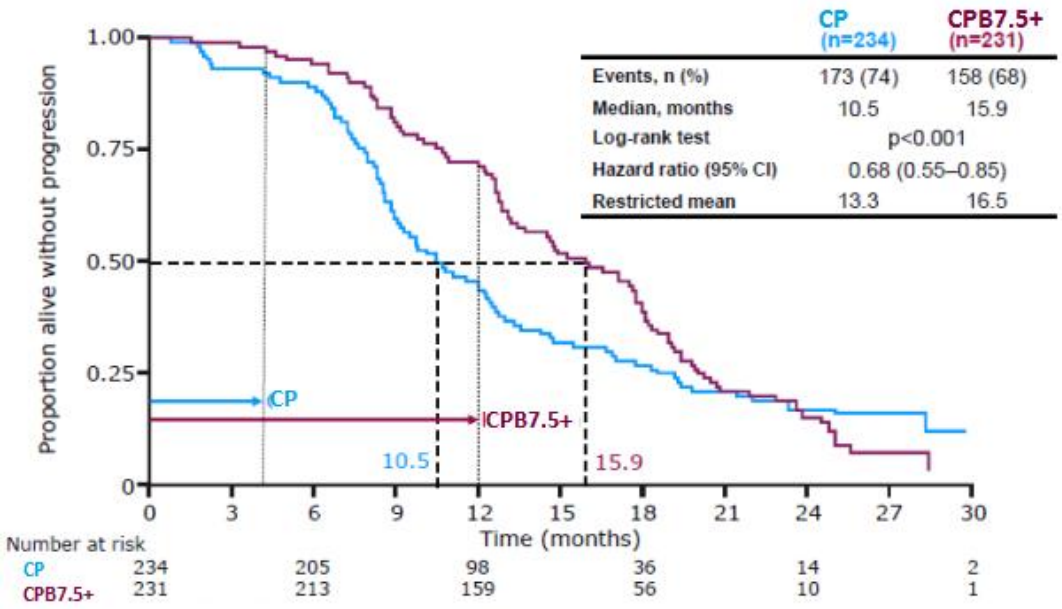


Table 18 - PFS analysis of FIGO stage III suboptimal and FIGO stage IV patients with debulking[1]

	CP (n= 234)	CPB7.5+ (n=231)
Median PFS (months) (updated)	10.5	16.0
Hazard ratio (95% CI)		0.73 (0.60-0.93)
p –value		0.002

Updated PFS analysis with additional 9 months analysis (data cutoff 30 November 2010)

The subgroup analyses for the stratification factors FIGO stage and outcome of surgery are shown below (Table 19;Figure 11). Patients in Stratum 2 (FIGO Stage I-III and residuals <1cm) had a HR for PFS of 0.72 (95% CI 0.54-0.95) p=0.020 and in Stratum 3 (FIGO Stage III inoperable and Stage IV) the HR for PFS was 0.66 (0.48-0.91) p=0.011. These data from stratified subgroups reinforce those shown in the 'high risk' subgroup analysis above.

Table 19 - Subgroup analysis of the three FIGO staging strata

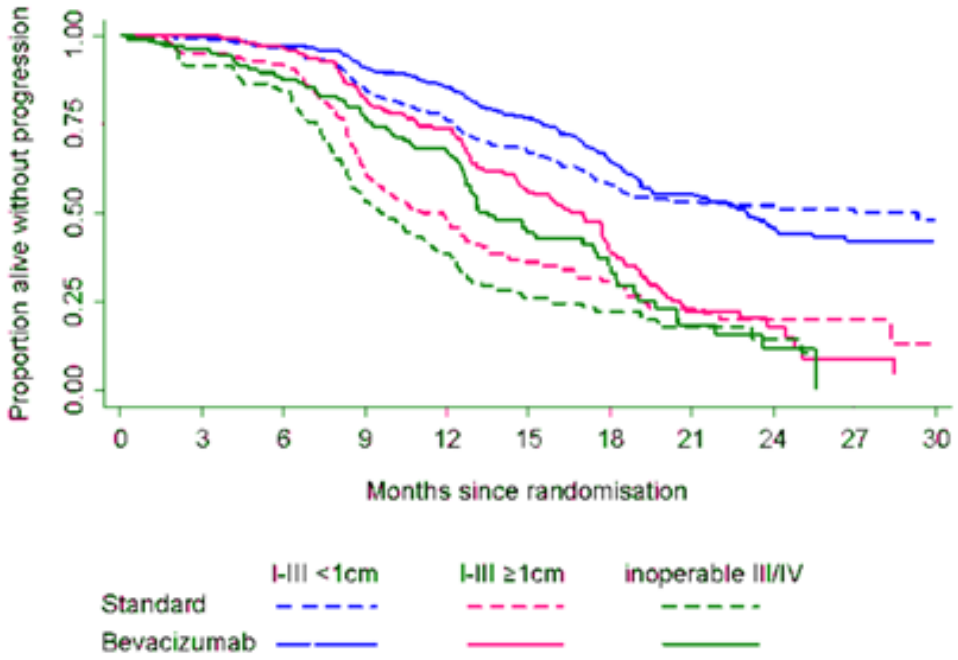
	[no. events/no. entered] Bevacizumab	Standard	Hazard Ratio	HR (95% CI), p
FIGO stage & outcome of surgery				
I-III ≤1cm	199/518	204/508		0.88 (0.72-1.07), 0.16
I-III >1cm	97/140	106/150		0.72 (0.54-0.95), 0.020
Inoperable III or IV	71/106	82/106		0.66 (0.48-0.91), 0.011

0 0.5 1 1.5 2

Bevacizumab Better Standard Better

Interaction Test: p=0.25

Figure 11 - Subgroup analysis of the three FIGO staging strata



A pre-planned exploratory analysis of PFS was also conducted by disease stage/debulking status subgroups in the ITT population (Table 20). All analyses demonstrate an improvement in PFS with bevacizumab and chemotherapy compared to chemotherapy alone. However, in contrast to

GOG-0218 there was not a significant increase in PFS with bevacizumab in the Stage III optimally debulked patients in ICON7.

Table 20 - PFS Results by Disease Stage and Debulking Status from ICON7[1]

Randomised patients stage III optimally debulked disease [2,3]		
	CP (n = 368)	**CPB7.5+ (n = 383)**
Median PFS (months)	17.7	19.3
Hazard ratio (95% CI) [4]		0.89 (0.74, 1.07)
Randomised patients with stage III suboptimally debulked disease[3]		
	CP (n = 154)	**CPB7.5+ (n = 140)**
Median PFS (months)	10.1	16.9
Hazard ratio (95% CI)[4]		0.67 (0.52, 0.87)
Randomised patients with stage IV disease		
	CP (n = 97)	**CPB7.5+ (n = 104)**
Median PFS (months)	10.1	13.5
Hazard Ratio (95% CI)[4]		0.74 (0.55, 1.01)

[1] Investigator assessed PFS analysis with data cut-off date of 30 November 2010 [2] With or without gross residual disease. [3] 5.8% of the overall randomized patient population had Stage IIIB disease. [4] Relative to the control arm

6.5.3.10 ICON7: Overall survival

ITT analysis of overall survival

Early analyses showed no detrimental effect of treatment on overall survival when comparing the CPB7.5+ arm with the CP arm (HR 0.85, 95% CI 0.69; 1.04, log-rank p-value = 0.1167) (Table 21). The hazard ratio was in favour of the CPB7.5+ arm though the effect was not statistically significant as at the time of the data cut-off for the analysis of PFS, the OS data were not mature. Due to the low number of events, a reliable estimate of the median duration of OS could not be determined. The protocol-specified, final OS analysis will be performed when 715 deaths have occurred and will provide more mature survival results.

Table 21 - Investigator assessed OS in the ICON7 study (ITT population)[1]

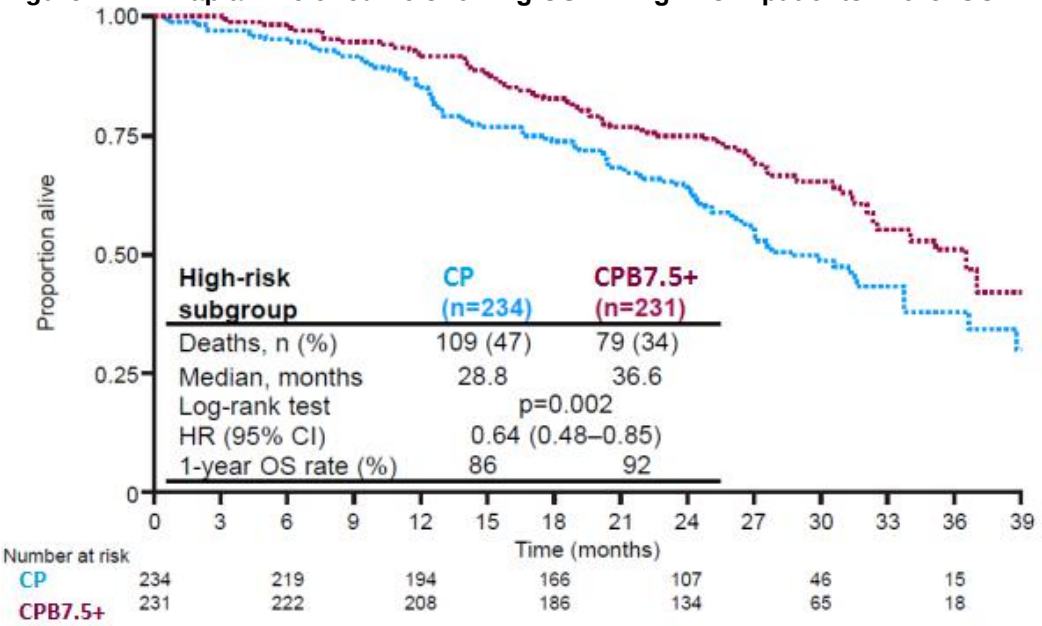
	CP (n= 764)	CPB7.5+ (n=764)
Deaths, n (%)	200 (26)	178 (23)
Median (months)	Not reached	
Hazard ratio (95% CI)	0.85 (0.69; 1.04)	
P-value	0.1167	
1 Yr OS rate (%)	86	92

[1] **Exploratory OS analysis when approximately 25% of patients had died**

Subgroup analysis of OS

An interim OS analysis, requested by regulatory authorities, arose after a median follow-up of 28 months. 47% of patients had died in the CP arm, and 34% of patients had died in the CP7.5+ arm. At this analysis, the Stage III suboptimal and Stage IV debulked patients, ("high-risk" patients), had a median OS improvement of 7.8 months in the CPB7.5+ arm compared to those treated in the CP arm (CP: 28.8 months, CPB7.5+: 36.6 months, $p<0.002$, HR = 0.64, 95% CI: 0.48-0.85) (Figure 12). The HR of 0.64 indicates a 36% reduction in relative risk of death in these "high risk" patients treated with CPB7.5+compared with CP patients. Patients in the ICON7 trial were not permitted to cross-over to receive bevacizumab , therefore OS from this trial will give a more reliable measure of the effect of first-line therapy on OS than trials allowing cross-over (such as GOG-0218).

Figure 12 - A Kaplan-Meier curve showing OS in "high risk" patients in the ICON7 trial



6.5.3.11 ICON7: Objective response rate

In patients with measurable disease at baseline, the percentage of patients with an ORR of CR or PR was significantly higher in the CPB7.5+ arm (168 of 257 patients; 67%) compared with the CP arm (118 of 263 patients; 48%, Table 22). The absolute difference in response rate between the CPB7.5+ arm and the CP arm was 19.4% with a p-value < 0.0001.

The higher reported response rate in the CPB7.5+ arm was due to an increase in the incidence of patients with both a complete (CP: 4.8%; CPB7.5+: 15.2%) and partial response (CP: 42.9%; CPB7.5+: 52.0%) as compared to the CP arm, and was accompanied by a reduction in the proportion of patients with stable (CP: 45.7%; CPB7.5+: 29.2%) or progressive disease (CP: 6.5%; CPB7.5+: 3.6%) as their best response.

Table 22 - Investigator assessed ORR from the ICON7 study[1]

	CP (n=263)	CPB7.5+ (n=257)
Objective Response rate	118 (48%)	168 (67%)
Complete response	4.8%	15.2%
Partial response	42.9%	52.0%
Stable disease	45.7%	29.2%
Progressive disease	6.5%	3.6%
P-value[2]	<0.0001	

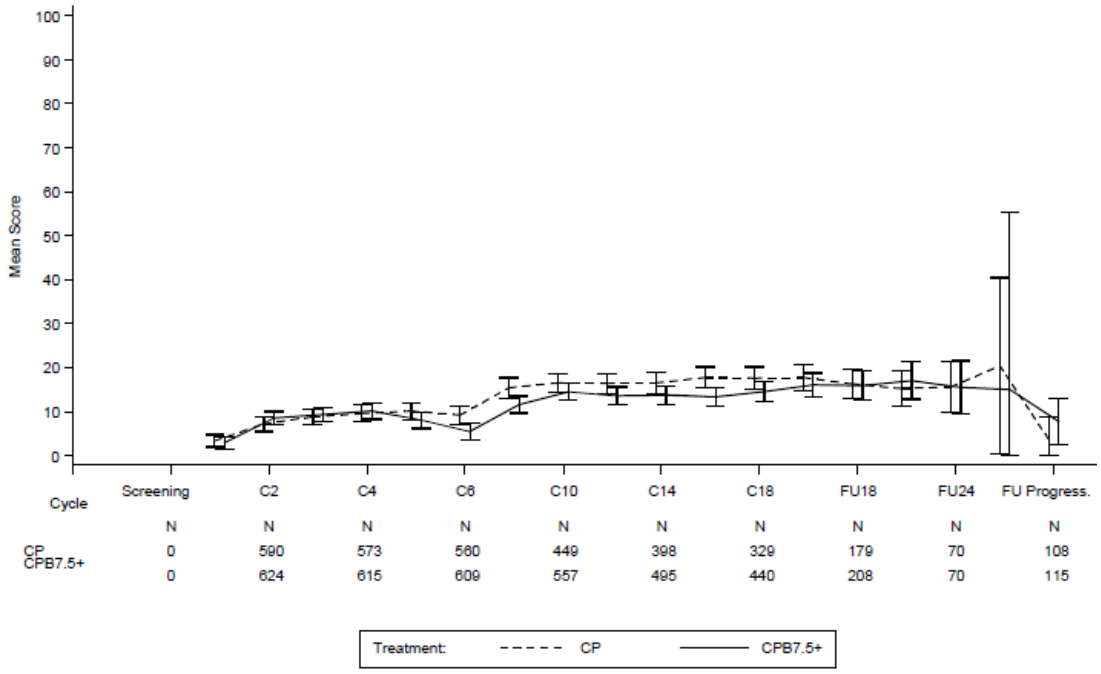
[1] Patients with measurable disease at baseline, who received ≥ 1 cycle of protocol treatment [2]p-value compared response rate between CP and CPB7.5+ arm.

6.5.3.12 ICON7 QOL

EORTC QLQ-C30

The EORTC QLQ-C30 questionnaire was used to assess QoL in the ICON7 trial. The number of assessments was balanced between treatment arms during chemotherapy and follow-up and was approximately 20% lower in the CP arm during the phase when bevacizumab was administered alone (cycles 7 -18) in the CPB7.5+ arm. Figure 13 shows the change in baseline of the global health status/QoL of patients by assessment over time (cycles [C1-18], follow-up [15-24 months] and after progression). The global health status generally increased in both the CP and CPB7.5+ arms over the treatment and follow-up phases. The degree of improvement from baseline in global health status/QoL for both treatment arms over the first 5 cycles of chemotherapy was similar. From cycle 7 to cycle 18 the positive changes in global health status score were maintained although were slightly lower for patients in the CPB7.5+ arm (who were receiving bevacizumab alone) than for patients in the CP arm (who in the observation phase and not receiving any treatment). During follow up, similar global health scores were recorded for patients in the CP and CPB7.5+ arms (up to 20% increase in mean score over baseline). Following disease progression, global health status/QoL scores in both arms fell to values comparable to those recorded at screening.

Figure 13 - Plot of change in mean global health status score QOL from screening with 95% confidence interval over time (EORTC QLQ C-30)



EORTC QLQ - OV28

The EORTC QLQ - OV28 was another measure of QoL used in the ICON7 trial, which specifically details QoL related to ovarian cancer. Patients show improvements of up to 20 to 25 points in the abdominal/GI symptoms and attitude scales. Improvements and worsening of less than 10 points were observed for chemotherapy, hormonal and body image scales. Patients experienced 30 to 40 point worsening in peripheral neuropathy symptoms. Analysis of the change from first to last assessment showed that the CPB7.5+ arm versus the CP arm for subscales of the EORTC QLQ-OV28 were not statistically significant expect for one scale, “chemotherapy side effects”. In comparison to the CP arm, patients in the CPB7.5+ arm had a slightly higher change from baseline in score for “chemotherapy side effects” (CP: 0.1 mean change; CPB7.5+: 2.9 mean change, p = 0.0044) where higher scores on this scale reflect a greater extent to which patients experienced symptoms or side effects.

In conclusion, some women receiving bevacizumab had a statistically significant but clinically small detriment in global QoL

6.5.3.13 ICON7: Summary

The addition of bevacizumab to carboplatin and paclitaxel as front-line therapy for patients with ovarian cancer resulted in a statistically significant reduction in the risk of progression or death by 13% in the CPB7.5+ arm versus the CP arm (hazard ratio 0.87, 95% CI [0.77-0.99] log-rank p-value = 0.04) based on the primary unstratified analysis of the ITT population. The median PFS was 17.4 months for the CP arm and 19.8 months for the CPB7.5+ arm.

No cross over from the CP arm to bevacizumab was allowed in this study. At the time of PFS data cut-off only a limited number of OS events had occurred (25% of the ITT patients had died). The hazard ratio favoured the bevacizumab containing arm (HR 0.85, 95% CI: 0.69-1.04). The median survival time in the CP arm was not reached and no reliable estimate could be obtained in the CPB7.5+ arm.

This study investigated the effect of bevacizumab in combination with carboplatin and paclitaxel in a diverse range of patients, from stage I to stage IV ovarian cancer. It is patients with the later stages of cancer that have particularly poor outcomes and are the patient population licenced for bevacizumab use. A pre-planned analysis of ‘high risk’ patients with Stage III suboptimal and Stage IV debulked disease demonstrated a significant increase in the PFS of 5.5 months and an increase in median OS of 7.8 months. This pre-planned analysis covered a population similar to 2 of the patient groups in GOG-0218, as optimal debulking was defined in a different fashion in the two studies.

Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

6.5.4 **The following steps should be used as a minimum when presenting a meta-analysis.**

- **Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.**
- **Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).**
- **Provide an adequate description of the methods of statistical combination and justify their choice.**
- **Undertake sensitivity analysis when appropriate.**
- **Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).**

The studies were at different doses and durations, with different study populations, thus a meta-analysis was not considered appropriate.

6.6 Indirect and mixed treatment comparisons

Data from head–to–head RCTs should be presented in the reference-case analysis, if available. If data from head–to–head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

6.6.1 **Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the**

published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.

No direct comparisons were required as relevant comparators were used in the GOG-0218 and ICON7 trials.

6.7 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

6.7.1 **If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.**

No relevant non-RCTs were identified from the literature searches.

6.8 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

6.8.1 **If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.**

Safety was a secondary outcome in the GOG-0218 and ICON7 trial, thus no searches were undertaken for this purpose.

6.8.2 **Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.**

6.8.2.1 GOG-0218 Safety Analyses

The extent of bevacizumab/placebo and chemotherapy exposure in the different treatment arms of GOG-0218 is displayed in Table 23. Patients in the CPB15 and CPB15+ arms received more cycles of bevacizumab/ placebo (median, 12.0 and 13.0 cycles, respectively) than the patients in the CPP arm (median, 11.0 cycles) with an associated longer time on therapy. The exposure to chemotherapy was comparable across all three treatment arms.

Table 23 - Exposure to bevacizumab/placebo and chemotherapy in the GOG-0218 study: Safety evaluable patients

	CPP (n=601)	CPB15 (n=607)	CPB15+ (n=608)
Duration of bevacizumab /placebo (months)			
n	591	593	592
Mean (SD)	8.1 (4.4)	8.1 (4.6)	8.8 (5.0)
Median	7.7	8.1	9.0
Range	0-19	0-17	0-19
Number of cycles of bevacizumab/placebo			
Mean (SD)	11.8 (6.1)	11.9 (6.4)	12.7 (6.7)
Median	11.0	12.0	13.0
Range	1-21	1-22	1-21
Total dose of bevacizumab / placebo			
Mean	12423.1	12520.2	13185.
Median	11232.0	11421.5	12934.3
Range	768-4000	565-36800	450-34366
Total number of carboplatin cycles			
n	601	607	608
Mean (SD)	5.8 (0.7)	5.8 (0.)	5.7 (0.8)
Median	6.0	6.0	6.0
Range	2-7	2-9	2-7
Total number of paclitaxel cycles			
n	597	594	600
Mean (SD)	5.7 (1.0)	5.7 (1.1)	5.6 (1.0)
Median	6.0	6.0	6.0
Range	1-7	1-9	1-7

Table 24 displays a summary of the extent of all grade AEs, grade 3-5 AEs and death associated with treatment or disease. Almost all patients experienced at least 1 AE, with 45.6% of patients in the CPP arm, 50.6% of

patients in CPB15 arm and 55.4% of patients in the CPB15+ arm experiencing a grade 3-5 AE (excluding laboratory events).

Table 24 - Overview of Primary Safety Results: Safety-Evaluable Patients from the GOG-0218 study

	CPP (n =601)	CPB15 (n =607)	CPB15+ (n =608)
Any adverse event [a]	600 (99.8%)	607 (100%)	607 (99.8%)
Grade 3–5 adverse events, excluding laboratory data [b]	274 (45.6%)	307 (50.6%)	337 (55.4%)
Grade 3–5 adverse events, including laboratory data [b]	559 (93.0%)	577 (95.1%)	574 (94.4%)
Event reported through the NCI AdEERS	128 (21.3%)	144 (23.7%)	157 (25.8%)
Discontinued study treatment due to adverse event [c]	58 (9.7%)	83 (13.7%)	100 (16.4%)
Grade 5 adverse event	4 (0.7%)	9 (1.5%)	14 (2.3%)
All deaths (safety-evaluable patients)	145 (24.1%)	148 (24.4%)	131 (21.5%)
Deaths not due to this disease	10 (1.7%)	9 (1.5%)	13 (2.1%)

[a] Included adverse events that occurred since the start of Cycle 2 and within 30 days after the last protocol treatment and before or on the clinical cutoff date (5 February 2010) reported on the CRF or through the NCI AdEERS. [b] The GOG-0218 Toxicity Form was used to collect NCI CTCAE events associated with laboratory measurements of white blood cell counts, absolute neutrophil count/granulocytes, platelets, and haemoglobin in addition to collecting adverse events based upon investigator judgment. [c] Discrepancies in reported incidences may be the result of an artefact in CRF design and data collection.

Table 25 displays adverse events (all grades) that showed ≥5% difference between arms of the GOG-0218 trial. The adverse events for which the incidence was greatest (≥ 10% higher in the bevacizumab-containing arms compared with the chemotherapy-alone arm) were stomatitis, dysarthria, headache, epistaxis, and hypertension.

Table 25 - AEs that occurred since the start of cycle 2 with ≥5% higher incidence in a study drug relative to the control arm: safety evaluable patients.

MedDRA System Organ Class Preferred Term	CPP (n =601)	CPB15 (n =607)	CPB15+ (n =608)
Gastrointestinal disorders			
Diarrhoea	203 (33.8%)	238 (39.2%)	230 (37.8%)
Nausea	308 (51.2%)	319 (52.6%)	349 (57.4%)
Stomatitis	80 (13.3%)	117 (19.3%)	147 (24.2%)
General disorders and administration-site conditions			
Fatigue	438 (72.9%)	438 (72.2%)	485 (79.8%)
Musculoskeletal and connective tissue disorders			
Muscular weakness	52 (8.7%)	77 (12.7%)	87 (14.3%)
Pain in extremity	100 (16.6%)	118 (19.4%)	144 (23.7%)
Nervous system disorders			
Dysarthria	9 (1.5%)	58 (9.6%)	72 (11.8%)
Headache	126 (21.0%)	156 (25.7%)	202 (33.2%)
Respiratory, thoracic, and mediastinal disorders			
Dyspnea	121 (20.1%)	170 (28.0%)	157 (25.8%)
Epistaxis	55 (9.2%)	182 (30.0%)	184 (30.3%)
Nasal mucosal disorder	22 (3.7%)	45 (7.4%)	61 (10.0%)
Vascular disorders			
Hypertension	81 (13.5%)	143 (23.6%)	196 (32.2%)

The maximum severity was selected for each event for each patient. Only those adverse events that occurred within 30 days after the last study drug and before or on the cutoff date (5 February 2010) were included in this analysis.

Adverse events of special interest to bevacizumab treatment were assessed. Table 26 displays the adverse events – all grades and grade 3-5 of special interest from cycle 2 of treatment to follow-up. Adverse events of special interest (grade 3-5) that occurred with a higher incidence (more than 1% between arms) in patients in the CPB15+ arm relative to the CPP arm were hypertension, GI perforation and non-CNS bleeding.

Table 26 - AEs of special interest (all grade and grade 3-5) in the GOG-0218 trial

Adverse events of special interest	CPP (n =601)	CPB15 (n =607)	CPB15+ (n =608)
Bleeding (CNS) (all grade)	(0.0%)	(0.0%)	2 (0.3%)
Grade 3-5	(0.0%)	(0.0%)	1 (0.2%)
Bleeding (non-CNS), (all grade)	96 (16.0%)	216 (35.6%)	223 (36.7%)
Grade 3-5	5 (0.8%)	8 (1.3%)	13 (2.1%)
Hypertension, (all grade)	81 (13.5%)	143 (23.6%)	196 (32.2%)
Grade 3-5	12 (2.0%)	34 (5.6%)	60 (9.9%)
Proteinuria (all grade)	39 (6.5%)	32 (5.3%)	51 (8.4%)
Grade 3-5	4 (0.7%)	4 (0.7%)	10 (1.6%)
Neutropenia [a] (all grade)	40 (6.7%)	52 (8.6%)	51 (8.4%)
Grade 3-5	22 (3.7%)	18 (3.0%)	27 (4.4%)
Neutropenia, decreased neutrophil count term [a](all grade)	574 (95.5%)	577 (95.1%)	577 (94.9%)
Grade 3-5	522 (86.9%)	531 (87.5%)	524 (86.2%)
Febrile neutropenia (all grade)	21 (3.5%)	30 (4.9%)	26 (4.3%)
Grade 3-5	21 (3.5%)	30 (4.9%)	26 (4.3%)
Wound-healing complication (all grade)	17 (2.8%)	22 (3.6%)	18 (3.0%)
Grade 3-5	8 (1.3%)	12 (2.0%)	10 (1.6%)
VTE (all grade)	35 (5.8%)	32 (5.3%)	41 (6.7%)
Grade 3-5	16 (2.7%)	12 (2.0%)	14 (2.3%)
ATE [b] (all grade)	14 (2.3%)	19 (3.1%)	19 (3.1%)
Grade 3-5	14 (2.3%)	18 (3.0%)	18 (3.0%)
Gastrointestinal perforation (all grade)	2 (0.3%)	11 (1.8%)	12 (2.0%)
Grade 3-5	2 (0.3%)	10 (1.6%)	10 (1.6%)
Fistula/abscess (all grade)	7 (1.2%)	5 (0.8%)	12 (2.0%)
Grade 3-5	5 (0.8%)	4 (0.7%)	8 (1.3%)
Congestive heart failure (all grade)	(0.0%)	(0.0%)	3 (0.5%)
Grade 3-5	(0.0%)	(0.0%)	3 (0.5%)
RPLS (all grade)	(0.0%)	1 (0.2%)	1 (0.2%)
Grade 3-5	(0.0%)	0 (0.0%)	(0.0%)

[a] Absolute laboratory values (decreased neutrophil count) were routinely collected with associated NCI CTCAE grades on the Toxicity Form in Study GOG-0218 as well as the preferred term (neutropenia). [b] For a subset of 35 patients (8 in the CPP arm, 13 in the CPB15 arm, and 14 in the CPB15+arm) with embolism events categorised as ATEs, clinical review revealed the events to be VTEs in nature.

Secondary safety analyses in GOG-0218 assessed the first onset of selected adverse events, comparing onset in the chemotherapy phase (cycles 2-6) with onset during the maintenance phase (cycles 7 – 22). This comparison of the two phases is of particular importance, as it allows the tolerability profile of bevacizumab/placebo to be assessed independently from concurrent

chemotherapy. Table 27 shows the number of first events of selected adverse events occurring in the chemotherapy and maintenance phases for each treatment arm.

Table 27 - First onset of selected adverse events by treatment phase

Select adverse events (all grades unless specified)	CP		CPB15		CPB15+	
	CT	Maint	CT	Maint	CT	Maint
	(cycle 2-6) (n= 601)	(cycle 7-22) (n= 483)	(cycle 2-6) (n= 607)	(cycle 7-22) (n= 457)	(cycle 2-6) (n= 608)	(cycle 7-22) (n= 464)
Cycles, n	2906	4059	2911	4204	2891	4677
GI perforations (grade ≥ 2)	2	0	11	0	10	2
Fistula/abscess	7	0	4	1	12	0
Hypertension (grade ≥ 2†)	21	22	64	36	60	79
Proteinuria (grade ≥ 3)	2	2	4	0	0	10
Pain (grade ≥ 2)	127	123	117	135	112	174
Neutropenia (grade ≥ 4)	345	2	382	2	385	0
Febrile neutropenia	21	0	30	0	26	0
VTE	26	9	27	5	27	14
ATE	4	1	1	3	3	1
Wound-healing complications	11	6	14	8	13	5
CNS bleeding	0	0	0	0	0	2
Non-CNS bleeding (grade ≥ 3)	3	2	8	0	10	3
RPLS	0	0	1	0	0	1

CT= during chemotherapy, Maint= during maintenance therapy ATE: arterial thromboembolic event; CNS: central nervous system; GI: gastrointestinal; RPLS: reversible posterior leukoencephalopathy syndrome; VTE: visceral thromboembolic event. † Recurrent or persistent hypertension for >24 h or symptomatic increase by ≥ 20 mmHG diastolic or to > 150/100 mmHg if previously within normal range.

The occurrence of adverse events with a ≥ 5% incidence in the study group arms are shown in Table 28(chemotherapy phase [S1]) and Table 29 (maintenance phase [S2]). In the maintenance phase (S2), AEs that had more than a 5% difference between the CPP/CPB15 arm and the CPB15+ arm included diarrhoea, hypertension and nervous system disorders, such as headache and dysarthria.

Table 28 - S1 Analysis of AEs that arose from the start of Cycle 2 to the end of cycle 6. Reported on a CRF or through the NCI AdEERS, with ≥ 5% Higher Incidence in a Study Drug Arm Relative to the Control Arm: Safety-Evaluable Patients

MedDRA System Organ Class Preferred Term	CPP (n =601)	CPB15/CPB15+ (n =1215)
Gastrointestinal disorders		
Stomatitis	69 (11.5%)	229 (18.8%)
Nervous system disorders		
Dysarthria	6 (1.0%)	93 (7.7%)
Headache	82 (13.6%)	239 (19.7%)
Respiratory, thoracic and mediastinal disorders		
Dyspnea	93 (15.5%)	260 (21.4%)
Epistaxis	37 (6.2%)	324 (26.7%)
Vascular disorders		
Hypertension	63 (10.5%)	256 (21.1%)

Table 29 - S2 analysis of AEs that arose from the start of Cycle 7 to the end of follow-up. Reported on a CRF or through the NCI AdEERS, with ≥5% Higher Incidence in a Study Drug Arm Relative to the Control Arm: Safety-Evaluable Patients

MedDRA system organ class preferred term	CPP (n =601)	CPB15 (n =607)	CPB15+ (n =608)
Gastrointestinal disorders			
Diarrhoea	80 (13.3%)	97 (16.0%)	119 (19.6%)
Musculoskeletal and connective tissue disorders			
Arthralgia	101 (16.8%)	101 (16.6%)	145 (23.8%)
Myalgia	55 (9.2%)	63 (10.4%)	90 (14.8%)
Pain in Extremity	51 (8.5%)	71 (11.7%)	82 (13.5%)
Nervous system disorders			
Dysarthria	4 (0.7%)	23 (3.8%)	42 (6.9%)
Headache	62 (10.3%)	70 (11.5%)	125 (20.6%)
Respiratory, thoracic and mediastinal disorders			
Epistaxis	24 (4.0%)	50 (8.2%)	81 (13.3%)
Vascular disorders			
Hypertension	31 (5.2%)	44 (7.2%)	117 (19.2%)

6.8.2.2 ICON7 Safety analyses

The median dose and duration of therapy of each arm of the ICON7 study is shown in Table 30. The median dose intensity and duration of chemotherapy was similar between treatment arms of the study. 86% of patients received bevacizumab treatment over 7 cycles in the CP7.5+ arm.

Table 30 - Median dose and duration of therapy in the ICON7 study

	CP	CPB7.5+
Median duration of bevacizumab (days)	0	355 (1-472)
Median duration of carboplatin (days)	107 (1-178)	107 (1-213)
Median duration of paclitaxel (days)	106 (1-178)	107 (1-213)
Dose		
Median dose intensity of bevacizumab[a]	-	100%
Median dose intensity of carboplatin	99%	99%
Median dose intensity of paclitaxel	100%	100%

[a]Dose intensity calculated by actual dose administered divided by the planned dose for the treatment.

Table 31 displays a summary of safety results including the extent of all grade AEs, grade 3-5 AEs and death associated with treatment or disease. Almost all patients experienced at least 1 AE, with 54.3% of patients in the CP arm and 64.6% of patients in the CPB7.5+ arm experiencing a grade 3-5 AE.

Table 31 - A summary of safety from the ICON7 trial (safety population)

	CP N = 763	CPB7.5+ N = 746
Patients with at least one:		
Adverse event	755 (99.0%)	746 (100.0%)
NCI-CTCAE Grade 3, 4, 5 adverse event	414 (54.3%)	482 (64.6%)
Serious adverse event	179 (23.5%)	281 (37.7%)
AE leading to discontinuation	68 (8.9%)	164 (22.0%) [a]
All deaths	131 (17.2%)	107 (14.3%)
Deaths not due to disease progression	16 (2.1%)	19 (2.5%)
Patients with at least one:		
AE of special interest to bevacizumab[a]	362 (47.4%)	552 (74.0%)
NCI-CTCAE Grade 3/4/5 AE of special interest[a]	156 (20.4%)	240 (32.2%)
Serious AE of special interest[a]	49 (6.4%)	123 (16.5%)

[a] In addition to withdrawal from any study drug during the 6 cycles of concurrent chemotherapy, CPB7.5+ arm includes patients who discontinued bevacizumab due to an AE during the 12 additional cycles of bevacizumab

Table 32 displays the AEs (all grade) of special interest to bevacizumab in the ICON7 study.

Table 32 - Summary of all grade Adverse Events of Special Interest (Safety Population) in the ICON7 trial

Adverse event of special interest[a] (all grade)	CP n=763	CPB7.5+ n=746
Neutropenia	219 (29%%)	211 (29%)
Bleeding (all events)	87 (11.4%)	295 (39.5%)
Mucocutaneous bleeding	55 (7.0%)	276 (36.9%)
CNS bleeding	0	2 (0.2%)
Hypertension	47 (6.2%)	193 (25.8%)
Venous thromboembolic events	31 (4.1%)	50 (6.7%)
Proteinuria	19 (2.5%)	33 (4.4%)
Wound healing complication	16 (2.1%)	37 (5.0%)
Arterial thromboembolic events	11 (1.5%)	27 (3.6%)
Febrile Neutropenia	15 (2.0%)	21 (2.8%)
Abscesses and fistulae	10 (1.3%)	13 (1.7%)
Gastrointestinal perforation	3 (0.4%)	10 (1.3%)
Congestive heart failure	3 (0.4%)	2 (0.2%)
RPLS	0	0

Grade 3-5 adverse events of special interest were collected and assessed for both the whole population and the patients who were deemed ‘high risk’ (Table 33). These patients were Stage III sub-optimally debulked or stage IV. ‘High risk’ patients and are matched to the patients from the GOG-0218 trial on which the bevacizumab licence is based.

Table 33 - Grade 3-5 adverse events of special interest for the whole population and those with 'high-risk' disease

	Overall Population		High Risk Population	
Adverse event	**CP N = 763**	**CPB7.5+ N = 746**	**CP N = 234**	**CPB7.5+ N = 231**
Neutropenia	111 (14.5%)	114 (15.3%)	43 (18.4%)	46 (19.9)
Hypertension	2 (0.3%)	45 (6.0%)	1 (0.4%)	18 (7.8%)
Thromboembolic events (venous)	12 (1.6%)	3.0 (4.0%)	7 (3.0%)	10 (4%)
Febrile neutropenia	14 (1.8%)	19 (2.5%)	7 (3.0%)	3 (1.3%)
Thromboembolic events (Arterial)	11 (1.4%)	20 (2.7%)	7 (3.0%)	8 (3%)
Bleeding	3 (0.4%)	10 (1.3%)	1 (0.4%)	3 (0.4%)
Gastrointestinal perforations	3 (0.4%)	10 (1.3%)	0	3 (1.3%)
Fistula/Abcess	5 (0.7%)	7 (0.9%)	2 (0.8%)	0
Wound healing complication	1 (0.1%)	10 (1.3%)	1 (0.4%)	5 (6.7%)
CHF	3 (0.4%)	2 (0.3%)	1 (0.4%)	1 (0.4%)
Proteinuria	1 (0.1%)	4 (0.5)	0	2 (0.9%)
CNS bleeding	0	3 (0.4%)	0	1 (0.4%)
Mucocutaneous bleeding	0	2 (0.3%)	0	(0.4%)

6.8.1 **Give a brief overview of the safety of the technology in relation to the decision problem.**

6.8.1.1 GOG-0218

In this large, placebo-controlled study, the incremental increase in toxicity observed in the bevacizumab-containing arms was consistent with the known safety profile of bevacizumab. No new safety concerns were noted with the addition of bevacizumab to chemotherapy relative to events identified in the bevacizumab-prescribing information.

Adverse events reported in this study were summarised by treatment arm for the safety-evaluable population. Adverse events of special interest to bevacizumab treatment included ATE, VTE, hypertension, GI perforation, abscesses and fistulae, bleeding (CNS, non-CNS), proteinuria, wound-healing complications/dehiscence, congestive heart failure (CHF) or left ventricular systolic dysfunction, neutropenia, febrile neutropenia, and RPLS.

The adverse events occurring with at least a 5% higher incidence in the bevacizumab-containing arms than the CPP arm were generally manageable. Adverse events (all grades) with ≥ 10% higher incidence were stomatitis, dysarthria, headache, epistaxis, and

hypertension; those with a ≥ 5% higher incidence were gastrointestinal disorders (diarrhoea, nausea), constitutional symptoms (muscle weakness, pain in extremity), fatigue, dyspnea, and nasal mucosal disorder (Table 25).

The incidence of all deaths in the safety-evaluable population was comparable in the CPP arm (24.1%) and the CPB15 arm (24.4%) and was slightly lower in the CPB15+ arm (21.5%) (Table 24). More deaths from adverse events were observed in the two bevacizumab-containing arms (9 patients [1.5%] and 14 patients [2.3%] in the CPB15 and CPB15+ arms, respectively) compared with the control arm (4 patients [0.7%] in the CPP arm). These included fatal neutropenic infections and GI perforations observed during the period that bevacizumab was combined with chemotherapy.

The only adverse events of special interest that occurred more frequently (more than 1% difference between arms) in patients in the CPB15+ arm versus the CPP arm during the 15 months of maintenance treatment with bevacizumab were hypertension, proteinurea, pain and VTEs (Table 29). The adverse events associated with chemotherapy, such as neutropenia and febrile neutropenia, were low and similar across all three arms of the study during bevacizumab maintenance therapy.

During the chemotherapy phase, the rate of all grade GI perforations were increased in the bevacizumab-containing arms (1.8% and 1.6% in the CPB15 and CPB15+ arms, respectively) compared with the control arm (0.3% in the CPP arm), but the overall incidence and fatality rates resulting from this event in each arm were consistent with rates seen in other patient populations treated with bevacizumab. The incidence of GI events during the bevacizumab maintenance phase (cycle 7+) was identical across the three trial arms, suggesting that prolonged single agent therapy with bevacizumab does not increase the risk of GI perforation in patients with ovarian cancer (Table 29).

In summary, the safety profile in patients with newly diagnosed epithelial ovarian, peritoneal primary, or fallopian tube cancer in the GOG-0218 study was consistent with that seen in other trials (Miller et al. 2007;Sandler et al. 2006) with bevacizumab across indications.

6.8.1.2 ICON7:

In ICON7, the bevacizumab-specific safety observations were generally consistent with observations in previous studies of bevacizumab in other cancer indications (Miller et al.

2007;Sandler et al. 2006). No new safety concerns were noted with the addition of bevacizumab to chemotherapy relative to events identified in the bevacizumab prescribing information.

The dose intensity (planned versus received dose) in the safety population was 100% for bevacizumab and identical across the two treatment arms for carboplatin (99%) and paclitaxel (100%) chemotherapy. The extent of exposure was balanced between the arms. Therefore, no bias regarding imbalanced chemotherapy exposure was introduced.

Almost all patients (≥ 99%) in each treatment arm experienced one or more adverse events. Overall, 47.4% of patients in the CP arm and 74.0% of patients in the CPB7.5+ arm experienced an adverse event known to be associated with bevacizumab therapy (Table 31). The most common AEs of special interest (AESIs) (all grades) with a ≥ 2% higher incidence in the CPB7.5+ arm than in the CP arm were bleeding events (including mucocutaneous bleeding), hypertension, venous thromboembolic events, proteinuria and wound healing complications (Table 32). The majority of the increase in bleeding in the CPB7.5+ arm was grade 1-2 epistaxis.

There was also a higher incidence of Grade 3-5 AESIs in the CPB7.5+ arm (32.2%) compared with the CP arm (20.4%), including hypertension and bleeding events. The most frequently reported grade 3-5 AE was neutropenia, the incidence of which was similar in both treatment arms (CP: 14.5%; CPB7.5+: 15.3%). Grade 3-5 adverse events in which the incidence was ≥ 2% higher in the CPB7.5+ arm compared to the CP arm were hypertension (CP: 0.3%; CPB7.5+: 6.0%), diarrhoea (CP: 1.8%; CPB7.5+: 3.9%) and arthralgia (CP: 1.9%; CPB7.5+: 2.9%).

The incidence of these events was comparable to other large phase III studies of bevacizumab in combination with components of the chemotherapy used in the ICON7 study.

The incidence of serious adverse events of special interest was higher in the CPB7.5+ arm (16.5%) than in the CP arm (6.4%) (Table 33). The higher incidence of Grade 3-5 AESIs and SAEs of special interest in the bevacizumab-containing arm may be explained by the longer treatment duration, the fact that patients in the CPB7.5+ arm were seen more frequently by the investigator and the open-label nature of the trial.

Analyses of adverse events in patients with ‘high-risk’ disease demonstrated no major differences between the incidences of grade 3 -5 AEs in the overall population. Overall, the safety profile of the CPB7.5+ arms in the high risk population was similar to the safety profile observed in the ITT population.

In summary, the safety data reported in this study are consistent with the established safety profile of bevacizumab in other cancer indications. No new or unexpected safety signals were observed.

6.9 Interpretation of clinical evidence

6.9.1 **Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.**

6.9.1.1 Summary of results

Two large international phase III, randomised, controlled trials that investigated the clinical benefit of adding long duration bevacizumab to standard chemotherapy in patients with ovarian cancer were described in sections 6.1-6.8. The GOG-0218 trial was a double-blind, placebo-controlled trial in over 1800 patients which formed the primary submission for bevacizumab’s ovarian cancer licence. ICON7 was an open-label phase III trial in over 1500 patients; this methodology is considered less robust by several licensing authorities and therefore formed the supporting submission for the licence. Thus bevacizumab is licensed for the front-line treatment of advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with carboplatin and paclitaxel. The recommended dose is 15 mg/kg every 3 weeks, for up to 6 cycles in combination with chemotherapy followed by use as a single agent until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier.

Both trials demonstrated a clinically meaningful and statistically significant increase in PFS with first-line bevacizumab and chemotherapy, compared to standard chemotherapy (GOG-0218: 6.0 months increase, ICON7: 2.4 months increase). Final OS data are only available for GOG-0218 and show a non-significant increase in OS in the bevacizumab-containing arm (compared to chemotherapy). Subgroup analysis of high-risk ovarian cancer patients (those with stage III suboptimal debulked and debulked stage IV cancer) in the ICON7 trial demonstrated an OS increase of nearly 8 months and PFS increase of 5.4

months with bevacizumab and chemotherapy compared to chemotherapy alone. This ICON7 subgroup is most closely matched to the population of patients represented in the GOG-0218 study, where all patients received debulking surgery.

In the ICON7 trial the Stratum 2 (Stage I-III with >1cm residuals) and Stratum 3 (Stage III inoperable and Stage IV) patients, who made up 32-34% of the trial population, included the inoperable patients excluded from the 'high risk' subgroup shown above. These 2 Strata combined are the closest population in ICON7 to the licensed population (Stage IIIb-IV). They had very similar efficacy outcomes to the 'high risk' subgroup shown above.

6.9.1.2 Progression Free Survival – ITT population

In the GOG-0218 trial, the primary Regulatory endpoint analysis of investigator-assessed PFS (censoring for CA-125 progressions and NPT) demonstrated a stratified hazard ratio of 0.645 for the CPB15+ arm compared to the CPP arm (95% CI: 0.551-0.756, p< 0.001), representing a 35.5% reduction in the risk of disease progression or death. A median PFS difference of 6 months in favour of the CPB15+ arm was observed (CPP PFS= 12.0 months, CPB15+ PFS= 18.0 months). Independent analysis of the PFS (censored for CA-125 progressions and NPT) similarly observed a significant median increase of 6 months in the CPB15+ arm compared to the CPP arm (CPP PFS= 13.1 months, CPB15+ PFS= 19.1 months, HR: 0.62; 95% CI: 0.50-0.77, p< 0.0001). 20% of the CPP arm and 29% of the CPB15+ arm had censored events in the primary PFS analysis in GOG-0218. The secondary endpoint of PFS including all patients, showed a statistically significant increase in the median PFS of 3.8 months in GOG-0218, which related to a 29.3% reduction in the risk of disease progression or death (CPP PFS= 10.3 months, CPB15+ PFS= 14.1 months, HR: 0.717; 95% CI: 0.625-0.824, p<0.0001).

In the ICON7 trial, where CA-125 alone was not used to demonstrate progression, a PFS benefit was observed in the ITT population; a significant increase in the median PFS of 2.4 months arose in the CPB7.5+ arm compared to the CP arm (CP PFS= 17.4 months, CPB7.5+ PFS= 19.8 months, HR: 0.87; 95% CI: 0.77-0.99, p = 0.04).

The PFS analysis of the ITT population in both trials demonstrated a significant improvement in patients with ovarian cancer who were administered standard chemotherapy with maintenance bevacizumab for up to 12 or 15 months.

6.9.1.3 Progression Free Survival – Subgroup analyses

The bevacizumab licence (based on GOG-0218) stipulates that only patients with advanced ovarian cancer (FIGO stage IIIB, IIIC and IV) are eligible for treatment. It was therefore of interest to evaluate populations of patients in the ICON7 trial which excluded those not covered in the licence. A pre-planned subgroup analysis for 'high-risk' ICON7 patients (stage III sub-optimally debulked and stage IV debulked) included those patients most similar to the GOG-0218 study population, where all patients were surgically debulked. The 18% of ICON7 patients with stage I or II ovarian cancer and ICON7 patients with unresectable disease were excluded from this analysis.

A median PFS increase of 5.4 months occurred in these 'high-risk' patients who received bevacizumab and chemotherapy compared to chemotherapy alone (HR= 0.68, 95% CI: 0.55-0.85). These results show that bevacizumab was more effective in 'high-risk' patients, than in the ITT population of the ICON7 trial, which included patients with earlier stage disease. These subgroup PFS results were similar to the 6 month PFS advantage observed in the ITT population of the GOG-0218 trial.

A second subgroup analysis, of the 3 recruitment strata in ICON7, showed that patients in Stratum 2 (FIGO Stage I-III and residuals >1cm) had a HR for PFS of 0.72 (95% CI 0.54-0.95) p=0.020 and in Stratum 3 (FIGO Stage III inoperable and Stage IV) the HR for PFS was 0.66 (0.48-0.91) p=0.011. These 2 strata, with the exception of any Stage I-IIIA patients in Stratum 2, include the patients in ICON7 most similar to the Stage IIIB-IV population of the license.

There was a major difference in the Stage III optimally debulked patients were recruited to the GOG-0218 and ICON7 trials. In the GOG-0218 trial, almost all Stage III optimally debulked patients had macroscopic (i.e. visible to the naked eye) residual tumour after surgery. Only 5% of patients in GOG-0218 lacked macroscopic residual disease. In the ICON7 trial, however the patients with optimal debulking had either macroscopic or microscopic residual disease (i.e. no residual tumour to the naked eye). This difference is reflected in the PFS values for Stage III 'optimally debulked' patients in the two studies. The median PFS for Stage III optimal patients given CP in ICON7 (17.7 months) was considerably longer than for Stage III optimal patients given CPP in GOG-0218 (12.4 months). The median increase in PFS with bevacizumab was only 1.2 months in the Stage III optimal patients in ICON7 (CP PFS= 17.7 months, CPB7.5+ PFS= 19.3 months, HR: 0.89; 95% CI: 0.74-1.07). However, in GOG-0218 the stage III optimally debulked patients gained much greater benefit with bevacizumab (CPP PFS= 12.4 months, CPB15+ PFS=

17.5 months, HR: 0.66; 95% CI: 0.50-0.86). These data bear out the findings that median PFS decreases with an increasing level of residual disease after surgery (du Bois et al. 2009;Heintz et al. 2006). They also confirm that bevacizumab provides greater benefit for ovarian cancer patients with a poor prognosis. Thus the results of these trials show that significant differences between treatment arms arose when there was a small interval between the end of bevacizumab treatment and disease progression, so that a large proportion of patients were treated to progression. For example, in GOG-0218 where patients received 15 months of bevacizumab, median disease progression occurred at 18 months in the CPB15+ arm, a median of 3 months after finishing treatment. Non-significant differences between treatment arms were observed when there was a longer time between patients finishing their treatment and progressing, as in the ICON7 stage III optimally debulked patients, who finished bevacizumab treatment at 12 months and had a further 7.3 months median PFS.

6.9.1.4 Overall Survival

OS was a secondary endpoint for both trials; GOG-0218 and ICON7 had approximately 65% and 80% power (respectively) to detect a difference in OS between treatment arms.

In the GOG-0218 trial, the final analysis showed an increase in OS of 3.2 months between the two arms (CPB15+ OS: 43.8 months, CPP OS: 40.6 months), with a hazard ratio of 0.88 (95% CI: 0.75-1.04; p=0.0641. However, this could be interpreted as a bordering on a significant benefit, as the data may be confounded by post-progression crossover of approximately 40% of placebo patients to bevacizumab as a subsequent therapy.

OS results from the ICON7 trial are also immature and were calculated when approximately 25% of patients had died. However, cross-over post-progression was not permitted. An interim hazard ratio of 0.85 was reported for the ITT population (95% CI: 0.70-1.04) which suggests a potential benefit from CPB7.5+ treatment. Subgroup analysis of ‘high-risk’ patients in the ICON7 trial (stage III sub-optimal and stage IV debulked) exhibited an increase in OS of 7.8 months (CP: 28.8 months, CPB7.5+: 36.6 months, p<0.002, HR: 0.64; 95% CI: 0.48-0.85). This OS improvement reinforces the borderline significant benefit seen in a similar population in GOG-0218. The ICON7 OS hazard ratio represents a 36% reduction in the relative risk of death in ‘high-risk’ patients given bevacizumab in addition to chemotherapy. These results are of importance to the decision

problem as they represent significant efficacy in high-risk patients who have poor outcomes and limited treatment options.

In conclusion, both trials demonstrate clinically and statistically significant increases in PFS when patients with ovarian cancer receive prolonged bevacizumab and chemotherapy compared to chemotherapy alone. Subgroup analysis showed that 'high-risk' patients gained the greatest benefit from bevacizumab treatment. There were non-significant OS improvements in the ITT population of both trials, though data are currently immature. In the ICON7 trial, OS analysis demonstrated that patients with 'high-risk' disease have a significant increase in OS with the bevacizumab-containing treatment, compared to chemotherapy alone. This increase is of great importance as these patients have a very poor prognosis and limited treatment options.

6.9.1.5 Safety

In both the GOG-0218 and ICON7 trials, AEs were consistent with the known safety profile of bevacizumab and no new safety concerns were noted. Both trials showed similar trends in the incidence and type of AE reported.

Five of the most frequently reported AEs in both trials (alopecia, nausea, fatigue, constipation and arthralgia) are commonly associated with carboplatin and/or paclitaxel and are consistent with data described in studies evaluating this chemotherapy combination (du Bois et al. 2003;Ozols et al. 2003). These AEs were experienced in both treatment arms - predominantly during the 6 cycles of chemotherapy and arose much less frequently during bevacizumab maintenance therapy.

The most frequently reported AEs of special interest in both trials were bleeding, neutropenia and hypertension. The overall incidence of patients experiencing a grade 3-5 AE was higher in the bevacizumab-containing arms (GOG-0218 [CPB15+] = 55.4% and ICON7 = 64.6%) than in the control arms (GOG-0218 = 45.6%, ICON7 = 54.3%). The majority of grade 3-5 events in both trials arose when bevacizumab was administered in combination with chemotherapy and less frequently during the cycles when bevacizumab was administered alone, indicating that bevacizumab causes little increase in toxicity during maintenance therapy. Blood pressure is easily monitored and manageable with standard antihypertensive medications, so it occurs relatively infrequently at higher grades.

Deaths associated with treatment arose in 2.3% and 0.5% of patients in the bevacizumab-containing arms of the GOG-0218 and ICON7 trial and in 0.7% and 0.9% of patients in the chemotherapy arms of the GOG-0218 and ICON7 trial respectively. Grade 5 adverse events did not differ from the levels previously observed in other bevacizumab trials.

Overall, the safety data reported in these studies is consistent with the established safety profile of bevacizumab in other cancer indications. No new or unexpected AEs were observed.

6.9.2 **Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.**

6.9.2.1 Strengths

The GOG-0218 trial was a double-blind, randomised, controlled trial that was conducted in centers throughout the US, Canada and Asia. This patient population is genetically similar to the demographic in the UK. The ICON7 trial was conducted across Europe, with 46 centers and 375 patients enrolled in the UK.

Patients who have advanced ovarian cancer, particularly those with sub-optimally debulked stage III and stage IV disease, have a poor prognosis and few treatment options. The GOG-0218 and ICON7 trials represent two of the largest trials that have investigated a new biological agent in combination with the standard of care for advanced ovarian cancer. Patients in the ICON7 trial had all stages of disease, though the majority (82%) of patients exhibited advanced disease. All patients in GOG-0218 had advanced ovarian cancer, with 65% of patients presenting with stage III sub-optimally debulked or stage IV cancer.

Sensitivity analysis of the primary endpoint, PFS, was permitted in both trials. An independent review of PFS supported the investigator assessed results in the GOG-0218 trial, and exploratory subgroup analyses supported PFS and OS results in both trials.

Disease progression in the ICON7 trial was evaluated using RECIST criteria and global deterioration scores. CA-125 (which did not determine disease progression in ICON7), may yield false-positive or false-negative results. In the GOG-0218 trial, disease progression was assessed through an increase in CA-125 levels, as well as RECIST criteria and global clinical deterioration. The ICON7 data may therefore be seen as more

relevant, given the dominant role of clinical criteria, rather than CA-125, in determining progression.

6.9.2.2 Limitations

Many patients from the GOG-0218 trial were from the US, where bevacizumab is widely used to treat women with relapsed ovarian cancer. This may have confounded the OS data in the GOG-0218 trial as approximately 40% of patients received subsequent bevacizumab therapy.

ICON7 was an open-label trial with no placebo control. As this could have caused bias in disease progression and outcome reporting the Regulatory Authorities determined that GOG-0218 should form the backbone of the licence submission.

6.9.3 **Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.**

6.9.3.1 Relevance of clinical evidence to the decision problem

The evidence base reviewed in section 6 is relevant to the decision problem, which highlights the need for effective first-line treatment in patients with ovarian cancer, in particular, high-risk patients who have sub-optimally debulked stage III and stage IV disease. Two relevant, large randomised controlled trials have been reviewed, both of which examine the effects of first-line bevacizumab and standard UK chemotherapy (carboplatin and paclitaxel) versus standard chemotherapy alone. There are three main factors that are important to consider when assessing the relevance of the two trials to the decision problem.

The first factor is the dose of bevacizumab used for the treatment of ovarian cancer. The licenced dose of bevacizumab is 15mg/kg for 15 months used in the GOG-0218 trial. In the UK, 48 centers enrolled 375 patients to the ICON7 study. With considerable ICON7 trial practice in the UK, current prescribing habits and clinicians' intentions to prescribe are based upon the dose (7.5mg/kg) used in the latter study. The second factor to be considered is the patient population in the two trials. All patients in the GOG-0218 trial had stage III-IV ovarian cancer and for 65% of the patients this was disease carrying the highest risk of early relapse and death – i.e. sub-optimally debulked stage III or stage IV

cancer. Moreover, almost all the stage III optimally debulked patients in this study had visible residual tumour, resulting in a particularly poor prognosis ITT group. The ICON7 trial examined a wider patient population with 18% of patients having early stage (I or II) tumours and only 32% of patients with stage III suboptimally debulked or stage IV debulked disease. A pre-planned subgroup analysis of the ICON7 trial provided data for the 'high risk' population of Stage III suboptimal and Stage IV debulked disease. PFS and OS data from all patients in GOG-0218 and the patients with 'high-risk' disease in ICON7 were similar and allowed the benefits of bevacizumab to be investigated in patients who have the highest degree of unmet clinical need.

The third important factor to consider is the determination of disease progression. In the GOG-0218 trial, disease progression could be assigned solely according to assessments of CA-125 levels, whereas the ICON7 trial assessed disease progression through RECIST guidelines only. In the UK, the majority of physicians will use the RECIST criteria to evaluate tumour progression. Thus, the ICON7 data may be seen as a more relevant given the dominant role of clinical criteria, rather than CA-125 levels, in determining progression in UK clinical practice.

6.9.3.2 Relevance and validity of using PFS

The primary outcome of both trials was to evaluate PFS in the first-line treatment of patients with ovarian cancer, receiving bevacizumab and standard chemotherapy versus chemotherapy alone.

Cancer survivors whose disease recurs have a worse quality of life in most indices than those who remain disease-free (Helgeson & Tomich 2005) and the most important distress factor among cancer survivors is the fear of disease progression (Herschbach et al. 2004). Therefore, the major objective of each successive line of therapy is to induce and maintain disease remission for as long as possible.

Both trials met their primary endpoint of improving PFS with bevacizumab and chemotherapy compared to chemotherapy alone in the ITT population. However, PFS subgroup analysis was important to ensure that 'high-risk' patients (as outlined in the decision problem) were evaluated.

6.9.3.3 Relevance and validity of overall survival

An improvement in overall survival is the ultimate goal for therapy in patients with advanced cancer. In the ICON7 trial, which did not allow crossover of patients post-progression, subgroup analysis for patients who were stage III sub-optimally or stage IV debulked demonstrated a significant 7.8 month increase in median OS. This reinforces the smaller, but close to significant, benefit in OS seen in the GOG-0218 trial, where about 40% of placebo patients received bevacizumab in subsequent therapy. An increased OS of nearly 8 months has not been observed in the first-line treatment of ovarian cancer in many years.

6.9.4 **Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?**

6.9.4.1 The relevance of GOG-0218 and ICON7 to UK practice

The decision problem highlights the need for treatment in patients with advanced ovarian cancer. Both the GOG-0218 and ICON7 trials support the decision problem and show clear benefits of adding bevacizumab to the UK standard of care, paclitaxel and carboplatin. The following three factors demonstrate the validity of the trials in the UK.

Firstly, both RCTs examined a population of patients that have similar genetic characteristics to the UK. The ICON7 trial was particularly relevant as 375 UK patients were enrolled to the trial.

Secondly, the two trials investigated the addition of bevacizumab to the UK's standard of care for ovarian cancer patients. Currently, the UK guidance regarding the treatment of ovarian cancer is outlined by NICE TA55 that recommends paclitaxel with a platinum-based compound or platinum-based therapy alone (cisplatin or carboplatin) for first-line chemotherapy. It is estimated that 75% of women with ovarian cancer receive a paclitaxel/ platinum combination as first-line therapy (NICE 2003). GOG-0218 and ICON7 therefore reflect the principle UK prescribing habits for the treatment of first-line ovarian cancer.

6.9.4.2 The relevance of GOG-0218 and ICON7 to the Bevacizumab SPC

The bevacizumab licence recommends its use in patients with epithelial ovarian, primary peritoneal and fallopian tube carcinoma (stage IIIB-IV). The patients investigated in these studies had similarly located cancers, but not all patients had advanced cancer. In the ICON7 trial, 18% of patients had high-risk stage I and II cancer. However a pre-planned subgroup analysis of PFS in ICON7 patients who had grade III sub-optimally debulked and stage IV debulked cancer was conducted, i.e. a similar population to the patients outlined in bevacizumab's licence.

The bevacizumab licence recommends a dose of 15mg/kg, every three weeks for a total of 15 months, as in the GOG-0218 trial. The ICON7 study used a lower dose of bevacizumab (7.5mg/kg) for a shorter time period (a total of 12 months). ICON7 was however evaluated and assessed by the EMA when licencing bevacizumab for the treatment of OC and its data are included in section 5.1 of the bevacizumab SPC. Due to considerable ICON7 enrolment in the UK the Cancer Drugs Fund listings of all 10 English SHAs are for the 7.5mg/kg dose and so most UK patients are likely to receive bevacizumab at 7.5mg/kg for a total of 12 months for the first-line treatment of their ovarian cancer.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.

The search strategy was designed to retrieve all cost effectiveness publications and economic evaluations relating to bevacizumab (or Avastin) in Advanced or Metastatic Ovarian Cancer from a UK perspective. No limits were placed on publication types, study design or date. The following broad medical databases were searched, Embase (EMYY), Embase Alert, (EMBA), Medline (MEYY) as well as health economic databases, EconLIT and NHS EED. The methodology used was based upon on the methods outlined in the CRD's Guidance for undertaking reviews in health care (2008).

For details of how each of the databases were searched, please refer to **Error! Reference source not found.** in section 10.10, appendix 10. Full details of the search strategy are also detailed in section 10.10, appendix 10. An overview of the search is summarised below.

EMBASE/ EMBASE Alert / Medline

Searches used index and text words which included bevacizumab and ovarian cancer as major descriptors, and economic evaluation/cost-effectiveness terms as descriptors. The search was not restricted according to publication type or study design. The search was restricted to metastatic or advanced ovarian cancer. Only documents published in English were included.

NHS EED and ECONLIT

Searches used the economic evaluation terms of cost effectiveness, Markov model, cost benefit analysis, and keywords bevacizumab (Avastin) and advanced ovarian cancer. There were no restrictions by article type or date.

Method: Each title and abstract was assessed for relevance according to the pre-defined inclusion and exclusion criteria. These were:

1. Cost effectiveness terms are contained in the abstract? If No exclude
2. Disease is metastatic of advanced ovarian cancer? If No exclude
3. Intervention is bevacizumab? If No exclude

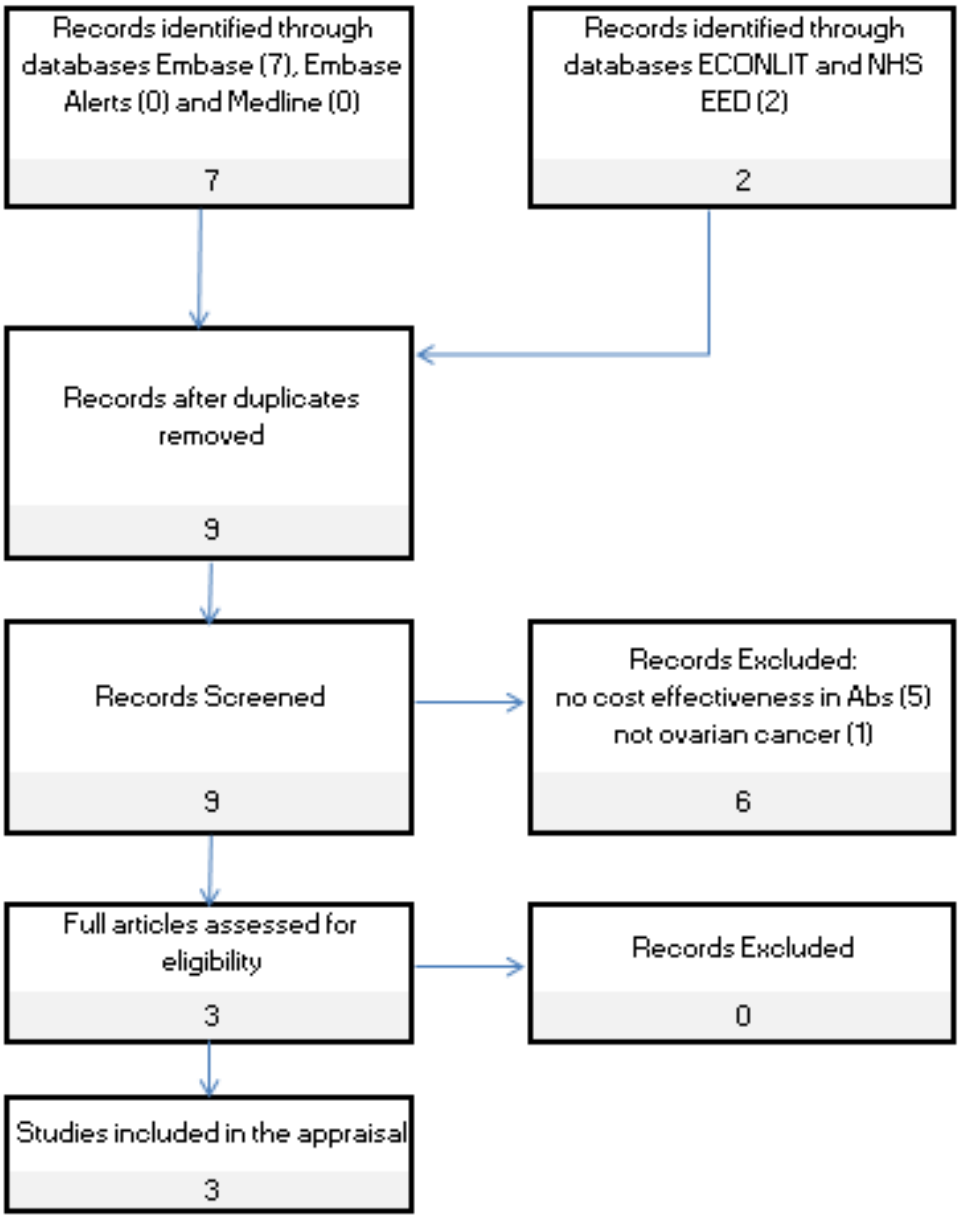
If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria in Table 34 below.

Table 34: Inclusion/exclusion criteria for Cost Effectiveness

INCLUSION	EXCLUSION
Intervention: Bevacizumab	
Disease: metastatic or advance ovarian cancer	Disease is not metastatic or advanced ovarian cancer
Abstract contains cost effectiveness terms: cost analysis, cost benefit, economic, direct cost, markov, decision analysis	contains no useful cost effectiveness data

Results: The search produced 9 results; see the PRISMA diagram Figure 14 for the full flow of documents and rationale for exclusions. From the 9 results, 5 were excluded as they did not include cost effectiveness terms in the abstract, 1 was excluded since it did not relate to ovarian cancer. The remaining 3 papers were found to be relevant and were retrieved and read in full.

Figure 14: PRISMA Flow showing economic studies identified through searching of the databases



Description of identified studies

7.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided.

3 studies were identified, as detailed in Figure 14. Refer to appendix 11 section 7.1 for the detailed quality assessment of these 3 studies

7.1.2.1 "At what cost does a potential survival advantage of Avastin make sense for the primary treatment of ovarian cancer? A cost effectiveness analysis" - David E Cohn et al. 2011

Aims: the USA based study aimed to determine if the addition of bevacizumab to paclitaxel and carboplatin for the primary treatment of advanced ovarian cancer is cost effective.

Methods: A cost effectiveness analysis compared three arms of the GOG-0218 study establishing actual and estimated cost of treatment plus the cost of complications for each arm. PFS and bowel perforation rates were taken from GOG-0218.

Results: Costs were estimated for the 600 patients in total on each arm. Costs and ICER per Progression Free Life Year Saved are show in Table 35. The conclusion of the study was that the addition of bevacizumab to standard chemotherapy in patients with advanced ovarian cancer is not cost effective. Bevacizumab maintenance leads to improved PFS but with increased direct and indirect costs.

Table 35: Base case results of cost effectiveness model

Treatment	PFS - months	Total Cost $	Cost Effectiveness Ratio $	ICER per PF-LYS $
PC	10.3	2.5M	247.6k	
PCB	11.2	21.4M	1.9M	479.7k
PCB + B	14.1	78.3M	5.6M	401.1k

7.1.2.2 "Consolidation paclitaxel is more cost effective than bevacizumab following upfront treatment of advanced epithelial ovarian cancer" Jamie L Lesnock et al. 2011

Aim: the USA based study evaluated the cost effectiveness of consolidation paclitaxel (P) and bevacizumab (B) following cytoreduction and adjuvant carboplatin(C)/paclitaxel (CP) for advanced ovarian cancer. Costs incorporated medication, administration, major complications and surveillance

Method: Based on GOG-0178 and GOG-0218. 3 arms were assessed.

Results: the costs, QALY's and ICER's can be found in Table 36. CPB +B was more costly and less effective than CP +P.

Table 36: Cost effectiveness ratios for CP+P and CPB+B compared to CP

Treatment	Cost $	Incremental Cost $	QALYs	ICER $
CP	18.9k		2.99	
CP + P	23.9k	4.9k	3.36	13.4k
CPB + B	122.9k	99.0k	3.31	326.5k

7.1.2.3 "Economic evaluation of bevacizumab for the treatment of advanced ovarian cancer in Mexico" D Lechuga et al. 2012

Aim: this Mexican based study aimed to evaluate if bevacizumab in first line treatment for advance ovarian cancer represents a cost effective strategy for health institutions in Mexico.

Method: A complete economic evaluation of ICON7 was completed for FIGO stage III and IV, high risk patients.

Results: Using 3 x GDP as a measure of willingness to pay (3 GDP $28.4k) BCP +B is cost effective with an ICER of $25.5k generating an increase in OS of 9.7 months. Table 37 shows the PFS, OS and ICER from the study.

Table 37: Results of evaluation of bevacizumab and standard chemotherapy plus maintenance in Mexico

Treatment	PFS – months	OS - months	ICER (USD)
CP	14.4	31.17	
BCP + B	16.77	40.89	25.5k

7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[1] or Philips et al. (2004)[2]. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

A full quality assessment for each of the 3 studies identified can be found in section 10.11, appendix 11.

[1] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.
[2] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

7.2 De novo analysis

Patients

7.2.1 What patient group(s) is (are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

Given the design of GOG-0218 (e.g. progression based on elevated CA-125 levels for some patients, confounding of OS due to use of bevacizumab after progression), it was felt that any economic evaluation based on this study would be technically challenging. Furthermore, the lack of UK patients in GOG-0218 would leave it open to criticism on the basis of a lack of relevance to the UK healthcare system. Because the ICON7 trial design incorporated a PFS measurement more commensurate with UK practice and did not permit cross-over, an economic evaluation based on the PFS and OS results observed in this study would not be associated with the same technical challenges as GOG-0218. Therefore we have chosen to develop and present a model based on results from the ICON7 trial in addition to a model based on data from GOG-0218. The differing definitions of ‘optimal’ debulking in the GOG-0218 and ICON7 trials mean that many of the optimally debulked Stage III patients from the ICON7 trial may lie outside the population recruited to GOG-0218, which defined the licensed indication. The economic model for ICON7 therefore covers only the patients from the pre-stratified groups 2 and 3 of ICON7, i.e. with stage III sub-optimally debulked or stage IV disease at randomization or patients for whom surgery was not appropriate (as reported in Table 4 in section 6.3.1 and described further in section 6.3.3).

7.2.1.1 GOG-0218

The model based on the GOG-0218 study uses survival, safety and dosing data from the ITT population and is fully within the limits of the marketing authorization.

7.2.1.2 ICON7

An economic evaluation was conducted on an expanded 'high risk' subgroup of the ICON7 study, including all patients with FIGO stage III disease and sub-optimal debulking, FIGO stage IV disease or patients whose tumour was unresectable. The outcomes of this subgroup are presented in table 16 of the Summary of Product Characteristics (Roche Products Ltd 2012) submitted to the EMA and subsequently updated on 3rd May 2012 and is a subset of 2 pre-stratified subgroups in ICON7. In ICON7 stratum 1 included patients with Stage I-III and less than 1 cm residual disease after debulking surgery, stratum 2 was patients with Stage I-III with more than 1 cm residual disease and stratum 3 included all inoperable patients and those with Stage IV disease (see section 6.5.3.9, page 91) for published clinical outcomes associated with these strata).

Table 38: Composition of 3 pre-specified subgroups in the ICON7 trial

	Stratum 1	Stratum 2	Stratum 3	Total
ITT	1026	290	212	1528
Unlicenced (Stage I-IIIa)	325	10	1	336
Licenced (Stage IIIb-IV)	701	280	211	1192
High Risk cohort (MRC defined)	-	280	182	462
High Risk cohort (expanded) – focus of this economic model	-	283	212	495

As Table 38 shows, this 'expanded high risk cohort' includes 33 additional patients from stratum 3 over and above the MRC-defined 'high-risk' cohort. The latter excluded unresected patients from stratum 3.

It should be noted that this subgroup includes patients outside the license in as much as there were 3 patients recruited to ICON7 who were diagnosed with Stage IIIa disease who are included in strata 2 and 1 patient in strata 3. Since these patients represent less than 1% of this subgroup, it is unlikely to have a significant effect on clinical outcomes.

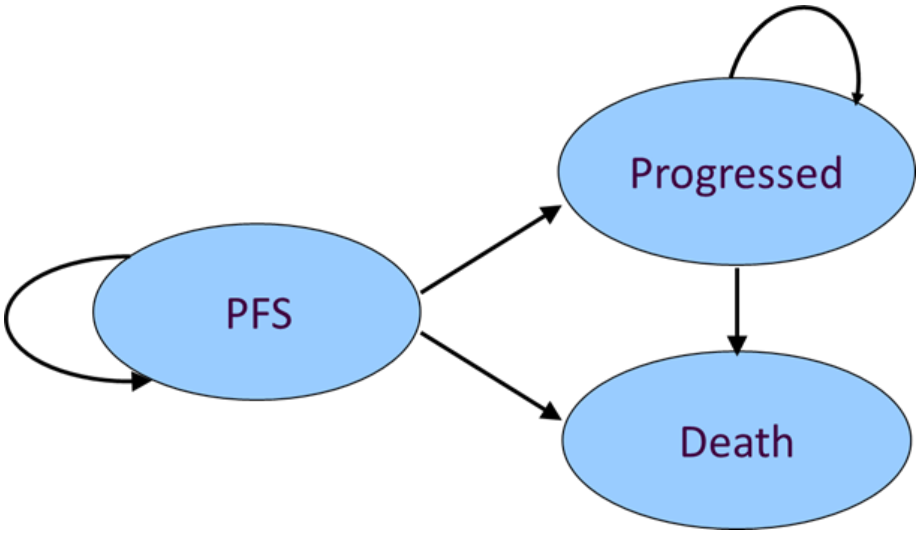
There are a number of reasons why we believe a model based on the ICON7 study is justified in this submission despite the fact that the dose of bevacizumab used is lower than that recommended in its license. Firstly, in GOG-0218 progression could be determined based solely on a rising CA-125. The regulatory analysis of this study required censoring of CA-125-only progression events, which occurred in approximately a quarter of patients overall and as a consequence the study analysis is not complete. The PFS analysis in ICON7 used only RECIST or clinical evidence of progression and this is the method generally used in UK clinical practice. Secondly, the design of ICON7 did not allow patients to receive bevacizumab after progression, in contrast to GOG-0218 where

estimates of overall survival benefit are difficult to make because of substantial use of bevacizumab by patients in both study and control arms in subsequent lines of therapy. Thirdly, the ICON7 study was conceived, designed and run from the UK where a quarter of patients were recruited, compared to GOG-0218 which recruited exclusively from USA, Canada and Asia. Fourthly, the study design incorporated the collection of robust quality of life data using validated tools including EQ-5D which can be directly applied to UK patients. Finally, 48 of the key centres of excellence in ovarian cancer care in the UK participated in ICON7 and so there is already significant experience in using bevacizumab at this dose and setting.

Model structure

7.2.2 Please provide a diagrammatical representation of the model you have chosen.

Figure 15: Model schema



The base case time horizon for both models is 10 years and costs and outcomes were discounted at 3.5% per annum (Table 39). The perspective of the model is the UK National Health Service and the primary outcome of the model is an incremental cost effectiveness ratio (ICER).

7.2.2.1 GOG-0218

The model is a 3-state semi-Markov model with health states consisting of PFS, Progression and Death (Figure 15). A Markov model was chosen primarily due to the confounding of OS as a consequence of the large proportion of patients randomized to the

chemotherapy alone group who later received bevacizumab following their initial disease progression (approximately 27.7%). As a consequence, the analysis was simplified by assuming a similar rate of death post-progression in both arms.

Initial analyses on the primary endpoint of the GOG-218 clinical trial were conducted using a snapshot taken on 29 September 2009. The current model was based on the more recent snapshots for both PFS (25 February 2010) and OS (5 February 2010). The updated PFS analysis used in the model was specified within the statistical analysis plan and included censoring for patients who were presumed to experience progression based on CA-125 levels or switching to non-protocol therapies.

7.2.2.2 ICON7

A 3-state, Area-Under-the-Curve model, (Figure 15) founded on the PFS and OS endpoints of the ICON7 study, was constructed in Microsoft Excel. All patients enter the model in the Progression-free survival (PFS) health state and in each weekly cycle can either progress to a worse health state (i.e. from PFS to a progressed disease state (PD) or Death, or from PD to Death), or remain in the current health state. Death is an absorbing health state within the model. The model was developed using patient-level data from the 30 November 2010 clinical cut-off date which corresponded to a median follow-up period of 23.98 months (within the defined subgroup) and 25% of patients had died.

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

The model structure is fully aligned with two of the primary objectives of treatment in advanced ovarian cancer; namely:

- Prolonging life
- Delaying disease progression

This model structure and the health states utilised are typical of modelling in metastatic oncology and have been utilised in numerous NICE appraisals including those specifically in advanced ovarian cancer (Papaioannou et al. 2010).

7.2.4 Please define what the health states in the model are meant to capture.

The health states used in the models are those typically used in the modelling of advanced cancer. The PFS health state is designed to capture an advanced OC patient’s relatively

high ‘quality of life period’ prior to their disease progression. The PD state is designed to capture the relatively poor ‘quality of life phase’ following disease progression/relapse.

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The models presented are both 3-state models of the kind typically used in the modelling of advanced or metastatic cancer. As noted previously this structure captures both the length and quality of a patient’s life via the dichotomisation of a patient’s time alive into a relatively high quality of life pre-progression phase and a lower quality of life post-progression phase.

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table 39: Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	10 years	Limits of reliable estimates of long-term survival in target cohort	(du Bois A. et al. 2009)
Cycle length	1 week	To facilitate simple calculation of costs and outcomes as per the reference case given the treatment cycle of 3 weeks in this indication.	(NICE 2008)
Half-cycle correction	Yes	As per NICE guide to methods.	(NICE 2008)
Were health effects measured in QALYs; if not, what was used?			
Discount of 3.5% for utilities and costs			
Perspective (NHS/PSS)			
NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years			

Technology

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and

1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

7.2.7.1 GOG-0218

Both intervention (bevacizumab in combination with carboplatin + paclitaxel) and comparators (carboplatin + paclitaxel) are implemented in the model according to their marketing authorisations.

7.2.7.2 ICON7

Bevacizumab at 7.5 mg/kg (intravenous infusion) every 3 weeks until disease progression or for a maximum of 12 months or unacceptable toxicity (whichever occurs first) in combination with carboplatin (AUC 5 or 6) and paclitaxel (175 mg/m^2) administered as intravenous infusions both every 3 weeks for 6 cycles. Although this dose differs from the marketing authorisation for bevacizumab in this indication, which recommends a dose of 15mg/kg for up to 15 months, data from the ICON7 trial, which used this reduced dosing regimen, was presented as supportive evidence in the marketing authorisation application (Roche Products Ltd 2012).

The comparator in this model is the combination chemotherapy regimen of Carboplatin (AUC 6) and paclitaxel (175 mg/m^2) administered as intravenous infusion both every 3 weeks for 6 cycles.

It should be noted that this is more restrictive than the trial protocol which allowed for a target AUC of 5 or 6 mg/ml/min and was chosen to be more conservative and represents a simpler costing assumption (given that more total chemotherapy cycles were administered in the bevacizumab arm).

7.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).

- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

N/A

7.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 6). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

7.3.1 Please demonstrate how the clinical data were implemented into the model.

7.3.1.1 PFS

GOG-0218

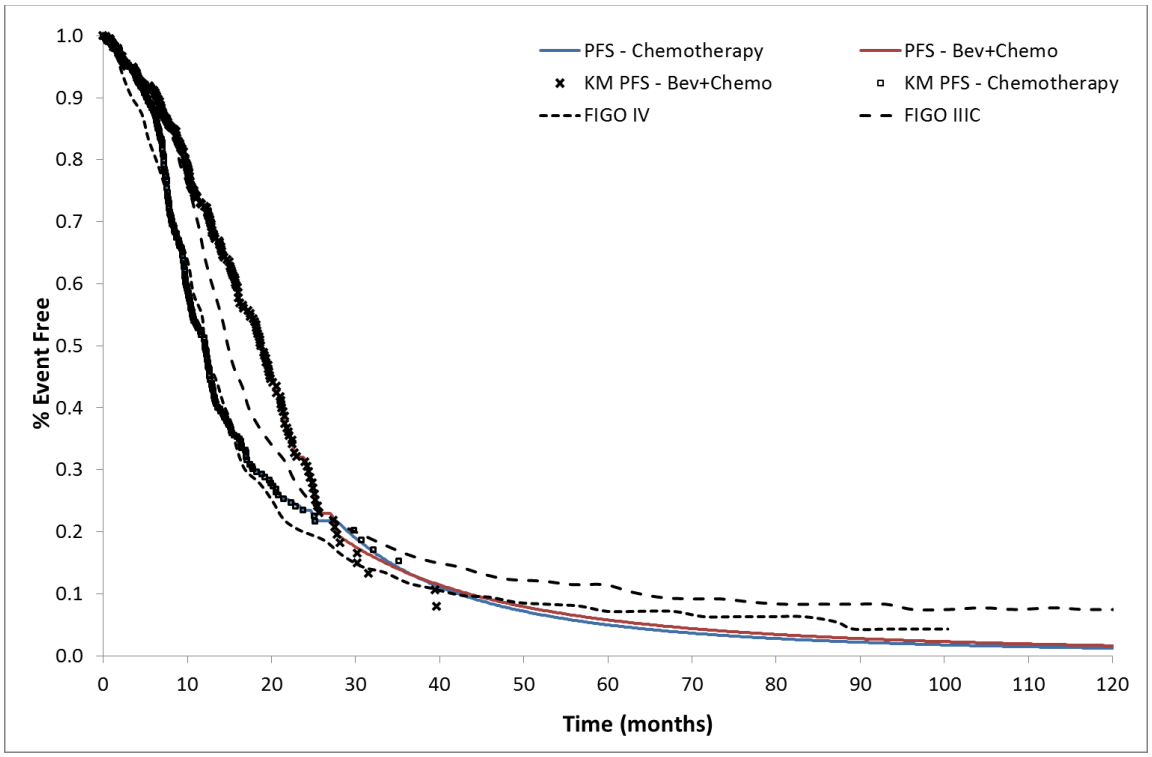
In order to extrapolate survival times beyond the point of clinical follow up in the clinical trial (until all patients have left the PFS health state), it is required to fit a parametric survival function of observed time to disease progression. Summary of the goodness of fit statistics for PFS are summarized in Table 40.

Table 40: Summary of Parametric Functions' Goodness of Fit for PFS in GOG-0218

	Bevacizumab + Carboplatin + Paclitaxel Treatment Arm		**Carboplatin + Paclitaxel Treatment Arm**	
Parametric Model (PFS)	**AIC**	**BIC**	**AIC**	**BIC**
Gamma	**996.784**	1010.087	1184.515	1197.829
Weibull	998.710	1012.014	1200.515	1213.828
Log Logistic	1014.630	1023.499	**1159.495**	1168.370
Log Normal	1048.715	1057.584	1209.981	1218.856
Exponential	1073.102	1077.536	1269.764	1274.201

For the Bevacizumab plus chemotherapy treatment arm, the gamma parametric function was determined to be the best fit, with the Weibull function as second best. Conversely, for the chemotherapy alone arm, the Log Logistic function was the best fit, with the Gamma function as second best. However, in order to eliminate uncertainty associated with choosing different parametric forms, it is common to choose the same type of parametric function when making comparisons. Based on visual inspection and comparison with published PFS curves for patients with similar characteristics (du Bois A. et al. 2009), it was determined that Kaplan Meier data from GOG-0218 should be used until convergence at 28 months followed by extrapolation using a Log Logistic parametric function (Figure 16).

Figure 16: PFS observations from GOG-0218 and Log Logistic extrapolation (from 28 months) compared to published survival curves for comparable patients (du Bois A. et al. 2009)



ICON7

Similar to the approach taken for GOG-218 modelling described above, the proportion of patients remaining in the PFS state for the first 24 months of the model is calculated directly from the Kaplan-Meier survival curves for bevacizumab + carboplatin/paclitaxel

and carboplatin/paclitaxel arms of the ICON7 trial. This data reflected a median PFS gain of 5.68 months, HR=0.70 (95% CI: 0.577 – 0.851) (Roche Products Ltd 2012).

Extrapolation beyond the clinical follow-up period was performed by fitting a parametric distribution to the PFS times observed within the clinical trial period of the ICON7 trial. Parametric functions were assessed for their goodness of fit to the data using Akaike (AIC) and Bayesian Information Criteria (BIC) and graphical assessment of each function (Table 41).The available parametric functions were derived using the PROC LIFEREG procedure in SAS v9.2.

Table 41: Summary of Parametric Functions' Goodness of Fit for PFS in ICON7

Parametric Model (PFS)	AIC	BIC
Log Logistic	**1020.179**	1032.793
Gamma	1039.941	1056.759
Weibull	1054.547	1071.365
Log Normal	1070.038	1082.652
Exponential	1192.686	1201.095
Gompertz	1534.009	1546.623

None of the parametric functions provided a satisfactory fit to the data and therefore it was determined that Kaplan Meier data from ICON7 should be used until convergence at 24 months followed by extrapolation using a Log Logistic parametric function. Table 42 summarizes the parameter estimates used to calculate PFS with the Log Logistic distribution after 24 months.

Table 42: Table of parameter estimates (PFS – Log Logistic)

Efficacy Endpoint	Lambda (λ)	Gamma (γ)
Chemotherapy Alone	0.00214	2.56484
Bevacizumab + Chemotherapy	0.00094	2.56484

7.3.1.2 OS

GOG-0218

After disease progression, patients leave the "PFS" health state and enter the "Post-Progression Survival" health state. Using patients' time from disease progression to death (or censoring), from the GOG-218 trial, the probability of post-progression death was generated. It was assumed that the probability of death following progression was constant (the same probability of death regardless of how long since the patients' progression) and

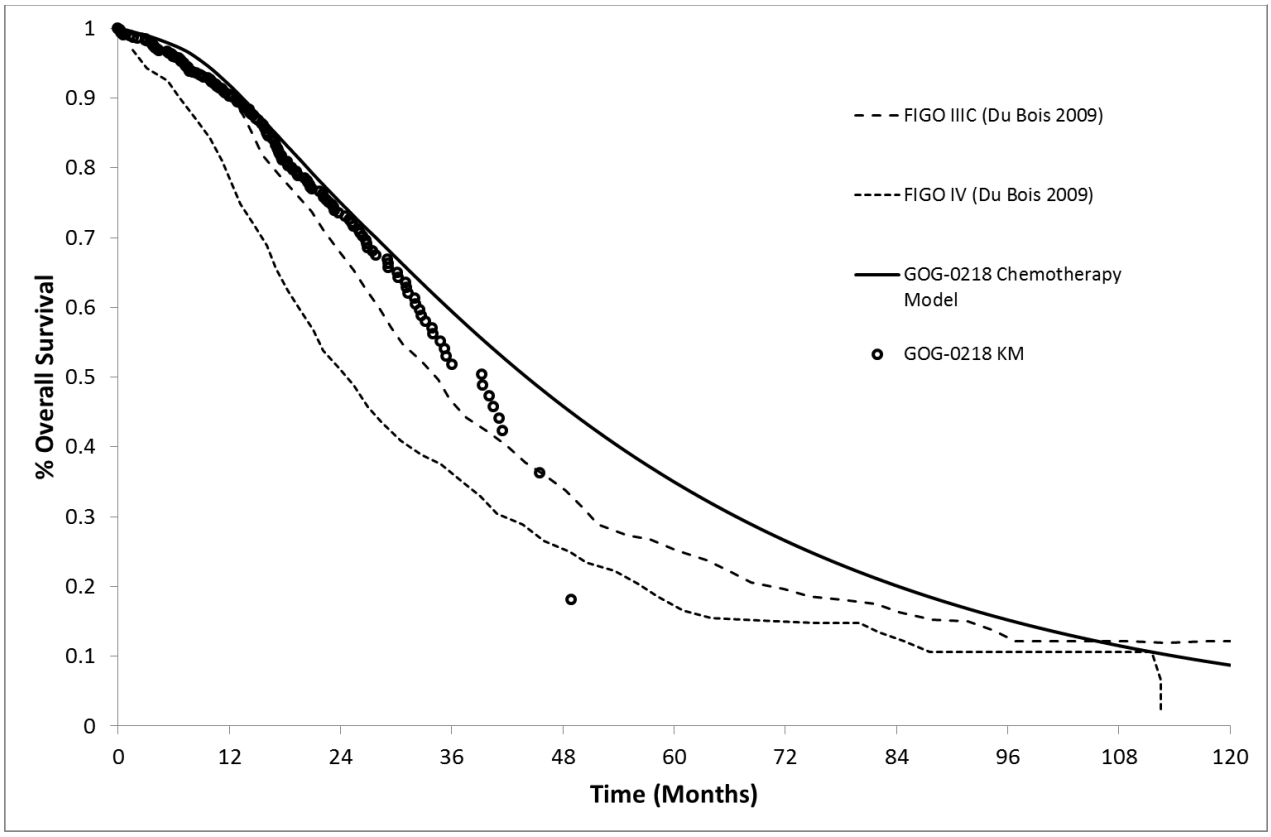
therefore the hazard was fit to an exponential distribution. Parameter estimates and weekly post-progression mortality rates are summarized in Table 43. Sensitivity analysis explored the impact of treatment arm-specific post-progression mortality rates.

Table 43 Table of parameter estimates (PPS)

	Bevacizumab + Carboplatin + Paclitaxel Treatment Arm	Carboplatin + Paclitaxel Treatment Arm	Combined Population
Weekly Probability of death	0.00600	0.00598	0.00599

The overall survival predicted by these parameter settings was compared to estimates from an external source using ovarian cancer patients with similar disease severity and surgical outcome (for more details, please see page 140). The effect of using the post-progression survival parameter curve is to over-estimate survival of patients receiving chemotherapy after approximately 30 months (Figure 17).

Figure 17: Overall survival of patients receiving chemotherapy in the GOG-0218 study compared to external sources (du Bois A. et al. 2009)



ICON7

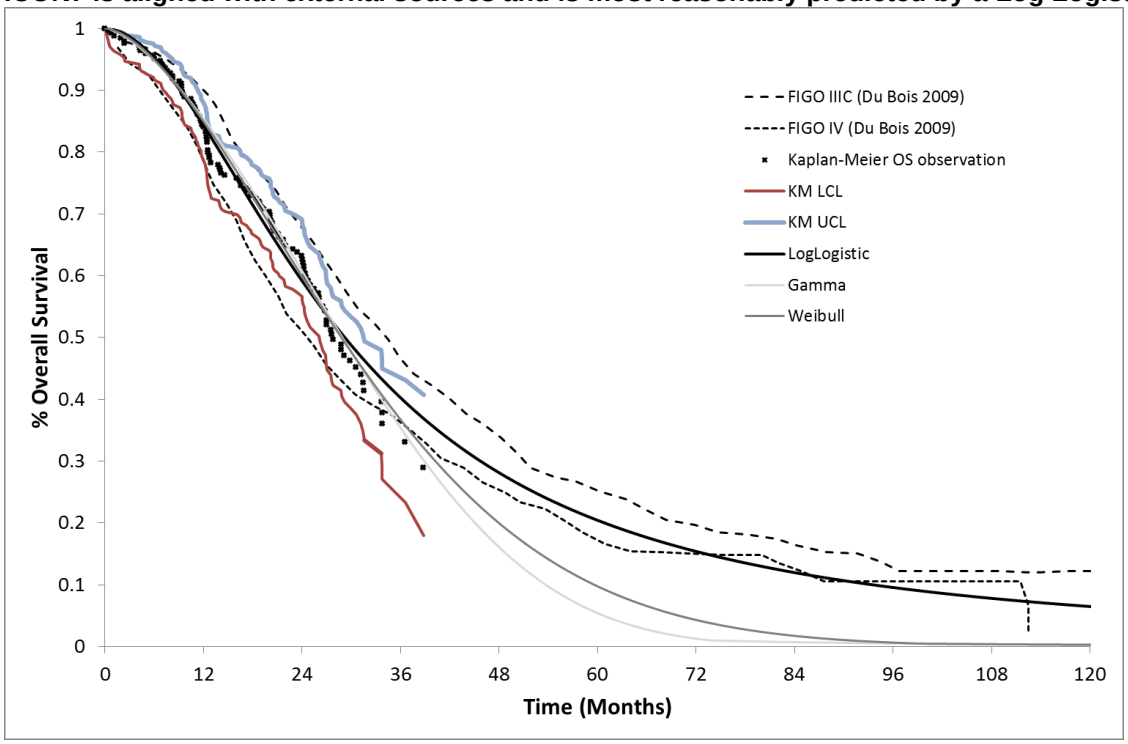
Similar to the method of survival analysis used to model PFS times, a parametric function was fitted to OS times to calculate survival estimates beyond the clinical trial period. Goodness of fit statistics for the OS function are listed in Table 44 which suggest that the Gamma function provided the best fit to the observed survival times.

Table 44: Summary of Parametric Functions' Goodness of Fit for OS

Parametric Model (PFS)	AIC	BIC
Gamma	**898.357**	915.175
Weibull	899.444	916.263
Log Logistic	903.262	915.875
Log Normal	929.924	941.537
Exponential	948.180	956.589
Gompertz	1001.745	1014.359

However, leading ovarian cancer clinicians consulted in the development of this model have suggested that a small but significant percentage of Stage III and IV patients (typically 5-10%) experience long term survival (in excess of 10 years). These verbatim opinions are in accord with a number of articles in the literature which record the survival of Stage III and IV patients and those who have residual disease after surgical debulking (du Bois A. et al. 2009;Heintz et al. 2006). Data from one of these references (du Bois A. et al. 2009) are plotted in Figure 18 and it appears that a Log Logistic function provides the best fit to these observed long-term patient survival data and is used in the base case analysis. The gamma and Weibull distributions are used in a one-way sensitivity analysis (see section 7.6.2).

Figure 18: Overall survival of patients receiving chemotherapy after sub-optimal debulking surgery in ICON7 is aligned with external sources and is most reasonably predicted by a Log Logistic function



NOTE: The Gamma and Weibull curves are also shown (light grey and grey, respectively) for comparison as alternative functions for overall survival according to statistical analysis of goodness of fit described in Table 44.

Table 45: Parameter values (and standard errors) for the Log Logistic functions predicting OS of patients in ICON7

Parameter	Value	S.E.
Intercept	3.67213536	0.07549945
Placebo	-0.29777142	0.09505761
Scale	0.52942336	0.03261643

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Transition probabilities were not used within the models with the proportion of patients in each health state determined directly via observations or parametric fitting of survival curves from the relevant studies.

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

N/A

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

No surrogate or intermediate outcomes were used to derive final clinical outcomes. Both PFS and OS are clinically relevant outcomes that are highly relevant to a patient's length and quality of life.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[3]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

As noted in section 20.3.1.2., clinical expert opinion was sought on appropriate sources to describe baseline survival for advanced ovarian cancer patients.

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission.

Table B2 Summary of variables applied in the economic model

Variable	Value	Measure of variance (distribution)	Reference to section in submission
Patient characteristics		**SD (Log Normal)**	
Age	56.34	N/A	Section 7.5.5
Weight	60.49	13.08	
Height	161.87	N/A	
BSA	1.71	0.1802	
Utilities		**SE (Beta)**	
PFS			
Weeks 0-2	0.6571	0.0133	Section 7.4.3
Weeks 3-5	0.7153	0.0118	
Weeks 6-8	0.7443	0.011	
Weeks 9-11	0.7683	0.01	
Weeks 12-14	0.7643	0.0112	
Weeks 15-20	0.7444	0.0121	
Weeks 21-26	0.7638	0.0131	
Weeks 27-32	0.7718	0.0129	
Weeks 33-38	0.7638	0.0136	
Weeks 29-44	0.7785	0.0155	
Weeks 45-50	0.7533	0.0165	
Weeks 51-53	0.776	0.017	
Weeks 54 +	0.8129	0.0113	
PD	0.7248	-	
Costs		**(Gamma)**	
Expected cost of bevacizumab per visit			
GOG-0218	£2,229.41	N/A	Section 7.5.5
ICON7	£1,176.83	N/A	
Expected cost of carboplatin per visit	£18.51	N/A	
Expected cost of paclitaxel per visit	£21.80	N/A	
First visit administration and pharmacy costs	£274.57	upper and lower quartiles from NHS Reference costs	Section 7.5.5.5 and 7.5.5.6
Subsequent visit administration and pharmacy costs	£94.27	upper and lower quartiles from NHS Reference costs	

Weekly Supportive Care Costs (£)			
PFS (£)	£10.31	+/- 10%	Section 7.5.6
PD (£)	£44.10	+/- 10%	
Cost of post progression therapies (£)			
Chemotherapy arm (ICON7 only)	£3,642.84	N/A	Section 7.5.8.1
Bevacizumab arm (ICON7 only)	£2,958.23	N/A	
Palliative care	£6,726.53	N/A	Section 7.5.8.2

7.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

See response to Section 7.3.1 (p135-140).

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

- It was assumed that the outcomes (PFS, OS, AEs) and treatment durations observed in GOG-0218 and ICON7 would hold in clinical practice.
- The base case assumed that outcomes from GOG-0218 and ICON7 would hold for a UK-specific cohort of patients with distinct baseline characteristics which affect the amount of drugs (both bevacizumab and chemotherapy agents) administered in each treatment cycle.
- The base case models assumed that no vial sharing was permitted for patients receiving bevacizumab, although this was tested in the sensitivity analysis.
- Adverse events requiring treatment were assumed to occur in the first week of the model.

- The base case models assumed that the observed increases in reported utility over time spent in PFS during the ICON7 study were applicable to the UK patient population as a whole.

- The base case models assumed that costs of disease management in progression-free and progressed disease states were similar to those described in a previous appraisal of ovarian cancer (Papaioannou et al. 2010).

7.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Cancer survivors whose disease recurs have a worse HRQoL in most indices than those who remain disease-free (Helgeson et al. 2005) and the factor causing most distress among cancer patients (and therefore impacting on HRQoL) has been found to be the fear of disease progression (Herschbach et al. 2004).

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

Health-related quality of life is expected to decrease with each line of treatment failure due to disease progression.

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the

reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

The protocol design for ICON7 included measurement of patients' HRQoL through EQ-5D. Given the overlap of patient recruitment in GOG-0218 and ICON7, the results from EQ-5D are used in the economic models for both studies.

The first QoL assessment using EQ-5D in ICON7 was completed during the screening visit, then at the onset of every chemotherapy cycle (i.e. every 3 weeks) until the end of chemotherapy and then every 6 weeks until the end of the first year. Subsequent measurements were taken every 3 months until progression or to the end of year 2 (whichever happened first). HRQoL was also measured on day 1 of the first cycle of chemotherapy at first relapse, and in the cohort at three years from randomisation.

7.4.3.1 PFS

A log-rank test confirmed that there was no difference in utility values whilst patients were progression-free across the intervention and control arms, therefore it was assumed that utility estimates from both treatment arms at each time-point could be combined. Furthermore, a trend test suggested that utility values did change over time, so this effect was included in the model. The literature, as well as clinical expert opinion, validates this assumption because it is not uncommon for patients' quality of life to improve over time following an initial diagnosis as they become more able to cope with the symptoms of the disease, the effects of chemotherapy and other treatments become more apparent to her and the fear of disease progression or recurrence lessens.

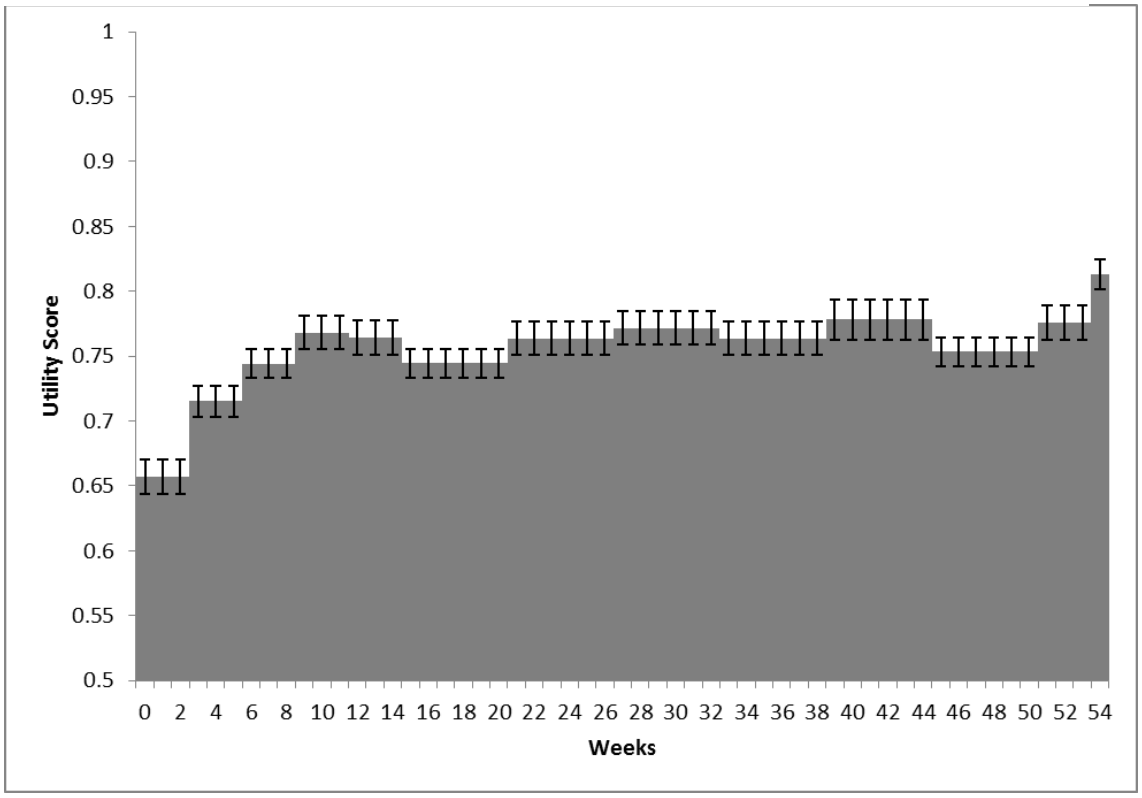
Table 46: Utility estimates for patients remaining in PFS

Weeks	Number of respondents	Mean score	Standard error
0-2	335	0.6571	0.0133
3-5	378	0.7153	0.0118
6-8	375	0.7443	0.0110
9-11	361	0.7683	0.0100

12-14	363	0.7643	0.0112
15-20	353	0.7444	0.0121
21-26	303	0.7638	0.0131
27-32	295	0.7718	0.0129
33-38	282	0.7638	0.0136
29-44	220	0.7785	0.0155
45-50	202	0.7533	0.0165
51-53	178	0.7760	0.0170
54 +	338	0.8129	0.0113

Thus, patients remaining in PFS in the first 3 weeks of the model are assumed to have a utility of 0.6571 in each of those weeks. In weeks 3, 4 and 5, the utility of patients in PFS increases to 0.7153 (Table 46 and Figure 19).

Figure 19: Utility estimates (and SE) for progression-free patients in the ICON-7 trial



7.4.3.2 Progressed Disease

The paucity of data from ICON7 available to estimate time-dependent utility for patients in the progressed disease health state has resulted in the calculation of a point estimate of utility which will apply for the entirety of the time spent in that health state. In ICON7, QoL data was not routinely available for patients whose disease had progressed, and the mean utility was 0.7248. Although this data point is based on relatively few observations, it is comparable to utility data available from the trabectedin trial which studied a progressed (2nd line/refractory) patient population with metastatic ovarian cancer (mean utility of

relapsed patients with stable disease = 0.718 (95% CI, 0.699-0.737) (Papaioannou et al. 2010). This may be conservative as the patient population described by the 2nd line trabectedin refractory trial, as a whole, may be considered to have more severe disease than the whole of the population that relapse following treatment with bevaciziumab in the ICON7 study.

Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

N/A

HRQL studies

7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

The search strategy was designed to retrieve utility values for different health states in advanced or metastatic ovarian cancer. No limits were placed on publication types, study design or date. Only publications in English were included in the search. The following broad medical data bases were searched Embase (EMYY), Embase Alert (EMBA), Medline (MEYY), as well as health economic databases NHS EED and ECONLIT. The methodology used was based upon on the methods outlined in the CRD‘s Guidance for undertaking reviews in health care (2008).

For details of how each of the databases were searched, please refer to **Error! Reference source not found.** in section 10.10, appendix 10. Full details of the search strategy are detailed in section 10.12 appendix 12.

An overview of the search is summarised below.

EMBASE/ EMBASE Alert / Medline

Searches used index and text words that included quality of life and utility terms such as EQ-5D, SF-36, quality adjusted life year, time trade off, standard gamble. The search also included disease descriptors including ovarian cancer, metastatic and advanced.

NHS EED and ECONLIT

Searches used the economic terms QALY, EQ-5D, SF-36, SF12, Utility value, utility score, time trade off, standard gamble and keywords ovarian cancer or ovarian carcinoma

Method: The title and abstract for each search result were assessed for relevance according to the pre-defined inclusion and exclusion criteria, which were:

1. Does the abstract mention one or more utility terms (Quality of Life, HRQoL, Utility Values, or Utility Scores) If NO – Exclude

2. Is the disease area metastatic or advanced ovarian cancer? If No – Exclude

If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria in Table 47 below.

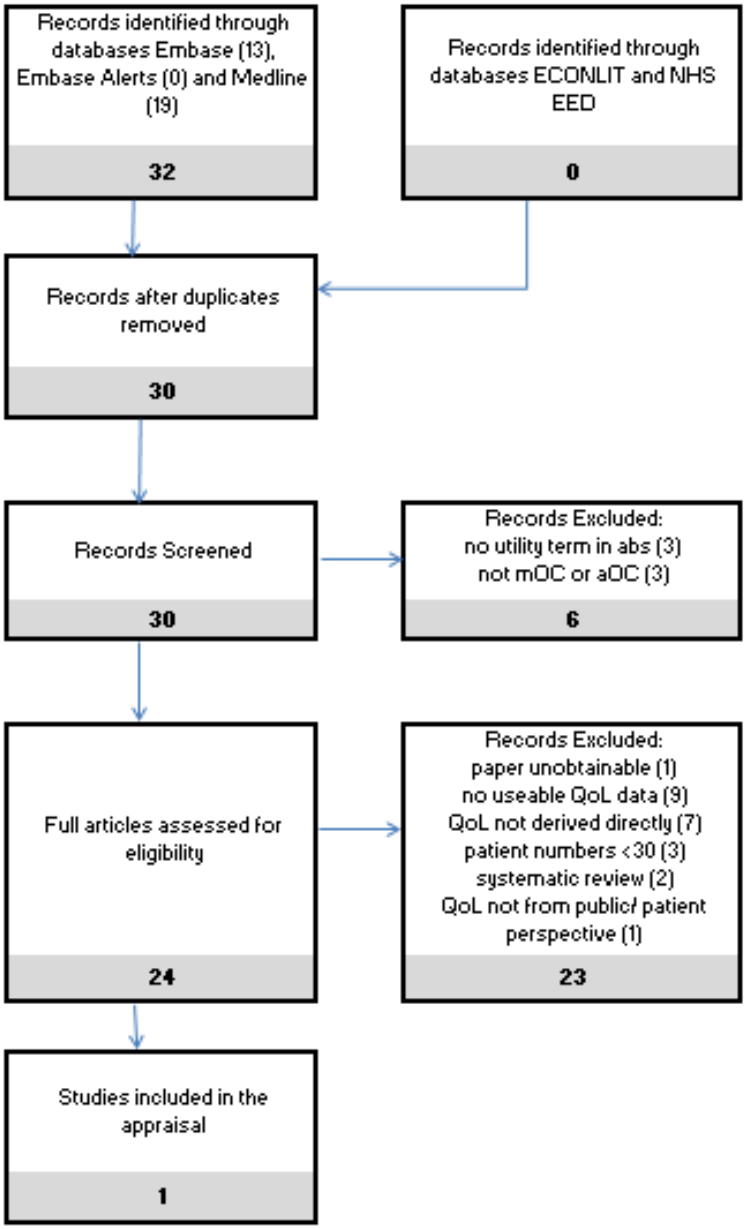
Table 47: Inclusion/ Exclusion criteria for health effects

INCLUSION	EXCLUSION
Utility term included in the abstract (HRQoL, QoL, Utility Values, Utility Scores)	No useable utlility or HRQoL values
Utilities are derived directly	Not QoL study
Time trade off or Standard gamble	Utility not from the patient or general public perspective
	Less than 30 patients
Disease is metastatic or advanced Ovarian Cancer	Disease is not metastatic or advanced Ovarian Cancer
	literature review

Results: In total 32 individual records were identified via the five databases, 2 of these were duplicates. At initial screening of the abstract and title 6 studies were excluded .The PRISMA diagram Figure 20 shows the document selection and rationale for these

exclusions. 24 records were deemed potentially relevant. These 24 results were then retrieved and assessed more comprehensively against the inclusion/exclusion criteria, 3 were found to be relevant.

Figure 20: PRISMA flow showing health effect studies selected though database search



7.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.

- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis

Table 48 provides a summary of the 1 paper found to be appropriate.

Table 48: Summary of K Stein et al 2007

	K Stein et al. 2007
Population in which health effects were measured	Advanced ovarian cancer patients on chemotherapy.
Information on recruitment	Patients had participated in a randomised control trialof routine quality of life measurement
Interventions and comparators	Not reported
Sample size	66 women receiving chemotherapy for ovarian cancer
Response rates	Not reported
Description of health states	6 health states were developed from the distribution of EORTC QLQ-C30 item scores Cluster 1 - performance status good, overall few limitations - responses above average for study population Cluster 2 - physical function worse than average. Average age older than Cluster 1, more metastatic disease, more PS=2 Cluster 3 - symptoms worse than mean except physical function which is above average. Younger than average. Cluster 4 - high degree of fatigue, limitation of physical role and social functioning. Lower impact of emotional and cognitive function. Average age close to the mean Cluster 5 - higher levels of fatigue, relatively severe sleep disturbance and high levels of emotional and cognitive symptoms. Physical function is relatively less severely impaired.GI disturbance is worse than average. Younger age, better performance status. Disproportionately affected by psychological aspects of the disease. Cluster 6 - high levels of physical role and social impairment.

	Emotional and cognitive function worse than all other clusters. Average age over than overall mean. Less impact on sleep, psychological symptoms and cognition than cluster 5.
Adverse Events	N/A
Appropriateness of health states given condition and treatment pathway	Health states were derived from EORTC QLQ-30 (a validated measure of QoL in ovarian cancer) questionnaires completed by the 66 patients at each outpatient attendance over a 6 month period. The health states were created using principle components analysis and k means clustering to identify coherent subgroups within the data to ensure each health state was statistically and medically distinct.
Method of elicitation	preferences elicited using standard gamble technique from 39 members of the Value of Health Panel (VHP)
Method of valuation	Health state descriptions presented to a group of 39 members of the VHP and standard gamble carried out using the titration approach. The utility values from the standard gamble exercise were then compared against EORTC QLQ-C30 global health status scores for each health state.
Mapping	N/A
Uncertainty around values	Patient data only gathered over a 6 month period. Members of the public from VHP who provided the utility estimates for the 6 heath states were not representative of the UK general population in socio economic status and ethnicity.
Consistency with reference case	EQ-5D has not been used
Results with confidence intervals	Mean utilities / Global QoL domain score Cluster 1 0.97 78.12 Cluster 2 0.93 67.10 Cluster 3 0.886 56.53 Cluster 4 0.817 49.43 Cluster 5 0.788 46.10 Cluster 6 0.694 30.31 confidence interval data not reported
Appropriateness for cost effective analysis	This study used a disease specific QoL measure (EORTC QLQ-C30) to validate a standard gamble exercise from the public perspective. The utility values have not been mapped to EQ-5D

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Comparison of the utility estimates from the paper identified from the literature search and the values calculated from responses of patients in the ICON7 study is not possible due to differences in methodology and techniques used.

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

Serious adverse events are expected to result in either a short or long term detriment to health-related quality of life. Since EQ-5D was administered to patients at regular intervals before disease progression, it is expected that any impact on HRQoL by an adverse event has been captured and is reflected in the overall utility score.

Quality-of-life data used in cost-effectiveness analysis

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

Table B3 Summary of quality-of-life values for cost-effectiveness analysis

State	Utility value	Standard error	Reference in submission	Justification
PFS			Section 7.4.3.1 (Table 46)	NICE Reference case
Weeks 0-2	0.6571	0.0133		
3-5	0.7153	0.0118		
6-8	0.7443	0.0110		
9-11	0.7683	0.0100		
12-14	0.7643	0.0112		
15-20	0.7444	0.0121		
21-26	0.7638	0.0131		
27-32	0.7718	0.0129		
33-38	0.7638	0.0136		
29-44	0.7785	0.0155		
45-50	0.7533	0.0165		
51-53	0.7760	0.0170		
54 +	0.8129	0.0113		
PD	0.7248	-	Section 7.4.3.2	

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

N/A

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

Please see Table 46 and Figure 19 in Section 7.4.3 for details of how utility estimates for patients in the PFS health state change over time.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

N/A

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

N/A

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

Please see Table 46 and Figure 19 in Section 7.4.3 for details of how utility estimates for patients in the PFS health state change over time.

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

N/A

7.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

The recommended process for the clinical management of ovarian cancer is (NICE 2011) and formed the basis of our costing assumptions for disease management. Please see Section 7.5.6 for details.

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

NHS Reference costs (Department of Health 2011) are the source of cost data for this appraisal as they include sufficient detail to adequately capture the main differential costs of this intervention and its comparator.

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study

- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs

The search strategy was designed to identify studies assessing resource utilisation of patients with advanced or metastatic ovarian cancer. The search was designed to evaluate potentially relevant BSC and adverse event costs for ovarian cancer that are relevant for the United Kingdom. No limits were place on publication types, study design or date. Only results published in English were considered.

The following databases were searched Embase (EMYY), Medline (MEYY), Medline in Process (MEIP), NHS EED and ECON LIT. For details of the methods used to search each database refer to **Error! Reference source not found.** in section 10.10, appendix 10. The full details of the search strategy are provided in section 10.13, appendix 13. The methodology used was based upon on the methods outlined in the CRD‘s Guidance for undertaking reviews in health care (2008).

An overview of the search is provided below.

EMBASE/ EMBASE alert/ Medline

Searches used index and text words for resource terms including cost analysis, cost control, financial management, NHS cost, resource utilization. The search was also restricted to disease descriptors including metastatic, ovary cancer or carcimona.

NHS EED and ECONLIT

Searches used the terms resource utilization, NHS reference costs, costs analysis as well as ovarian cancer or ovarian carcinoma and advanced or metastatic

Method: Each search result‘s title and abstract were assessed for relevance according to the pre-defined inclusion and exclusion criteria which were:
1. Does the abstract mention cost estimate of cost collection – if NO Exclude

2. Is the disease metastatic or advanced ovarian cancer - if NO Exclude

3. Are the costs specific to the UK – if NO Exclude

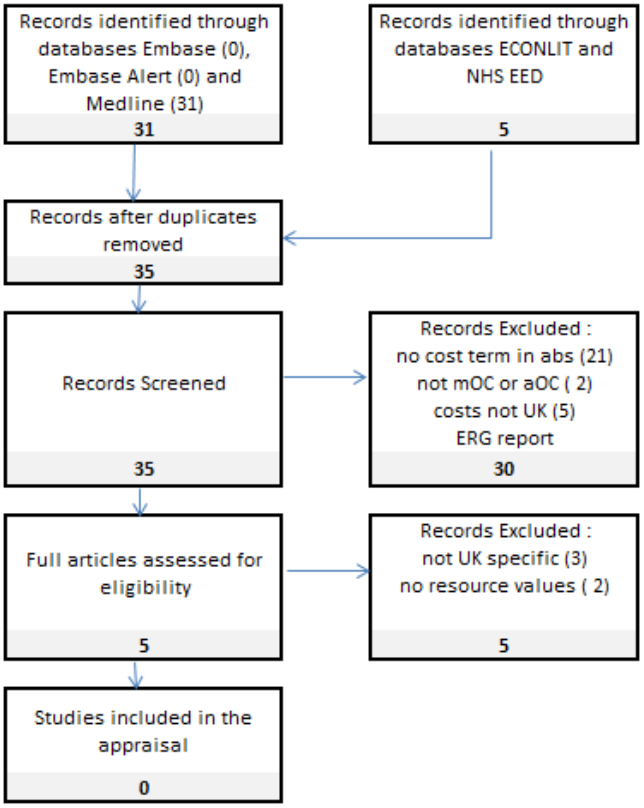
If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria shown in Table 49. PRISMA diagram Figure 21 shows the full flow of documents and reason for exclusion

Table 49: inclusion/exclusion criteria for resource search of the 5 databases

INCLUSION	EXCLUSION
Advanced or metastatic Ovarian cancer	Disease is not metastatic or advanced Ovarian Cancer
Resource utilitisation from an NHS perspective	Resource utilisation from outside of UK
Cost Estimation of Cost Collection included in abstract	Papers already included
	no useful cost values

Results: In total 36 records were identified via the five databases, 1 of which was a duplicate. Of these, 30 studies were excluded upon initial screening of title and abstract (PRISMA diagram Figure 21 shows for the rationale for these exclusions). The remaining 5 were deemed potentially relevant. These 5 results were then retrieved and assessed more comprehensively against the inclusion/exclusion criteria in Table 49, 0 were found to be relevant.

Figure 21: PRISMA flow showing resource studies identified through searching of the 5 databases



7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

N/A

Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

7.5.5.1 Patient characteristics influencing dosing

All medications received by patients in the first line setting (bevacizumab, carboplatin and paclitaxel) are administered through IV infusion and actual doses are calculated based on patient body weight (bevacizumab), body surface area (paclitaxel) or according to creatinine clearance rates which are dependent on patient age and weight (carboplatin).

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

The base case assumes that since carboplatin and paclitaxel are popular chemotherapy agents, it is reasonable to assume that unused material from vials is re-allocated to other preparations by the pharmacist. In contrast, bevacizumab is not routinely used in many hospitals and so unused drug in opened vials is assumed to be wasted in the base case. However, we are aware that many centres arrange delivery of chemotherapy and other treatments to patients with a particular tumour type during a specific clinical session and therefore it is likely that several patients would be given bevacizumab in one particular day and little to no wastage of drug would be incurred (referred to as 'vial sharing'). The impact of this alternative scenario is explored in sensitivity analyses.

7.5.5.2 Assumptions regarding bevacizumab preparation

No vial sharing of bevacizumab

In order to more accurately model the amount of drug required by UK patients, and to aid comparison of results from one model to the other, the base case scenario of each model uses the characteristics of a published cohort of UK patients with ovarian cancer (Sacco et al. 2010). This study reported the age and BSA of 321 women who were treated in 3 centres for ovarian cancer in 2005.

The mean and standard deviation of body weight was estimated from the overall survey female population (68.15kg, 14.74kg) adjusted proportionately using the Du Bois & Du Bois BSA formula (Du Bois D. & Du Bois 1989) so that:

$$\text{Mean body weight} = 68.15 * (\text{mean BSA} / \text{mean population BSA})^{(1/0.425)} = 60.495$$

$$\text{Standard deviation} = 14.74 * (\text{mean BSA} / \text{mean population BSA})^{(1/0.425)} = 13.084$$

The proportions of patients falling into 100mg dosing bands (the smallest vial size for bevacizumab) were estimated based on the log-normal distribution using parameters (s, M) estimated by the method of moments, i.e.:

$$S = \text{Ln}(1 + sd^2 / \text{weight}^2)^{0.5}$$

$$M = \text{Ln}(wt) - 0.5 * S^2$$

Table 50: Expected number of vials and cost of drug required (assuming no vial sharing) by patient cohorts considered in the economic evaluation

Source of patients	Source of data	N	Patient weight		Log-normal distribution parameters		Average number of vials used		Cost
			Mean	SD	S	M	400mg	100mg	
15mg/kg									
UK	Sacco*	321	60.49kg	13.08kg	0.2138	4.0797	2.030	1.454	£2,229
N. Am & Japan	GOG-0218	1248	70.68kg	18.6kg	0.2588	4.2247	2.403	1.490	£2,583
7.5mg/kg									
UK	Sacco*	321	60.49kg	13.08kg	0.2138	4.0797	0.983	1.107	£1,177
UK	ICON7 ITT	375	66.69kg	14.08kg	0.2088	4.1783	1.034	1.367	£1,287
UK	ICON7 HR	132	66.07kg	13.16kg	0.1972	4.1713	1.025	1.355	£1,276

*** Mean and SD weights calculated from BSA data provided. Underlined values are used in the base case scenario.**

It is noteworthy that the mean body weight of women recruited to GOG-0218 is more than 10kg more than the mean weight of UK ovarian cancer patients described in Sacco et al (Sacco et al. 2010). Bevacizumab can be purchased in two vial sizes at 25 mg/ml concentration (Joint Formulary Committee 2012): 4-ml (100-mg) vial = £242.66, 16-ml (400-mg) vial = £924.40.

Vial sharing of bevacizumab permitted

In the scenario where local clinical practice allows for vial contents to be shared between patients, the amount of bevacizumab required by patients of average body is calculated (i.e. mean weight (kg) * 15 mg/kg or 7.5 mg/kg) and used to estimate the average cost of drug per visit (Table 51).

Table 51: Expected amount and cost of drug required (assuming vial sharing) by patient cohorts considered in the economic evaluation

Source of patients	Source of data	N	Patient weight		Amount of drug required	Cost per administration
			Mean	SD		
15mg/kg						
UK	Sacco*	321	60.49kg	13.08kg	907.35mg	£2,109
N. Am & Asia	GOG-0218	1248	70.68kg	18.6kg	1060.20mg	£2,480
7.5mg/kg						
UK	Sacco*	321	60.49kg	13.08kg	453.68mg	£1,055
UK	ICON7 ITT	375	66.69kg	14.08kg	500.18mg	£1,167
UK	ICON7 HR	132	66.07kg	13.16kg	495.53mg	£1,156

*** Mean and SD weights calculated from BSA data provided. Underlined values are used in the base case scenario.**

7.5.5.3 Carboplatin drug costs

In the model, carboplatin is administered by intravenous infusion every 3 weeks at a dose calculated to result in a target AUC of 6 mg/ml/min (according to well established formulae (Calvert et al. 1989;Cockcroft & Gault 1976)). It should be noted that this is more restrictive than the trial protocol which allowed for a target AUC of 5 or 6 mg/ml/min and was chosen to be a more conservative assumption. Since carboplatin is a popular chemotherapy agent, it is reasonable to assume that unused material from vials is re-allocated to other preparations. Carboplatin can be purchased in vials of 600 mg at £21.84 (standard deviation of average price, £5.66) (Commercial Medicines Unit 2012). The cost per cycle of carboplatin for patient cohorts considered in the economic evaluation is presented in Table 52 and this is applied to all patients remaining on treatment every 3 weeks of the model.

Table 52: Calculation of carboplatin dose and cost for patient cohorts considered in the economic evaluation

	N	Age (years)	Weight (kg)	CrCl (ml/min)	Total dose (mg)	Cost (£)
Sacco	321	56.34	60.49	59.748	508	18.51
GOG-0218	1248	58.9	70.68	67.671	556	20.24
ICON7 ITT	374	56.4*	66.69	65.819	545	19.83
ICON7 HR	132	56.4*	66.07	65.206	541	19.70

*** Mean age of ICON7 HR patients (UK only) was not available and these patients were therefore assumed to have the same mean age as entire group. Underlined values are used in the base case scenario.**

7.5.5.4 Paclitaxel drug costs

Paclitaxel is administered by intravenous infusion every 3 weeks at a dose of 175 mg/m^2. Since paclitaxel is a popular chemotherapy agent, it is reasonable to assume that unused material from vials is re-allocated to other preparations. Paclitaxel can be purchased at a concentration of 6 mg/ml in vials of 25 ml (i.e. 150 mg units) at £10.91 (standard deviation of average price, £1.14) (Commercial Medicines Unit 2012). The cost per cycle of paclitaxel for patient cohorts considered in the economic evaluation is presented in Table 53 and this is applied to all patients remaining on treatment every 3 weeks of the model.

Table 53: Calculation of paclitaxel dose and cost for patient cohorts considered in the economic evaluation

	N	BSA	Total dose (mg)	Cost (£)
Sacco	321	1.713	299.72	21.80
GOG-0218	1248	1.754*	307.00	22.33
ICON7 ITT	375	1.706	298.55	21.71
ICON7 HR	132	1.698	297.15	21.61

*** Calculated from mean height (161.94cm) and weight (70.68kg) using (Du Bois D. et al. 1989). Underlined values are used in the base case scenario.**

7.5.5.5 Chemotherapy administration and pharmacy costs

Carboplatin and paclitaxel are administered by intravenous infusion in a hospital on the first day of every third week in the model. There is a cost associated with both the pharmacy preparation of the infusion and the administration of the drug itself (typically within a hospital setting).

The cost of administration of chemotherapy is applied to those patients remaining on treatment in every third week of the model. The first cycle is taken to be £265 (NHS Reference costs 2010/11 (SB13Z): Deliver more complex Parenteral Chemotherapy at first attendance (Daycase)). Subsequent cycles of chemotherapy delivery are costed at £85 (NHS Reference costs 2010/11 (SB97Z): Same day Chemotherapy admission/attendance (Daycase and Regular Day / Night)).

As pharmacy costs are not included within the drug delivery reference costs they were costed separately. It was assumed the time taken to prepare carboplatin and paclitaxel in pharmacy would be 12 minutes, as determined in a prospective time-and-motion study conducted in the UK for oxaliplatin (Millar et al. 2008).One hour of a hospital pharmacists' time performing patient related activities (accounting for overheads, qualifications, and salary on costs) costs £46 (PSSRU 2011). This equates to a total per cycle administration cost of bevacizumab of £9.20.

Therefore, the total 'per cycle' administration and pharmacy cost of carboplatin and paclitaxel for the first cycle is £274.57 while subsequent cycles cost £94.27.

7.5.5.6 Bevacizumab administration and pharmacy costs

In cycles where bevacizumab is administered in addition to carboplatin and paclitaxel, additional pharmacy time is assumed to be the only additional cost and therefore the total

incremental ‘per cycle’ administration and pharmacy cost of bevacizumab for the first 6 cycles is £9.20, assuming an additional 12 minutes of pharmacy time (Millar et al. 2008).

In cycles 7-18, where bevacizumab is prepared and administered alone, pharmacy costs are held constant (at £9.20 per cycle). This administration requirement equates to a cost £85 (NHS Reference costs 2010/11 (SB97Z): Same day Chemotherapy admission/attendance (Daycase and Regular Day / Night)).

Therefore, the total ‘per cycle’ administration and pharmacy cost of bevacizumab, when given as a monotherapy, is £94.27.

7.5.5.7 Treatment duration

Regardless of the method used to calculate the dose received by patients described above (i.e. inclusive or exclusive of wastage) treatment duration is defined by observations in the respective trials on which the models are based (Table 54 and Figure 22 for GOG-0218, Table 55, Figure 23 and Figure 24 for ICON7).

Table 54: Mean treatment duration for patients in GOG-0218 according to treatment arm

	Bevacizumab		**carboplatin + paclitaxel**	
Treatment arm	**weeks**	**Months**	**weeks**	**months**
bevacizumab + chemotherapy	41.93	9.68	17.66	4.07
chemotherapy	-	-	16.55	3.82

Figure 22: Proportion of patients in GOG-0218 remaining on treatment

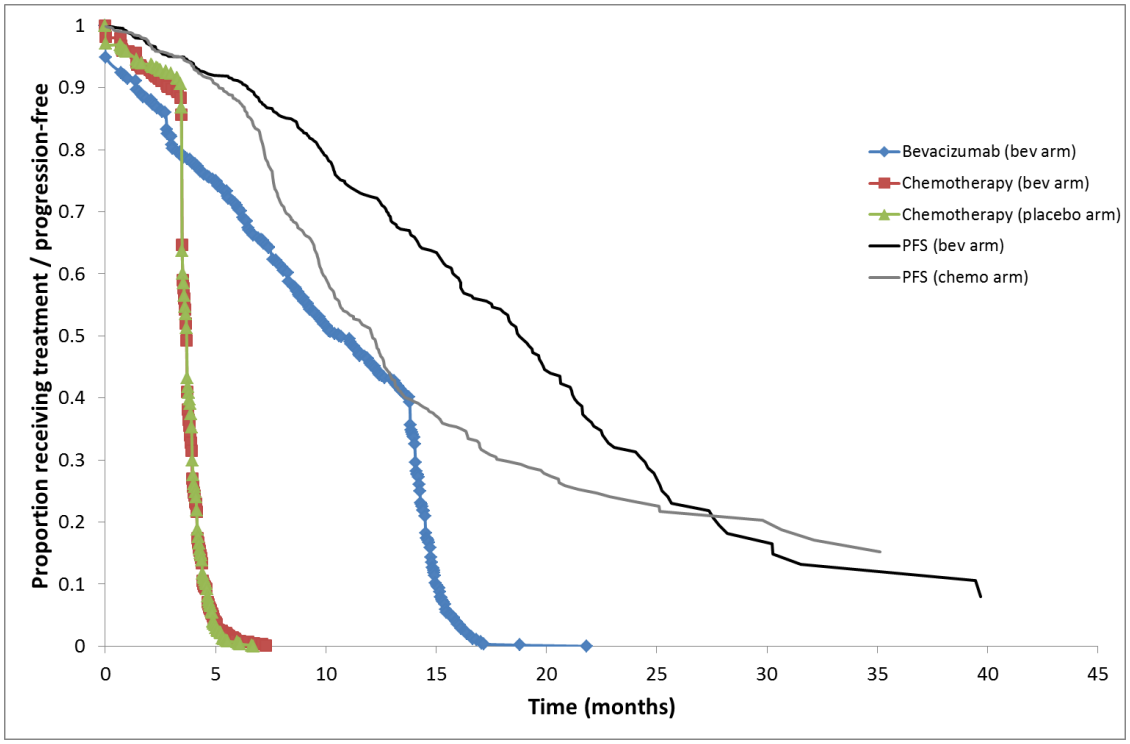


Table 55: Mean treatment duration for patients in ICON7 according to treatment arm

	Bevacizumab		carboplatin		paclitaxel	
Treatment arm	**weeks**	**Months**	**weeks**	**months**	**weeks**	**months**
bevacizumab + chemotherapy	42.99	9.92	16.35	3.89	16.17	3.73
chemotherapy	-	-	15.96	3.68	15.66	3.61

Figure 23: Proportion of patients in the bevacizumab arm of ICON7 remaining on treatment

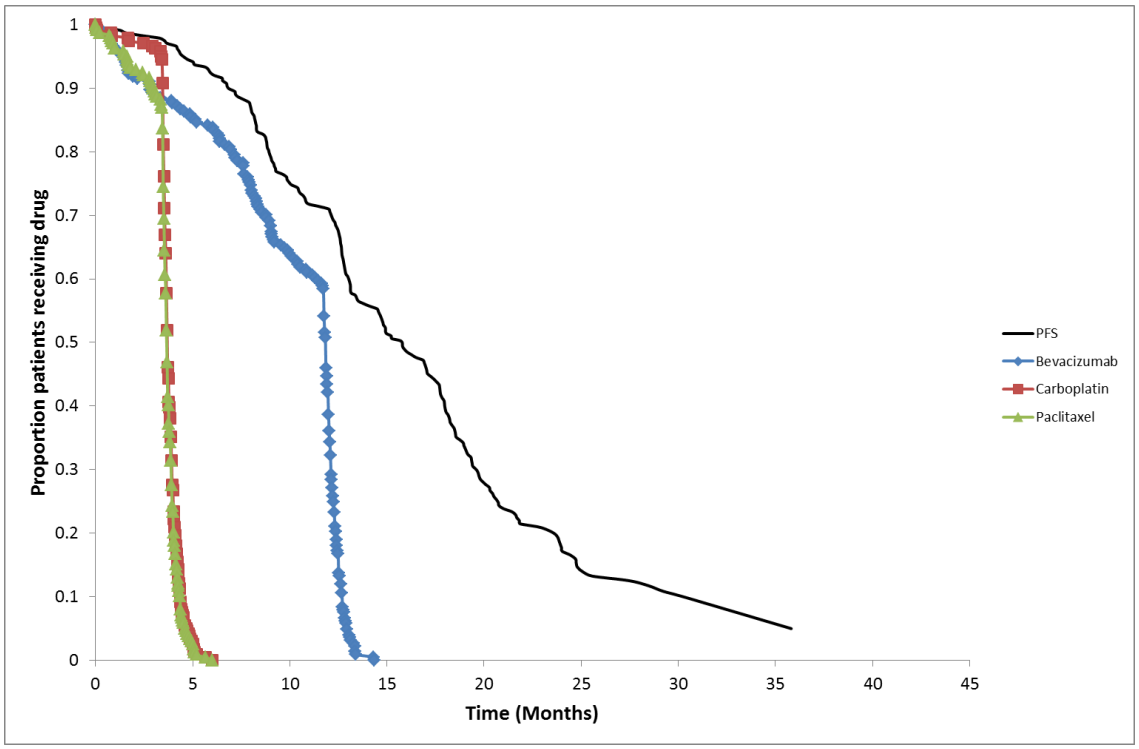
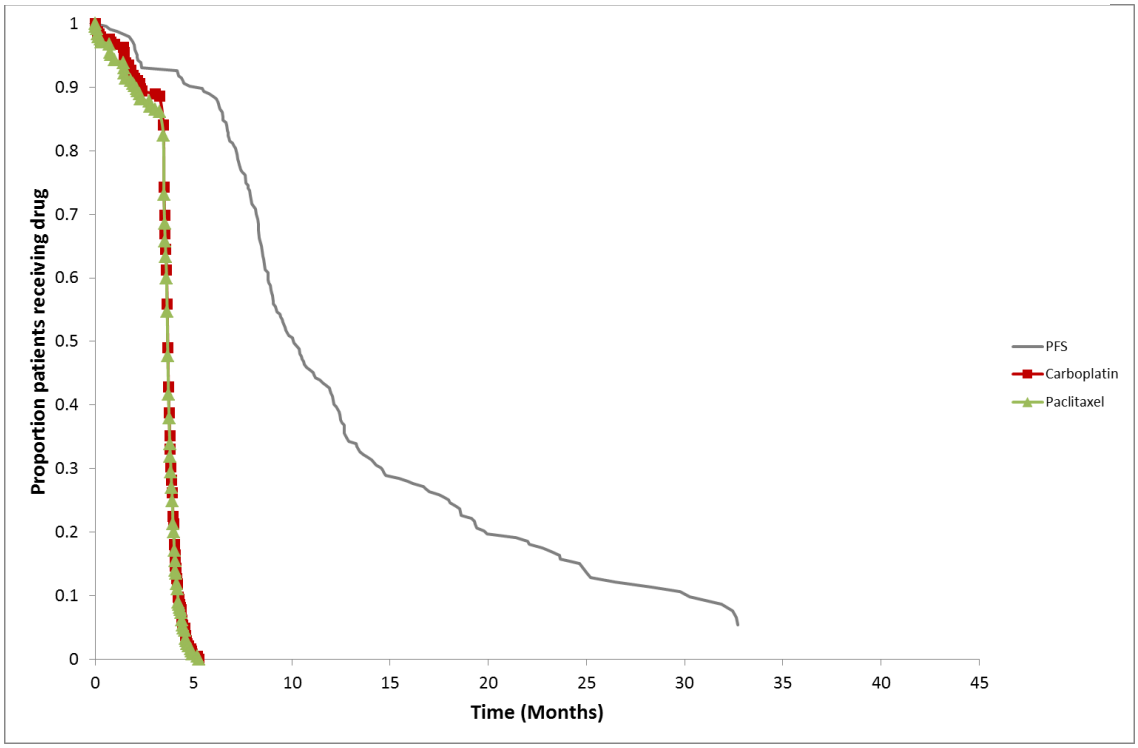


Figure 24: Proportion of patients in the chemotherapy arm of ICON7 remaining on treatment



Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

In normal clinical practice, disease progression is typically assessed by Computed Tomography (CT) scan following a routine clinical assessment by the consulting physician every 3 months (Clinical expert advice). Patients with progressed disease (PD) are assumed to have an outpatient review by a consultant oncologist every month, with a CT scan performed every 2 months as described in a previous Health Technology Assessment (Trabectedin in relapsed ovarian cancer (Papaioannou et al. 2010)). The total weekly costs of supporting patients in either PFS or PD health states are shown in Table 56.

Table 56: List of health states and associated costs in the economic model

Health	Items	Frequency	Unit	Average	Reference Cost Source

states			cost	weekly Value	(Department of Health 2011)
PFS	Outpatient visit to consultant oncologist	once every 3 months	£134	£10.31	Outpatient attendance data (503; Gynaecological Oncology)
	Total			**£10.31**	
PD	Outpatient visit to consultant oncologist	once per month	£134	£30.92	Outpatient attendance data (503; Gynaecological Oncology)
	CT scan	once every 2 months	£114	£13.15	Weighted average of Outpatient CT scans (RA08Z-14Z),
	Total			**£44.07**	

Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

Only those adverse events occurring in greater than 2% of patients at grade 3/4 severity were incorporated into the analysis (Table 57). Where possible, NHS reference costs were utilised (Department of Health 2011). It was assumed that certain AEs do not involve significant additional cost for the Health System (e.g. wigs for alopecia are often paid by patients themselves and the usual treatment for nausea/vomiting, hypertension or thrombosis is low-cost generic medication). Similarly, where clinical advice indicated that the usual treatment pathway for the adverse event was discontinuation of treatment, it was assumed this had been accounted for elsewhere in the model and no additional costs were incurred. Decreased neutrophil/white blood cell counts as a result of cytotoxic chemotherapy was assumed to be treated by a course (14 daily subcutaneous injections) of filgrastim (granulocyte colony stimulating factor) which is available in pre-filled syringes from a number of manufacturers, however, for practical purposes we assumed the cheapest available option would be preferred (Neupogen 30M units: £52.71, (Joint Formulary Committee 2012)).

All adverse events were assumed to occur in the first cycle of the model for both the treatment (bevacizumab + chemotherapy) and control (chemotherapy alone) arms, and so were not discounted.

Table 57: List of adverse events and summary of costs included in the economic model (>2% incidence in either arm)

Adverse event	N (%) patients experiencing event		Cost per episode	NHS Reference Costs 2010/11, (Department of Health 2011)
	Chemotherapy	Bevacizumab		
GOG-0218				
Constipation	7 (1.12)	15 (2.41)	N/A	Treatment with generic laxatives. Negligible cost.
Dehydration	14 (2.24)	21 (3.37)	£940	KC05E: Fluid and Electrolyte Disorders 69 years and under with Intermediate CC
Diarrhoea	20 (3.2)	16 (2.57)		
Fatigue	38 (6.08)	56 (8.99)	N/A	Non-interventional treatment
Febrile Neutropenia	23 (3.68)	30 (4.82)	£5,373	PA45Z: Febrile Neutropenia with Malignancy
Haemaglobin decreased	84 (13.44)	63 (10.11)	£58	821 – Blood Transfusion
Hypersensitivity	15 (2.4)	11 (1.77)	N/A	Withdrawal of treatment
Hypertension	12 (1.92)	53 (8.51)	N/A	Treatment with generic anti-hypertensives. Negligible cost.
Hypokalaemia	15 (2.4)	13 (2.09)	£940	KC05E: Fluid and Electrolyte Disorders 69 years and under with Intermediate CC
Hyponatraemia	9 (1.44)	14 (2.25)		
Nausea	26 (4.16)	20 (3.21)	N/A	Treatment with generic anti-emetics. Negligible cost.
Neutrophil count decreased	431 (68.96)	430 (69.02)	£738	Course of G-CSF (14 days subcutaneous injection with 30M units of Neupogen)
Neutrophil count decreased (Grade 4)	354 (56.64)	387 (62.12)		
Peripheral sensory neuropathy	20 (3.2)	24 (3.85)	N/A	Withdrawal of treatment
Platelet count decreased	78 (12.48)	100 (16.05)	£58	821 – Blood Transfusion
Platelet count decreased (Grade 4)	27 (4.32)	36 (5.78)		
Thrombosis	14 (2.24)	12 (1.93)	N/A	Treatment with generic thrombolytics. Negligible cost.
Vomiting	24 (3.84)	15 (2.41)	N/A	Treatment with generic anti-emetics. Negligible cost.
White blood cell count decreased	300 (48)	311 (49.92)	£738	Course of G-CSF (14 days subcutaneous injection with 30M units of Neupogen)
White blood cell count decreased (Grade 4)	22 (3.52)	28 (4.49)		
ICON7				
Alopecia	13 (5.18)	18 (7.38)	N/A	Out of pocket patient expense
Anaemia	7 (2.79)	4 (1.64)	£ 518	SA04F –Iron deficiency anaemia without CC
Drug Hypersensitivity	6 (2.39)	1 (0.41)	N/A	Withdrawal of treatment

Adverse event	N (%) patients experiencing event		Cost per episode	NHS Reference Costs 2010/11, (Department of Health 2011)
	Chemotherapy	Bevacizumab		
Dyspnoea	1 (0.40)	7 (2.87)	£ 236	PS06A –06 Breathing Problems; Breathing Difficulty
Fatigue	6 (2.39)	4 (1.64)	N/A	Non-interventional treatment
Febrile Neutropenia	7 (2.79)	2 (0.82)	£ 5,373	PA45Z – Febrile Neutropenia with Malignancy
Hypersensitivity	6 (2.39)	4 (1.64)	N/A	Withdrawal of treatment
Hypertension	1 (0.40)	13 (5.33)	N/A	Treatment with generic anti-hypertensives. Negligible cost.
Nausea	8 (3.19)	11 (4.51)	N/A	Treatment with generic anti-emetics. Negligible cost.
Neutropenia	24 (9.56)	21 (8.61)	£ 253	XD25Z – Neutropenia drugs band 1
Neutropenia (Grade 4)	12 (4.78)	9 (3.69)	£ 253	
Neutrophil Count	7 (2.79)	5 (2.05)	N/A	Non-interventional treatment
Pulmonary Embolism (Grade 4)	0 (0.00)	6 (2.46)	£ 1,362	DZ09B - Pulmonary Embolus with CC
Thrombocytopenia	5 (1.99)	9 (3.69)	£ 58	821 – Blood Transfusion
Vomiting	4 (1.59)	9 (3.69)	N/A	Treatment with generic anti-emetics. Negligible cost.

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

7.5.8.1 Post-progression treatments

GOG-0218

The type and duration of treatments received by patients after their tumour had progressed are not available in sufficient detail for either the effect on overall survival or the appropriate costs incurred to be estimated. Therefore, post-progression costs are not included in this model and we recommend caution when interpreting the results of the model based on the GOG-0218 study.

ICON7

In common with many clinical trials, patients were free to receive treatment as recommended by their physician following progression of disease and discontinuation of study drugs – information on these treatments were collected in the ICON7 trial. The cost of some of these treatments was calculated in order to provide an accurate estimate of the total cost of disease progression. Since more than 80 different treatments (or treatment combinations) were received by patients after progression it was necessary to focus attention on the most relevant for this situation. Therefore treatments were excluded from further analysis if they satisfied any of the following criteria:

- Equivalent duration and numbers of patients in both arms (costs and benefits likely to balance out)
- Interventional procedures (i.e. surgery, radiotherapy or transplants) (difficult to cost)
- Clinical trial drugs/Placebo (impossible to cost)
- Only received by a single patient in one arm (negligible impact on survival or cost)
- Interventions not expected to impact survival (e.g. haemostasis drugs)

Assumptions concerning the most likely dose and frequency of administration were taken from the appropriate SPC (accessed from www.medicines.org.uk), while costs of drugs were taken from BNF 63 (Joint Formulary Committee 2012). Medicines administered by an

intravenous infusion, attracted an additional cost of £85 per administration (NHS Reference costs 2010/2011 (SB97Z): Same day Chemotherapy admission/attendance (Daycase and Regular Day / Night)), however pharmacy costs were not included for simplicity. The total cost of disease-modifying treatments received by patients after progression was calculated to be £3643 for patients randomised to the chemotherapy arm, compared to £2958 for patients randomised to the bevacizumab arm (Table 58). These were applied as a one-off cost added to the total cost of post-progression treatment in the model.

7.5.8.2 Palliative care costs

Palliative care of cancer patients close to death in the UK NHS is known to vary considerably according to cancer type (GUEST et al. 2006). In order to capture the costs associated with this period of intense care and pain management, the average cost of palliative care in ovarian cancer patients from this study (£4789, 2000/01 cost year) was inflated to current costs (£6727) using the Hospital and Community Health Services Pay and Pricing index (PSSRU 2011) and applied to subjects as they transitioned to the Death state.

Table 58: Estimate of total cost of treatments received by patients after progression

TREATMENT	Number of patients		Dosing regimen			Expected dose (mg)	price per mg	Number of Administrations		Cost of Administrations		Total cost per patient	
	CHEMO	BEV	flat dose (mg)	mg per kg	mg per m2			CHEMO	BEV	CHEMO	BEV	CHEMO	BEV
BEVACIZUMAB	7			7.5		469.275	£ 2.43	6.8	0.0	£ 4,023	£ -	£ 231	£ -
CAPECITABINE		2			1250	2081.25	£ 0.00	0.0	14.0	£ -	£ -	£ -	£ 1
CARBOPLATIN	98	115	570			570	£ 0.43	4.6	4.8	£ 38,409	£46,718	£ 597	£ 747
CARBOPLATIN/ DOCETAXEL		2	570			570	£ 0.43	0.0	0.5	£ -	£ 93	£ -	£ 1
CARBOPLATIN/ DOXORUBICIN	1	1	570			570	£ 0.43	4.2	2.4	£ 361	£ 203	£ 6	£ 3
CARBOPLATIN/ GEMCITABINE	1	2	570			570	£ 0.43	5.0	3.2	£ 429	£ 547	£ 7	£ 9
CARBOPLATIN/ PACLITAXEL	2	1	570			570	£ 0.43	2.2	5.4	£ 373	£ 458	£ 6	£ 7
CISPLATIN	10	11			85	141.525	£ 0.50	2.6	2.9	£ 2,244	£ 2,714	£ 16	£ 20
CYCLOPHOSPHAMIDE	4	2			150	249.75	£ 0.00	67.8	20.0	£ -	£ -	£ 1	£ 0
DOCETAXEL	5	5			75	124.875	£ 5.14	3.7	3.6	£ 1,572	£ 1,535	£ 54	£ 54
DOXORUBICIN	120	91			50	83.25	£ 1.94	2.6	2.5	£ 26,968	£19,452	£ 311	£ 231
ETOPOSIDE	12	5			90	149.85	£ 0.12	20.0	20.0	£ 20,418	£ 8,507	£ 99	£ 42
GEMCITABINE	30	23			1000	1665	£ 0.16	10.0	8.0	£ 25,522	£15,654	£ 424	£ 268
GEMCITABINE HYDROCHLORIDE	9	6			1000	1665	£ 0.16	6.0	12.0	£ 4,594	£ 6,125	£ 76	£ 105
LETROZOLE		2	2.5			2.5	£ 1.21	0.0	36.0	£ -	£ -	£ -	£ 1
OXALIPLATIN	6	1			85	141.525	£ 3.00	4.6	3.1	£ 2,327	£ 261	£ 55	£ 6
PACLITAXEL	67	79	290			290	£ 2.00	4.4	4.5	£ 25,307	£30,375	£ 789	£ 975
TAMOXIFEN	12	6	20			20	£ 0.00	39.4	60.2	£ -	£ -	£ 0	£ 0
TOPOTECAN	47	23			1.5	2.4975	£ 65.39	20.0	20.0	£ 79,970	£39,134	£ 930	£ 468
TREOSULFAN	11	1			5	8.325	£ 0.03	9.4	53.9	£ 8,763	£ 4,582	£ 35	£ 19
VINORELBINE	2				27.5	45.7875	£ 2.78	3.1	0.0	£ 535	£ -	£ 5	£ -
												£ 3,643	**£ 2,958**

7.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

7.6.1.1 Vial sharing

In centres where oncology drugs are prepared in batches for groups of patients, vial sharing is possible and this impacts on the expected cost per patient. The following drug costs were used in a sensitivity analysis to explore the impact of this assumption on the cost-effectiveness model results.

Table 59: Amount and cost of bevacizumab required where vial sharing is permitted (from Table 51)

		15mg/kg		7.5mg/kg	
Source of data	**Source of patients**	**Amount of drug required**	**Cost per administration**	**Amount of drug required**	**Cost per administration**
Sacco*	UK	907.35mg	£2,109	453.68mg	£1,055

7.6.1.2 Trial patient characteristics

The results of both GOG-0218 and ICON7 are influenced by the characteristics of the patients recruited to each study and as such it is useful to explore the impact of using baseline demographic data for patients in their respective cost-effectiveness models where vial sharing is, and is not, permitted.

Table 60: Amount and cost of bevacizumab, carboplatin and paclitaxel required for patients recruited to GOG-0218 and ICON7 (from Table 50 - Table 53)

Source of data	Source of patients	Drug	Amount of drug required	Cost per administration
15mg/kg				
GOG-0218	N. America & Japan	Bevacizumab	1060.20mg	£2,480
			2.030 x 400mg + 1.454 x 100mg vials*	£2,583*
		Carboplatin	556mg	£20.24
		Paclitaxel	307.00mg	£22.33
7.5mg/kg				
ICON7 ITT	UK	Bevacizumab	500.18mg	£1,167
			1.034 x 400mg + 1.367 x 100mg vials*	£1,287*
		Carboplatin	545mg	£19.83
		Paclitaxel	298.55mg	£21.71
ICON7 HR		Bevacizumab	495.53mg	£1,156
			1.025 x 400mg + 1.355 x 100mg vials	£1,276
		Carboplatin	541mg	£19.70
		Paclitaxel	297.15mg	£21.61

*** vial sharing not permitted for bevacizumab**

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Deterministic sensitivity analysis was carried out on the parameters listed in Table 61 and Table 62.

Table 61: Deterministic sensitivity analysis (GOG-218)

	Base case value	Alternative	Value High	Value Low	Rationale
PFS	KM + Log Logistic tail	Log Logistic	-	-	Best fit for chemotherapy arm according to AIC/BIC
		Gamma	-	-	Best fit for bevacizumab arm according to AIC/BIC
Post-progression survival	combined exponential parametric curve	separated exponential parametric curve	-	-	Treatments have different post-progression survival rates
Time to off treatment (bevacizumab)	Trial Observation	PFS	-	-	Alternative treatment duration
		15 months	-	-	Assume no withdrawal of bevacizumab due to AEs (License)
Utility					
PFS	ICON7 trial observation	0.755	-	-	Alternative assumption (no change in QoL in PFS)
		+/-10% of mean value	0.830	0.679	
PD	ICON7 trial observation: 0.718	Trabectedin HTA submission	0.7248	-	alternative source
		+/-10% of mean value			
Costs					
Administration costs	£85.07	Different Admin costs	£0	£95.52	Upper and Lower Quartile reference costs
PFS supportive care costs	£10.31	+/-10%			
PD supportive care costs	£44.10	+/-10%			
Palliative care costs	£6,726.53	no Palliative care costs	-	-	Assumption of no palliative care
AE costs	£ 3,511.61 Chemo; £ 3,575.71 Bevacizumab + Chemotherapy	no AE costs	-	-	Assumption of no adverse events
Time Horizon	10 yrs	+-50%	15 yrs	5 yrs	

	Base case value	Alternative	Value High	Value Low	Rationale
Discounting					
Costs and Benefits	3.50%		6%	0%	NHS reference case

Table 62: Deterministic sensitivity analysis (ICON7)

	Base case value	Alternative	Value High	Value Low	Rationale
PFS	KM + Log Logistic tail	Log Logistic	-	-	Best fit according to AIC/BIC
		Gamma	-	-	2nd best fit according to AIC/BIC
OS	Log Logistic	Gamma	-	-	Best fit according to AIC/BIC
		Weibull	-	-	2nd best fit according to AIC/BIC
Time to off treatment (bevacizumab)	Trial Observation	PFS	-	-	Alternative treatment duration
		12 months	-	-	Assume no withdrawal of bevacizumab due to AEs (ICON7)
		15 months	-	-	Assume no withdrawal of bevacizumab due to AEs (License)
Utility					
PFS	Trial Observation	0.755	-	-	Alternative assumption (no change in QoL in PFS)
		+/-10% of mean value	0.830	0.679	
PD	0.718	Trabectedin HTA submission	0.7248	-	alternative source
Costs					
Administration costs	£85.07	Different Admin costs			Upper and Lower Quartile reference costs
PFS supportive care costs	£10.31	+/-10%			
PD supportive care costs	£44.10	+/-10%			

	Base case value	Alternative	Value High	Value Low	Rationale
PD treatment costs	£ 3642.84 Chemo; £ 2958.23 Bevacizumab + Chemotherapy	no PD treatment costs	-	-	Assumption of no treatments after progression
Palliative care costs	£6,726.53	no Palliative care costs	-	-	Assumption of no palliative care
AE costs	£ 233.17 Chemo; £ 164.76 Bevacizumab + Chemotherapy	no AE costs	-	-	Assumption of no adverse events
Time Horizon	10 yrs	+-50%	15 yrs	5 yrs	
Discounting					
Costs and Benefits	3.50%		6%	0%	NHS reference case

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of ‘priors’. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

In order to explore parameter uncertainty around inputs used in the base case analysis, distributions were applied to the following parameters within the model:

- Utility values
- Parameter estimates for the parametric PFS and OS functions (as appropriate)
- Costs and frequency of adverse events
- Weekly supportive care costs in both the PFS and Progressed health states

No distributions were applied for to the cost of medication (bevacizumab, carboplatin or paclitaxel), treatment administration or duration or costs of treatments received following progression (i.e. post-progression treatments in ICON7 and palliative care costs for both models).

7.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Table B4 Summary of model results compared with clinical data

Outcome	Clinical trial result (median months)	Model result
GOG-0218		
Chemotherapy arm		
Progression-free survival	12.12	12.00
Post-progression survival	27.27	33.00
Overall survival	39.39	45.00
Bevacizumab arm		
Progression-free survival	18.79	19.00
Post-progression survival	20.96	28.00
Overall survival	39.75	47.00
ICON7		
Chemotherapy arm		
Progression-free survival	10.12	10.15
Post-progression survival	17.64	18.69
Overall survival	27.76	28.85
Bevacizumab arm		
Progression-free survival	15.80	15.69
Post-progression survival	19.32	21.23
Overall survival	35.12	36.92

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Given the model cycle length (1 week) and time horizon (10 years), it is not considered appropriate to include a full Markov trace for both models within the main body of the submission. Please see the Excel workbook (Sheet: Markov trace 1) provided as supplementary material.

7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Given the model cycle length (1 week) and time horizon (10 years), it is not considered appropriate to include a full Markov trace for both models within the main body of the submission. Please see Excel workbook (Sheet: Markov trace 2) provided as supplementary material.

7.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

Table B5 Model outputs by clinical outcomes (GOG-0218)

Comparator	Outcome	LY	QALY	Cost (£)
Bevacizumab + chemotherapy	PFS	1.849	1.448	£32,588
	PD	2.364	1.713	£5,418
	Overall survival	4.212	3.161	£44,254
Carboplatin + paclitaxel	PFS	1.545	1.205	£5,281
	PD	2.440	1.769	£5,593
	Overall survival	3.985	2.973	£17,166

Table B6 Model outputs by clinical outcomes (ICON7)

Comparator	Outcome	LY	QALY	Cost (£)
Bevacizumab + chemotherapy	PFS	1.518	1.179	£19,442
	PD	2.291	1.661	£14,399
	Overall survival	3.809	2.839	£33,841
Carboplatin + paclitaxel	PFS	1.201	0.927	£1,788
	PD	1.865	1.352	£14,323
	Overall survival	3.066	2.278	£16,111

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table B7 Summary of QALY gain by health state (GOG-0218)

Health state	QALY intervention (Bevacizumab + chemotherapy)	QALY comparator (Carboplatin + paclitaxel)	Increment	Absolute increment	% absolute increment
PFS	1.448	1.205	0.243	0.243	81.47%
PD	1.713	1.769	-0.055	0.055	18.53%
Total	3.161	2.973	0.188	0.299	100.00%

Table B8 Summary of QALY gain by health state (ICON7)

Health state	QALY intervention (Bevacizumab + chemotherapy)	QALY comparator (Carboplatin + paclitaxel)	Increment	Absolute increment	% absolute increment
PFS	1.179	0.927	0.252	0.252	44.94%
PD	1.661	1.352	0.309	0.309	55.06%
Total	**2.839**	**2.278**	0.561	0.561	100.00%

Table B9 Summary of costs by health state (GOG-0218)

Health state	Cost intervention (Bevacizumab + chemotherapy)	Cost comparator (Carboplatin + paclitaxel)	Increment	Absolute increment	% absolute increment
PFS	£32,588	£5,281	£27,307	£27,307	99.36%
PD	£5,418	£5,593	-£175	£175	0.64%
Total	£44,254	£17,166	£27,089	£27,482	100.00%

Table B10 Summary of costs by health state (ICON7)

Health state	Cost intervention (Bevacizumab + chemotherapy)	Cost comparator (Carboplatin + paclitaxel)	Increment	Absolute increment	% absolute increment
PFS	£19,442	£1,788	£17,654	£17,654	99.57%
PD	£14,399	£14,323	£76	£76	0.43%
Total	£33,841	£16,111	£17,729	£17,729	100.00%

Table B11 Summary of predicted resource use by category of cost (GOG-0218)

Item	Cost intervention (Bevacizumab + chemotherapy)	Cost comparator (Carboplatin + paclitaxel)	Increment	Absolute increment	% absolute increment
Mean total treatment cost (Bev + Carbo + Pac)	£26,361	£0	£26,361	26,361	96%
Administration cost (Bev + Carbo + Pac)	£722	£0	£722	722	3%
Mean total treatment cost (Carbo + Pac)	£227	£228	-£1	1	0%
Administration cost (Carbo + Pac)	£711	£714	-£3	3	0%
Mean Supportive Care Cost of PFS	£991	£828	£163	163	1%
Mean Supportive Care Cost of PD	£5,418	£5,593	-£175	175	1%
Cost of AE's	£3,576	£3,512	£64	64	0%
Total	£44,254	£17,166	£27,089	27,490	100%

Table B12 Summary of predicted resource use by category of cost

Item	Cost intervention (Bevacizumab + chemotherapy)	Cost comparator (Carboplatin + paclitaxel)	Increment	Absolute increment	% absolute increment
Mean total treatment cost (Bev + Carbo + Pac)	£16,653	£0	£16,653	£16,653	93%
Administration cost (Bev + Carbo + Pac)	£861	£0	£861	£861	5%
Mean total treatment cost (Carbo + Pac)	£224	£215	£9	£9	0%
Administration cost (Carbo + Pac)	£726	£697	£29	£29	0%
Mean Supportive Care Cost of PFS	£814	£644	£170	£170	1%
Mean Supportive Care Cost of PD	£14,399	£14,323	£76	£76	0%
Cost of AE's	£165	£233	-£68	£68	0%
Total	**£33,841**	**£16,111**	**£17,729**	**£17,866**	100%

Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Table B13 Base-case results (GOG-0218)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus incremental (LYG)	ICER (£) incremental (QALYs)
(Carbo + Pac)	£17,166	3.985	2.973					
(Bev + Carbo + Pac)	£44,254	4.212	3.161	£27,089	0.228	0.188	£118,876	£144,066

Table B14 Base-case results (ICON7)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus incremental (LYG)	ICER (£) incremental (QALYs)
(Carbo + Pac)	£16,111	3.066	3.809					
(Bev + Carbo + Pac)	£33,841	2.278	2.839	£17,729	0.743	0.561	£23,846	£31,592

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

GOG-0218

Table 63: Deterministic sensitivity analysis of GOG-0218

Parameter	Base case value	Alternative	Incremental costs	Incremental QALYs	ICER
BASE CASE			£27,089	0.188	£144,066
PFS	KM + Log Logistic tail	Log Logistic	£26,840	0.376	£71,417
		Gamma	£27,096	0.180	£150,333
Post-progression survival	combined exponential parametric curve	individual exponential parametric curve	£27,089	0.188	£143,982
Time to off treatment (bevacizumab)	Trial Observation	PFS	£34,422	0.188	£183,067
Utility					
PFS	ICON7 trial observation	0.755	£27,089	0.174	£155,394
		0.83	£27,089	0.197	£137,305
		0.679	£27,089	0.151	£178,974
PD	0.718	0.7248	£27,089	0.189	£143,669
		0.7898	£27,089	0.182	£148,435
		0.6462	£27,089	0.194	£139,947
Costs					
Administration costs	£265.47 and £85.07	£172.20 and £0	£26,459	0.188	£140,717
		£298.10 and £95.52	£27,166	0.188	£144,477
PFS supportive care costs	10.31	£11.341	£27,105	0.188	£144,153
		£9.279	£27,072	0.188	£143,979
PD supportive care costs	44.1	£48.51	£27,071	0.188	£143,973
		£39.69	£27,106	0.188	£144,159
Palliative care costs	6726.53	-	£27,132	0.188	£144,296
AE costs	£ 3,511.61 Chemo; £ 3,575.71 Bevacizumab + Chemotherapy	-	£27,025	0.188	£143,725
Time Horizon	10 yrs	15 yrs	£27,147	0.204	£133,225
		5 yrs	£26,874	0.139	£192,896
Discounting					
Costs and Benefits	0.035	0.06	£27,073	0.175	£155,046
		0	£27,113	0.210	£128,898

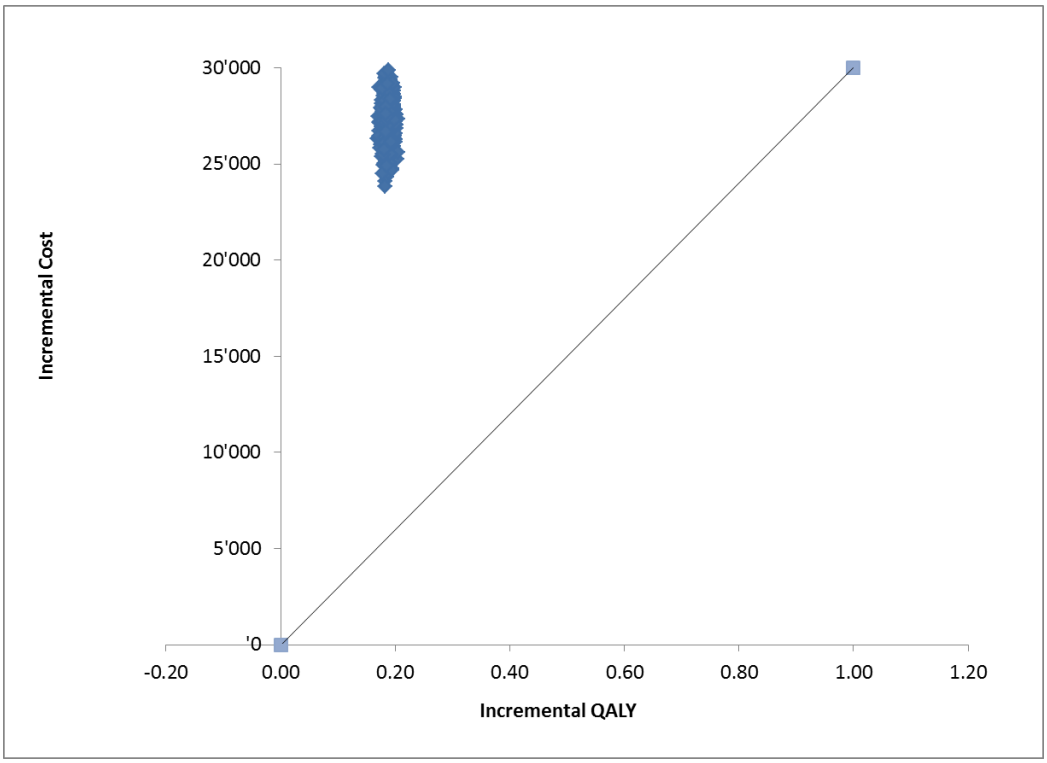
ICON7

Table 64: Deterministic sensitivity analysis of ICON7

Parameter	Base case value	Alternative	Incremental costs	Incremental QALYs	ICER
BASE CASE			£17,729	0.561	£31,592
PFS	KM + Log Logistic tail	Log Logistic	£17,568	0.570	£30,810
		Gamma	£17,759	0.562	£31,600
OS	Log Logistic	Gamma	£17,667	0.475	£37,173
		Weibull	£17,846	0.539	£33,085
Time to off treatment (bevacizumab)	Trial Observation	PFS	£34,020	0.561	£60,621
		12 months	£17,275	0.561	£30,783
Utility					
PFS	Trial Observation	0.755	£17,729	0.548	£32,328
		0.830	£17,729	0.572	£30,975
		0.679	£17,729	0.524	£33,803
PD	0.718	Trabectedin HTA submission	£17,729	0.558	£31,756
Costs					
Administration costs	£85.07	£95.52	£17,795	0.561	£31,710
		£0	£17,191	0.561	£30,632
PFS supportive care costs	£10.31	£11.34	£17,746	0.561	£31,622
		£9.28	£17,712	0.561	£31,562
PD supportive care costs	£44.10	£48.51	£17,827	0.561	£31,766
		£39.69	£17,632	0.561	£31,418
PD treatment costs	£3642.84 Chemo; £2958.23 Bevacizumab + Chemotherapy	0	£18,414	0.561	£32,812
Palliative care costs	£6726.53	0	£17,945	0.561	£31,977
AE costs	£233.17 Chemo; £164.76 Bevacizumab + Chemotherapy	0	£17,798	0.561	£31,714
Time Horizon	10 yrs	15	£18,088	0.637	£28,389
		5	£16,707	0.360	£46,446
Discounting					
Costs and Benefits	0.035	0.06	£17,630	0.513	£34,379
		0	£17,889	0.643	£27,832

7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

Figure 25: Cost-effectiveness plane for the addition of bevacizumab (15mg/kg) to carboplatin + paclitaxel



There is a 0.00% chance of the addition of 15mg/kg bevacizumab to standard carboplatin and paclitaxel chemotherapy being considered cost-effective at a willingness to pay threshold of £30,000 per QALY.

GOG-0218

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus incremental (LYG)	ICER (£) incremental (QALYs)
(Carbo + Pac)	£17,570 (£16,302, £19,087)	3.987 (3.76, 4.21)	2.976 (2.8, 3.17)					
(Bev + Carbo + Pac)	£44,704 (£43,300, £46,343)	4.214 (4, 4.43)	3.163 (2.99, 3.35)	£27,133 (£25,243, £29,072)	0.227 (0.215, 0.24)	0.188 (0.177, 0.199)	£119,367 (£108,879, £130,318)	£144,682 (£131,654, £158,355)
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

ICON7

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus incremental (LYG)	ICER (£) incremental (QALYs)
(Carbo + Pac)	£16,143 (£15,367, £17,068)	3.058 (2.731, 3.409)	2.272 (2.034, 2.518)					
(Bev + Carbo + Pac)	£33,891 (£32,899, £34,978)	3.813 (3.411, 4.237)	2.841 (2.548, 3.154)	£17,748 (£16,770, £18,821)	0.755 (0.342, 1.23)	0.569 (0.273, 0.918)	£25,844 (£15,005, £49,341)	£32,683 (£20,379, £61,861)
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Figure 26: Cost-effectiveness plane for the addition of bevacizumab (7.5mg/kg) to carboplatin + paclitaxel

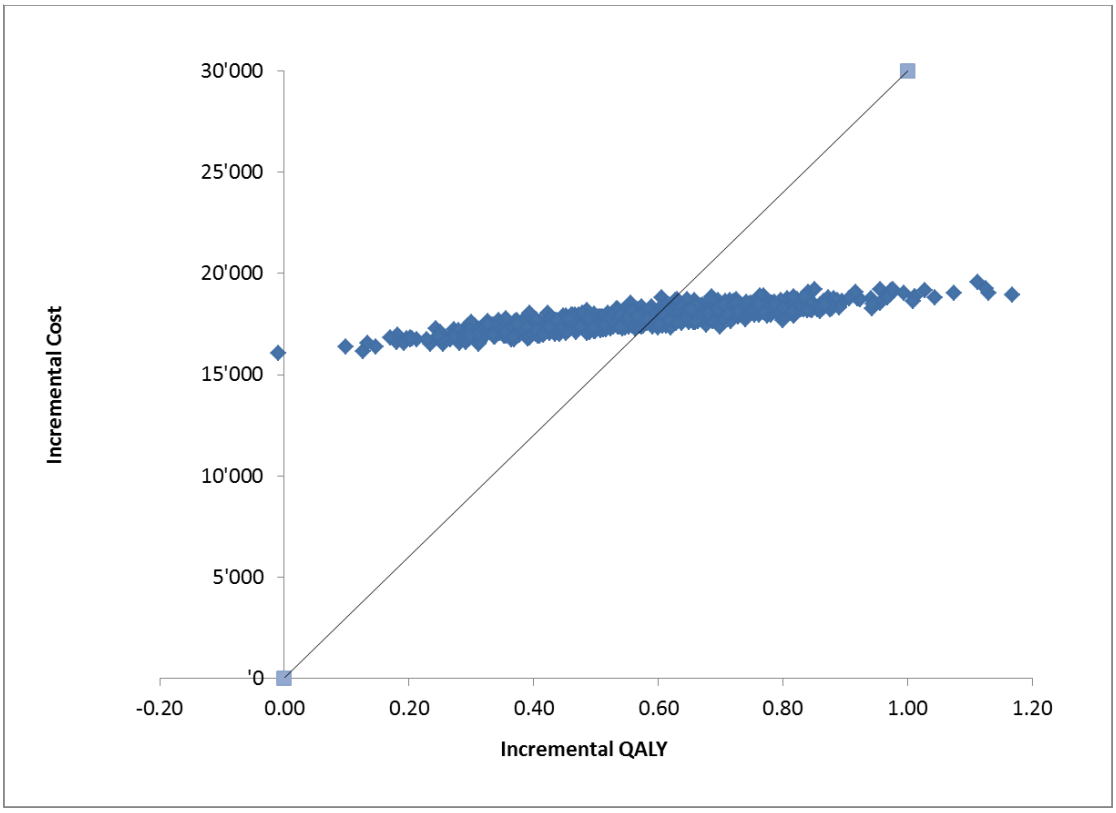
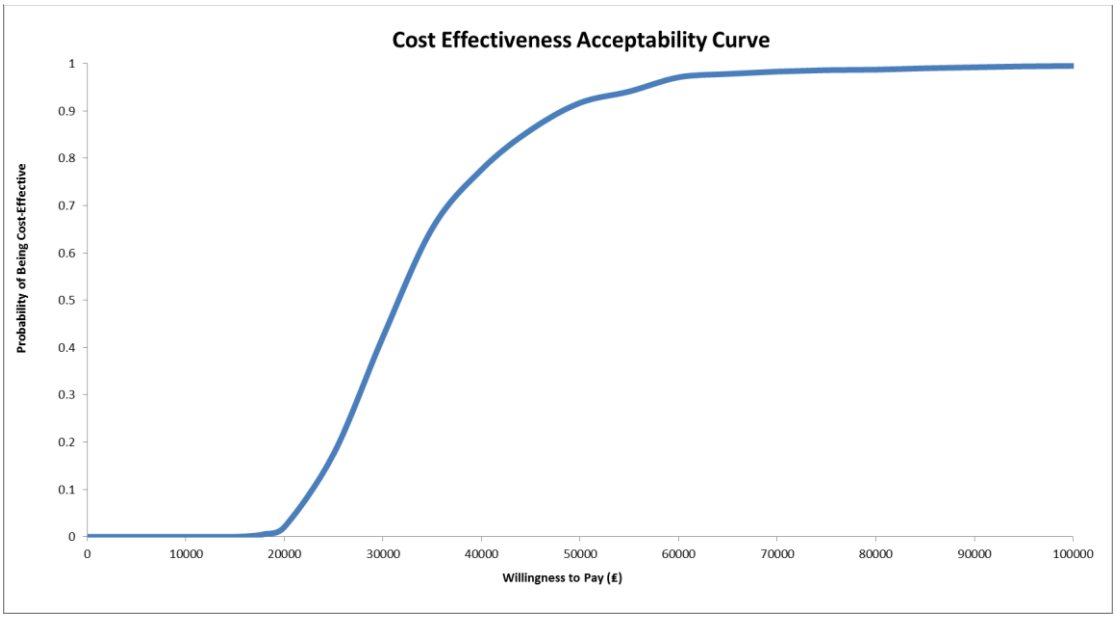


Figure 27: Cost-effectiveness acceptability curve for the addition of bevacizumab (7.5mg/kg) to carboplatin + paclitaxel



The probability of being cost-effective at £20,000 per QALY is 2.1%, and at £30,000 per QALY it is 42.3%.

7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

7.7.9.1 Vial sharing

Model	Base case value	Alternative	Incremental costs	Incremental QALYs	ICER versus incremental QALYs
	no vial sharing	vial sharing permitted			
GOG-0218	£2,229	£2,109	£25,668	0.188	£136,513
ICON7	£1,177	£1,055	£16,001	0.561	£28,513

7.7.9.2 Trial patient characteristics

Model	Base case value	Alternative	Incremental costs	Incremental QALYs	ICER versus incremental QALYs
No vial sharing	**Sacco**	**Study specific**			
GOG-0218	£2,229	£2,583	£31,267	0.188	£166,287
ICON7 (ITT)	£1,177	£1,287	£19,284	0.561	£34,363
ICON7 (HR)	£1,177	£1,276	£19,137	0.561	£34,101
Vial sharing					
GOG-0218	£2,109	£2,480	£30,054	0.188	£159,837
ICON7 (ITT)	£1,055	£1,167	£17,598	0.561	£31,357
ICON7 (HR)	£1,055	£1,156	£17,438	0.561	£31,073

7.7.10 What were the main findings of each of the sensitivity analyses?

The results of the deterministic sensitivity analysis demonstrated the insensitivity of both models to estimates of disease management costs for PFS and PD health states, inclusion of costs associated with management of adverse events and palliative care or post-progression treatments (Table 63

and Table 64). Both models were sensitive to assumptions around the modelling of PFS and OS, although it should be remembered that some of the parametric curves which fit observations in both studies do not necessarily reflect clinical expectations for this cohort of patients (Figure 18).

The results of the Probabilistic Sensitivity Analysis for both models suggest that there is limited uncertainty in the degree of cost-effectiveness of the GOG-0218 trial (Figure 25) whilst there is much more uncertainty in the cost-effectiveness of the ICON7 study (Figure 26). However, it is worth noting that when overall survival in ICON7 is modelled by the study Kaplan-Meier observations for the first 3 years (followed by a Log Logistic extrapolation), variability in incremental benefits is considerably reduced. This is likely due to study observations not being subject to uncertainty in the PSA. Thus, a PSA of both models when it is assumed that both PFS and OS are described by parametric functions, results in considerable uncertainty in the incremental benefits of adding bevacizumab to standard chemotherapy.

7.7.11 What are the key drivers of the cost-effectiveness results?

The key drivers of the cost-effectiveness results are the dose and cost of bevacizumab and the duration of treatment. Indeed, extending treatment in patients until progression doubles the ICER in the ICON7 model from £31k per QALY to £60k per QALY (in GOG-0218, the effect is less extreme; from £144k per QALY to £183k per QALY). However, the relevance of this sensitivity analysis is limited given the license restriction to 15 months and an uncoupling of costs from benefits that might have been observed if treatment was continued.

Both models are sensitive to the time horizon used in the analysis. Increasing the time horizon by 50% (from 10 to 15 years) reduces the ICER for the GOG-0218 model by 7.6% and the ICON7 model by 10%, whilst reducing the time horizon by the same amount increases the ICERs by 34% and 47%, respectively.

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

Please see Section 7.3.1.2 for details of how the expected long-term survival of these patients (du Bois A. et al. 2009) was used to validate the selection of the most appropriate extrapolation of overall survival.

7.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

The ICON7 expanded high risk subgroup model, presented in parallel to the base case GOG-0218 model above, is a subgroup analysis of one of the key studies of bevacizumab in the front-line treatment of advanced ovarian cancer.

7.9.2 Please clearly define the characteristics of patients in the subgroup.

N/A

7.9.3 Please describe how the statistical analysis was undertaken.

N/A

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

N/A

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.

N/A

7.10 Interpretation of economic evidence

7.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The results from the economic evaluation presented here are broadly consistent with the published literature with the caveat that the only similar evaluations retrieved from our search were based on non-UK healthcare systems. The model based on the GOG-0218 study presented here is in agreement with the 2 published economic studies (in the USA) however, discussion on the threshold to be used in the US still ongoing, and some

might consider that the intervention is cost-effective if below US$500,000/QALY. Similarly, in accordance with the model based on ICON7 presented in this submission, a recent economic evaluation suggested that bevacizumab added to standard chemotherapy at 7.5mg/kg was a cost-effective use of limited resources in Mexico when compared to a threshold of 3 x GDP.

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

Yes, the economic evaluations presented here have attempted to reflect the expected benefits and costs experienced by UK patients.

- The dose (and therefore costs) of bevacizumab and chemotherapies are calculated based on a representative sample of UK ovarian cancer patients.

- The utilities are estimated from EQ-5D responses of patients in the ICON7 study and as such are expected to accurately reflect the patient's experience of PFS while on treatment.

- The 2 models presented here reflect both the licensed dose (GOG-0218) and preferred clinical practice (ICON7).

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The evaluation presented here has a number of strengths which make it particularly relevant for UK patients and clinicians.

Firstly, evidence is presented which relates to both the licensed dose (15mg/kg) and the dose routinely used in UK clinical practice. Secondly, the base case scenario for both models uses estimates of drug costs based on a single, UK-specific cohort of ovarian cancer patients and therefore is as relevant as possible to expectations for the UK NHS. Finally, models of both GOG-0218 and ICON7 use utility estimates (derived from EQ-5D) from one of

the key studies and is expected to be representative of UK patients' experiences.

The main weaknesses of the economic evaluations presented here are that the effect of patients in GOG-0218 having access to bevacizumab after progression cannot be accurately calculated and accounted for (either by adjusting survival times or by allocating costs of treatments).

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The robustness of these results could be improved by the use of more complete survival data for patients in ICON7 (which is expected in 2013) and inclusion of estimates of the costs and/or benefits of post-progression therapies received by patients in the GOG-0218 study.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

We have calculated the number of patients in year 1 to be 2048 which covers this indication/subgroup exclusively. We have assumed a population growth rate of 0.5% per year. Resulting patient numbers per year are shown in Table 65 below

Table 65: Eligible patient numbers and uptake for 5 years (2013 – 2017)

	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible Population	2048	2058	2069	2079	2089
Assumed uptake	10%	20%	30%	40%	50%

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

Carboplatin and paclitaxel have been the standard of care for first-line ovarian cancer therapy for almost a decade.

8.3 What assumption(s) were made about market share (when relevant)?

Following positive recommendation, it has been assumed that uptake will grow by 10% year on year, as shown in Table 65 above

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

All relevant costs have been considered within the economic model and the budget impact model utilizes these costs entirely

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

All unit costs were based on national reference costs or adverse event costs from the 2 trials, GOG-0218 and ICON7.

8.6 Were there any estimates of resource savings? If so, what were they?

There were no estimated resource savings

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

The budget impact model covers 5 years. Based upon incremental costs per patient of £27,088 for the 15mg/kg dose the 5 year cumulative incremental impact is £84,337,942. Based upon a 7.5mg/kg dose the 5 year cumulative incremental impact is £55,198,884. Table 66 shows the incremental impact across 5 years (2013 – 2016) for both doses.

Table 66: 5 year budget impact

	Incremental Cost	Year 2013	2014	2105	2016	2017	Total
Eligible Population		2048	2058	2069	2079	2089	
Uptake of bevacizumab		10%	20%	30%	40%	50%	
Incremental Budget Impact for ***15mg dose***	***£27,088***	***£5,548,137***	***£11,151,756***	***£16,811,271***	***£22,527,104***	***£28,299,674***	**£84,337,942**
Incremental Budget Impact for **7.5mg dose**	***£17,729***	**£3,631,236**	**£7,298,784**	**£11,002,918**	**£14,743,910**	**£18,522,036**	**£55,198,884**

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No

9 References

Please use a recognised referencing style, such as Harvard or Vancouver.

References

Abdel-Rahman, M., Stockton, D., Rachet, B., Hakulinen, T., & Coleman, M. P. 2009, "What if cancer survival in Britain were the same as in Europe: how many deaths are avoidable?", *Br.J.Cancer*, vol. 101 Suppl 2, p. S115-S124.

Alvarez, A. A., Krigman, H. R., Whitaker, R. S., Dodge, R. K., & Rodriguez, G. C. 1999, "The prognostic significance of angiogenesis in epithelial ovarian carcinoma", *Clin.Cancer Res.*, vol. 5, no. 3, pp. 587-591.

Armstrong, D. K., Bundy, B., Wenzel, L., Huang, H. Q., Baergen, R., Lele, S., Copeland, L. J., Walker, J. L., & Burger, R. A. 2006, "Intraperitoneal cisplatin and paclitaxel in ovarian cancer", *N.Engl.J.Med.*, vol. 354, no. 1, pp. 34-43.

Baum, M., Priestman, T., West, R., & Jones, E. 1980, "A comparison of subjective responses in a trial comparing endocrine with cytotoxic treatment in advanced carcinoma of the breast.", *Eur J Cancer.*, vol. Suppl 1:223-6.

Benedet, J. L., Bender, H., Jones, H., Ngan, H. Y., & Pecorelli, S. 2000, "FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology", *Int.J.Gynaecol.Obstet.*, vol. 70, no. 2, pp. 209-262.

Bergers, G. & Benjamin, L. E. 2003, "Tumorigenesis and the angiogenic switch", *Nat.Rev Cancer*, vol. 3, no. 6, pp. 401-410.

Berrino, F., De, A. R., Sant, M., Rosso, S., Bielska-Lasota, M., Coebergh, J. W., & Santaquilani, M. 2007, "Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995-99: results of the EUROCARE-4 study", *Lancet Oncol.*, vol. 8, no. 9, pp. 773-783.

Boocock, C. A., Charnock-Jones, D. S., Sharkey, A. M., McLaren, J., Barker, P. J., Wright, K. A., Twentyman, P. R., & Smith, S. K. 1995, "Expression of vascular endothelial growth factor and its receptors flt and KDR in ovarian carcinoma", *J.Natl.Cancer Inst.*, vol. 87, no. 7, pp. 506-516.

Bookman, M. A., Brady, M. F., McGuire, W. P., Harper, P. G., Alberts, D. S., Friedlander, M., Colombo, N., ., Fowler, J. M., Argenta, P. A., De, G. K., Mutch, D. G., ., Burger, R. A., Swart, A. M., ., Trimble, E. L., Accario-Winslow, C., & Roth, L. M. 2009, "Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a Phase III Trial of the Gynecologic Cancer Intergroup", *J.Clin.Oncol.*, vol. 27, no. 9, pp. 1419-1425.

Burger, R. A., Sill, M. W., Monk, B. J., Greer, B. E., & Sorosky, J. I. 2007, "Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study", *J.Clin.Oncol.*, vol. 25, no. 33, pp. 5165-5171.

Calvert, A. H., Newell, D. R., Gumbrell, L. A., O'Reilly, S., Burnell, M., Boxall, F. E., Siddik, Z. H., Judson, I. R., Gore, M. E., & Wiltshaw, E. 1989, "Carboplatin dosage: prospective evaluation of a simple formula based on renal function", *Journal of Clinical Oncology*, vol. 7, no. 11, pp. 1748-1756.

Cancer Research UK. Ovarian cancer statistics – UK. 2011a. 2011a.

Cancer Research UK. Table 1.1: Ovarian Cancer (C56-C57), Number of New Cases, Crude and European Age-Standardised (AS) Incidence Rates per 100,000 Population, UK, 2008. http://info.cancerresearchuk.org/cancerstats/types/ovary/incidence/ . 18-7-2011b. 23-9-2011b.

Cannistra, S. A., Matulonis, U. A., Penson, R. T., Hambleton, J., Dupont, J., Mackey, H., Douglas, J., Burger, R. A., Armstrong, D., Wenham, R., & McGuire, W. 2007, "Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer", *J.Clin.Oncol.*, vol. 25, no. 33, pp. 5180-5186.

Cella DF, T. D. G. G. S. B. L. S. L. E. B. A. S. M. Y. S. W. P. B. J. E. K. P. S. B. C. G. M. B. M. S. I. M. M. B. P. K. E. T. S. T. C. H. J. 1993, "The Functional Assessment of Cancer Therapy (FACT) Scale: Development and validation of the general measure.", *J Clin Oncol*, vol. 11 (3), 570-579..

Coates A, G. V. B. J. J. P. W. R. S. R. T. M. B. M. H. V. G. G. 1987, "Improving the quality of life during chemotherapy for advanced breast cancer. A comparison of intermittent and continuous treatment strategies.", *N Engl J Med.*, vol. Dec 10;317(24):1490-5..

Cockcroft, D. W. & Gault, M. H. 1976, "Prediction of Creatinine Clearance from Serum Creatinine", *Nephron*, vol. 16, no. 1, pp. 31-41.

Coleman, M. P., Forman, D., Bryant, H., Butler, J., Rachet, B., Maringe, C., Nur, U., Tracey, E., Coory, M., Hatcher, J., McGahan, C. E., Turner, D., Marrett, L., Gjerstorff, M. L., Johannesen, T. B., Adolfsson, J., Lambe, M., Lawrence, G., Meechan, D., Morris, E. J., Middleton, R., Steward, J., & Richards, M. A. 2011, "Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995-2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data", *Lancet*, vol. 377, no. 9760, pp. 127-138.

Colombo, N., Peiretti, M., Parma, G., Lapresa, M., Mancari, R., Carinelli, S., Sessa, C., & Castiglione, M. 2010, "Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up", *Ann.Oncol.*, vol. 21 Suppl 5, p. v23-v30.

Commercial Medicines Unit. Electronic Market Information Tool. http://cmu.dh.gov.uk/electronic-market-information-tool-emit/ . 2012. Department of Health.

Cooper, B. C., Cooper, B. C., Ritchie, J. M., Ritchie, J. M., Broghammer, C. L. W., Broghammer, C. L., Coffin, J., Coffin, J., Sorosky, J. I., Sorosky, J. I., Buller, R. E., Buller, R. E., Hendrix, M. J. C., Hendrix, M. J., Sood, A. K., & Sood, A. K. 2002, "Preoperative serum vascular endothelial growth factor levels: significance in ovarian cancer", *Clin.Cancer Res.*, vol. 8, no. 10, pp. 3193-3197.

Department of Health 2011, *NHS reference costs 2010/11*, Department of Health.

du Bois A., Reuss, A., Pujade-Lauraine, E., Harter, P., Ray-Coquard, I., & Pfisterer, J. 2009, "Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO)", *Cancer*, vol. 115, no. 6, pp. 1234-1244.

Du Bois D. & Du Bois, E. F. 1989, "A formula to estimate the approximate surface area if height and weight be known. 1916", *Nutrition*, vol. 5, no. 5, pp. 303-311.

du Bois, A. 2001, "Treatment of advanced ovarian cancer", *Eur.J.Cancer*, vol. 37 Suppl 9, p. S1-S7.

du Bois, A., Luck, H. J., Meier, W., Adams, H. P., Mobus, V., Costa, S., Bauknecht, T., Richter, B., Warm, M., Schroder, W., Olbricht, S., Nitz, U., Jackisch, C., Emons, G., Wagner, U., Kuhn, W., & Pfisterer, J. 2003, "A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer", *J.Natl.Cancer Inst.*, vol. 95, no. 17, pp. 1320-1329.

du Bois, A., du, B. A., Reuss, A., Reuss, A., Pujade-Lauraine, E., Pujade-Lauraine, E., Harter, P., Harter, P., Ray-Coquard, I., Ray-Coquard, I., Pfisterer, J., & Pfisterer, J. 2009, "Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO)", *Cancer*, vol. 115, no. 6, pp. 1234-1244.

Dunnett CW 1955, " A multiple comparison procedure for comparing several treatments with a control,", *JASA*, vol. 50(272):1096-1121.

Ferrara, N. & Davis-Smyth, T. 1997, "The biology of vascular endothelial growth factor", *Endocr Rev*, vol. 18, p. 4.

Ferrara, N., Gerber, H. P., & LeCouter, J. 2003, "The biology of VEGF and its receptors", *Nat.Med.*, vol. 9, no. 6, pp. 669-676.

Gonzalez-Martin A, Gladieff L, Tholander B, Stroyakovsky D, Gore M, Segalla J, Reyners A, Kovalenko N, Oaknin A, Selle F, Bollag D, & Pignata S "Safety of front-line bevacizumab combined with weekly paclitaxel and Q3W carboplatin for ovarian cancer: results from OCTAVIA", in *ASCO*, p. S5017.

Guarneri, V., Piacentini, F., Barbieri, E., & Conte, P. F. 2010, "Achievements and unmet needs in the management of advanced ovarian cancer", *Gynecol.Oncol.*, vol. 117, no. 2, pp. 152-158.

GUEST, J. F., RUIZ, F. J., GREENER, M. J., & TROTMAN, I. F. 2006, "Palliative care treatment patterns and associated costs of healthcare resource use for specific advanced cancer patients in the UK", *European Journal of Cancer Care*, vol. 15, no. 1, pp. 65-73.

Heintz, A. P. M., Odicino, F., Maisonneuve, P., Quinn, M. A., Benedet, J. L., Creasman, W. T., Ngan, H. Y. S., Pecorelli, S., & Beller, U. 2006, "Carcinoma of the ovary. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer", *Int.J Gynaecol.Obstet.*, vol. 95 Suppl 1, p. S161-S192.

Helgeson, V. S. & Tomich, P. L. 2005, "Surviving cancer: a comparison of 5-year disease-free breast cancer survivors with healthy women", *Psychooncology.*, vol. 14, no. 4, pp. 307-317.

Herschbach, P., Keller, M., Knight, L., Brandl, T., Huber, B., Henrich, G., & Marten-Mittag, B. 2004, "Psychological problems of cancer patients: a cancer distress screening with a cancer-specific questionnaire", *Br.J Cancer*, vol. 91, no. 3, pp. 504-511.

Holschneider, C. H. & Berek, J. S. 2000, "Ovarian cancer: epidemiology, biology, and prognostic factors", *Semin.Surg.Oncol.*, vol. 19, no. 1, pp. 3-10.

Itakura, J., Ishiwata, T., Shen, B., Shen, B., Kornmann, M., & Korc, M. 2000, "Concomitant over-expression of vascular endothelial growth factor and its receptors in pancreatic cancer", *Int.J.Cancer*, vol. 85, no. 1, pp. 27-34.

Joint Formulary Committee. British National Formulary. 63. 2012. London, BMJ Goup and Pharmaceutical Press.

Katsumata N, Yasuda M, & Isonishi S. Long-term follow-up of a randomized trial comparing conventional paclitaxel and carboplatin with dose-dense weekly paclitaxel and carboplatin in women with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer: JGOG 3016 trial. Makoto Y, Isonishi S, Michimae H, Kimura E, Aoki D, Toshiko J, Kodama S, Terauchi F, Tsuda H, Sugiyama T, Ochiai K, and Japanese Gynecologic Oncology Group. Journal of Clinical Oncology 30, S5003. 5-6-2012.

Katsumata, N., Yasuda, M., Takahashi, F., Isonishi, S., Jobo, T., Aoki, D., Tsuda, H., Sugiyama, T., Kodama, S., Kimura, E., Ochiai, K., & Noda, K.

2009, "Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial", *Lancet*, vol. 374, no. 9698, pp. 1331-1338.

Kitchener, H. C. 2008, "Survival from cancer of the ovary in England and Wales up to 2001", *Br.J.Cancer*, vol. 99 Suppl 1, p. S73-S74.

Liu, C. D., Tilch, L., Kwan, D., & McFadden, D. W. 2002, "Vascular endothelial growth factor is increased in ascites from metastatic pancreatic cancer", *J.Surg.Res.*, vol. 102, no. 1, pp. 31-34.

Markman, M. & Bookman, M. A. 2000, "Second-line treatment of ovarian cancer", *Oncologist.*, vol. 5, no. 1, pp. 26-35.

McGuire, W. P. & Markman, M. 2003, "Primary ovarian cancer chemotherapy: current standards of care", *Br.J.Cancer*, vol. 89 Suppl 3, p. S3-S8.

Medical Research Council. ICON8: An international phase III randomised trial of dose-fractionated chemotherapy compared to standard three-weekly chemotherapy, following immediate primary surgery or as part of delayed primary surgery, for women with newly diagnosed epithelial ovarian, fallopian tube or primary peritoneal cancer. Current Controlled Trials . 2011. 4-7-2012.

Millar, D. R., Corrie, P., Hill, M., & Pulfer, A. PCN74 A SERVICE EVALUATION TO COMPARE SECONDARY CARE RESOURCE USE BETWEEN XELOX AND FOLFOX-6 REGIMENS IN THE TREATMENT OF METASTATIC COLORECTAL CANCER (MCRC) FROM A UK NATIONAL HEALTH SERVICE (NHS) PERSPECTIVE. Value in Health 11[6], A483. 1-11-2008.

Miller, K., Wang, M., Gralow, J., Dickler, M., Cobleigh, M., Perez, E. A., Shenkier, T., Cella, D., & Davidson, N. E. 2007, "Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer", *N.Engl.J Med.*, vol. 357, no. 26, pp. 2666-2676.

Modesitt, S. C. & Jazaeri, A. A. 2007, "Recurrent epithelial ovarian cancer: pharmacotherapy and novel therapeutics", *Expert.Opin.Pharmacother.*, vol. 8, no. 14, pp. 2293-2305.

Muggia, F. 2009, "Platinum compounds 30 years after the introduction of cisplatin: implications for the treatment of ovarian cancer", *Gynecol.Oncol.*, vol. 112, no. 1, pp. 275-281.

Neijt, J. P., Engelholm, S. A., Tuxen, M. K., Sorensen, P. G., Hansen, M., Sessa, C., de Swart, C. A., Hirsch, F. R., Lund, B., & van Houwelingen, H. C. 2000, "Exploratory phase III study of paclitaxel and cisplatin versus paclitaxel and carboplatin in advanced ovarian cancer", *J.Clin.Oncol.*, vol. 18, no. 17, pp. 3084-3092.

NICE 2003, *Review of the clinical effectiveness and cost effectiveness of paclitaxel for ovarian cancer: NICE Technology Appraisal 55*, National Institute of Health and Clinical Excellence.

NICE. Guide to Methods of Technology Appraisal. http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf . 23-6-2008. National Institute for Health and Clinical Excellence. 25-10-2011.

NICE 2011, *The recognition and initial management of ovarian cancer: Clinical Guideline 122*, National Institute of Health and Clinical Excellence.

O'Cearbhaill RE, e. al. 2010, "CA125 response to bevacizumab in recurrent ovarian cancer..", *J Clin Oncol*, vol. 28 (May 20 Suppl.):409s (Abstract 5077).

Office of National Statistics 2011a, *Mid-2010 Population Estimates: England; estimated resident population by single year of age and sex.*, Office of National Statistics.

Office of National Statistics 2011b, *Mid-2010 Population Estimates: Wales; estimated resident population by single year of age and sex.*, Office of National Statistics.

Olson C, e. a. 2010, "Tumor marker response in women treated with bevacizumab.", *Gynecol Oncol*, vol. 166 (Issue 3, Suppl.): (Abstract 256)..

Ozols, R. F., Bundy, B. N., Greer, B. E., Fowler, J. M., Clarke-Pearson, D., Burger, R. A., Mannel, R. S., DeGeest, K., Hartenbach, E. M., & Baergen, R. 2003, "Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study", *J.Clin.Oncol.*, vol. 21, no. 17, pp. 3194-3200.

Paley, P. J., Staskus, K. A., Gebhard, K., Mohanraj, D., Twiggs, L. B., Carson, L. F., & Ramakrishnan, S. 1997, "Vascular endothelial growth factor expression in early stage ovarian carcinoma", *Cancer*, vol. 80, no. 1, pp. 98-106.

Papaioannou, D., Rafia, R., Stevens, J., Stevenson, M., & Evans, P. 2010, *Trabectedin for the treatment of relapsed ovarian cancer: A Single Technology Appraisal* ScHARR, The University of Sheffield, 08/212/01.

PSSRU 2011, *Unit Costs of Health and Social Care 2011*, Personal Social Services Research Unit, Canterbury, Kent.

Ramakrishnan, S., Subramanian, I. V., Yokoyama, Y., & Geller, M. 2005, "Angiogenesis in normal and neoplastic ovaries", *Angiogenesis.*, vol. 8, no. 2, pp. 169-182.

Roche Products Ltd. Avastin Summary of Product Characteristics. http://www.medicines.org.uk/EMC/medicine/15748/SPC/Avastin+25mg+ml+concentrate+for+solution+for+infusion/ . 2012. 2012.

Rustin, G., van der, B. M., Griffin, C., Qian, W., & Swart, A. M. 2011, "Early versus delayed treatment of relapsed ovarian cancer", *Lancet.*, vol. 377, no. 9763, pp. 380-381.

Sacco, J. J., Botten, J., Macbeth, F., Bagust, A., & Clark, P. 2010, "The Average Body Surface Area of Adult Cancer Patients in the UK: A Multicentre Retrospective Study", *PLoS ONE*, vol. 5, no. 1, p. e8933.

Sandler, A., Gray, R., Perry, M. C., Brahmer, J., Schiller, J. H., Dowlati, A., Lilenbaum, R., & Johnson, D. H. 2006, "Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer", *N.Engl.J Med.*, vol. 355, no. 24, pp. 2542-2550.

Sant, M., Allemani, C., Santaquilani, M., Knijn, A., Marchesi, F., & Capocaccia, R. 2009, "EUROCARE-4. Survival of cancer patients diagnosed in 1995-1999. Results and commentary", *Eur.J.Cancer*, vol. 45, no. 6, pp. 931-991.

Seamon, L. G., Richardson, D. L., & Copeland, L. J. 2012, "Evolution of the Gynecologic Oncology Group protocols in the treatment of epithelial ovarian cancer", *Clin.Obstet.Gynecol.*, vol. 55, no. 1, pp. 131-155.

Smerdel, M. P., Steffensen, K. D., Waldstrom, M., Brandslund, I., & Jakobsen, A. 2010, "The predictive value of serum VEGF in multiresistant ovarian cancer patients treated with bevacizumab", *Gynecol.Oncol.*, vol. 118, no. 2, pp. 167-171.

Surveilance Epidemiology and End Results 2010, *SEER Cancer Statistics Review, 1975-2007*, National Cancer Institute., Bethesda, MD.

Therasse P, A. S. E. E. e. al. 2000, "New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada.", *J Natl Cancer Inst*, vol. 92:205.16..

Thomson, C. S. & Forman, D. 2009, "Cancer survival in England and the influence of early diagnosis: what can we learn from recent EUROCARE results?", *Br.J.Cancer*, vol. 101 Suppl 2, p. S102-S109.