NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single technology appraisal (STA)

Bevacizumab for the treatment of recurrent advanced ovarian cancer

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Executive summary

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). The anticipated new indication is in combination with carboplatin and gemcitabine, for the treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents. 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).

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%. Although up to 70% of presenting patients achieve a response after debulking surgery and first-line chemotherapy, 55-75% of these patients relapse with recurrent disease within 2 years. Additional chemotherapy in second and subsequent lines can alleviate symptoms and further prolong survival, but for the majority of patients treatment following recurrence is palliative rather than curative. It has long been accepted that platinum compounds are the most effective therapy for a majority of ovarian cancers. Platinum sensitive patients are those who have disease recurrence more than 6 months after previous platinum therapy. These patients have a wider choice of subsequent therapies and much better prognosis than those who have recurrence less than 6 months after platinum therapy (platinum resistant disease). Strategies which can delay recurrence and prolong the platinum-free interval after both first and subsequent lines of therapy are therefore very important for improving the outlook for ovarian cancer patients.

Data for this submission come from a single phase III study which addressed the efficacy, safety and quality of life seen with bevacizumab, in combination with chemotherapy, for second-line treatment of recurrent platinum-sensitive ovarian cancer. OCEANS (AVF4095g) was a multicentre, placebo-controlled, Phase III randomised trial in 484 patients with recurrent platinum sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer. The OCEANS trial evaluated the efficacy and safety of bevacizumab (BV), given in combination with six to ten cycles of carboplatin and gemcitabine followed by bevacizumab maintenance therapy (until disease progression), compared with carboplatin and gemcitabine given with placebo followed by placebo (PL) maintenance.

In OCEANS, the addition of bevacizumab gave a significant improvement in the primary endpoint of progression free survival, with a 4 month increase in median PFS (BV: 12.4 months; PL: 8.4 months). Additionally, the risk of progression was more than halved for the BV arm relative to the PL arm (HR: 0.484; 95% CI: 0.388 – 0.605; $p<0.0001$). In addition, significantly more patients achieved an objective complete or partial response with BV than with

PL (BV: 78.5%; PL: 57.4%). These PFS and Objective response rate (ORR) benefits were confirmed by an independent review committee. Data for overall survival are currently immature and represent 60% of events (final OS data are expected end 2013). The most recent analysis shows no significant difference in OS between the treatment arms (BV: 33.4 months; PL: 33.7 months; HR: 0.960; 95% CI: 0.760 – 1.214). However, several factors may have confounded the OS results, for example more patients in the PL than in the BV arm received post-progression bevacizumab (BV: 18.1%; PL: 34.7%).

The tolerability profile of bevacizumab in the OCEANS study was consistent with previous experience of bevacizumab in other cancer types and with the safety profile of bevacizumab in front-line therapy of ovarian cancer. No new safety concerns were identified and the elevated risk of gastrointestinal perforation seen in earlier Phase II trials of bevacizumab in recurrent ovarian cancer was not replicated.

Economic summary

A cost utility analysis was conducted comparing bevacizumab in combination with carboplatin and gemcitabine against carboplatin and gemcitabine chemotherapy alone in patients with recurrent platinum-sensitive ovarian cancer using patient-level data from the key clinical trial in this indication; OCEANS. 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.) and a 10 year time horizon was used to capture all relevant costs and benefits.

The model was 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 the OCEANS study. Resource use and utility for patients in each health state were 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).

The base case results of the economic evaluation demonstrate that the addition of bevacizumab to carboplatin and gemcitabine combination chemotherapy provides an additional 0.42 years (0.298 QALYs) to patients with an expected survival of approximately three and a half years. This benefit is achieved with an incremental cost of £44,428, resulting in an ICER of approximately £149,050 per QALY for bevacizumab at the licensed dose.

Table 1 Base-case cost-effectiveness results for OCEANS (Bevacizumab + carboplatin/gemcitabine vs carboplatin/gemcitabine alone)

	Bevacizumab + Chemotherapy	**Chemotherapy**
Technology acquisition cost	£44,879	£1,096
Other costs	£14,461	£13,816
Total costs	£59,340	£14,912
Difference in total costs		**£44,428**
LYG	3.3877	2.956
LYG difference		**0.420**
QALYs	2.276	1.978
QALY difference		**0.298**
ICER		**£149,050**

Sensitivity analysis revealed that this estimate was most sensitive to assumptions around the extrapolation of OS beyond the follow-up period of the trial, the duration of treatment and the utility of patients in the PFS health state. Caution must be exercised when interpreting these results since they are based on immature data from the OCEANS study.

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).

Bevacizumab does not currently have a UK marketing authorisation for the treatment of recurrent or relapsed advanced ovarian cancer. It is expected to be approved by EMA by November 2012 for the treatment of women with platinum-sensitive or partially platinum-sensitive recurrent epithelial ovarian carcinoma.

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).

One main issue concerns the proposed indication. Roche proposed that the indication should state “Avastin, in combination with carboplatin and gemcitabine, is indicated for treatment of patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer”. However, the CHMP stated that this did not adequately describe the population recruited to the pivotal OCEANS clinical study, where patients previously treated with bevacizumab or other anti-VEGF agents were excluded. The indication now agreed is shown below.

A second issue has arisen around the overall survival (OS) results available from the OCEANS clinical study. At the time of the initial analysis of PFS, when only 29% of patients had died an interim analysis of OS suggested a benefit for patients receiving bevacizumab in the pivotal study. The CHMP requested more mature OS data. A second interim analysis, when 48% of patients had died, suggested that there might be a deficit in OS for the patients given bevacizumab. Finally a third interim OS analysis, when 60% of patients had died in March 2012, showed no difference in OS between the 2 arms of the pivotal study.

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 gemcitabine, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents

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 data is expected in the reference population.

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), metastatic breast cancer (mBC) and for front-line treatment of advanced ovarian cancer (aOC). 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 is due to be made in November 2012 with final public guidance expected in March 2013.

Assessment is currently underway for front-line treatment for women with advanced ovarian cancer after surgery by NICE [ID435] and SMC with final public guidance anticipated in April 2013 and October 2012 respectively.

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 A1 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 platinum sensitive recurrent aOC bevacizumab has been studied at doses of 15mg/kg (OCEANS).
Dosing frequency	Bevacizumab has been administered in clinical trials every 21 days, until disease progression or unacceptable toxicity (OCEANS)
Average length of a course of treatment	The mean treatment duration in OCEANS was 7.5 months. This equates to 10.8 cycles on a 21 day treatment cycle.
Average cost of a course of treatment	£22,797 with vial sharing (10.8 cycles x £2111) or £25,208 full vials (10.8 cycles x £2,334) for 15mg/kg, based on a patient weight of 60.5kg.
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 recurrent 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?

6 to 10 x 3-weekly cycles of intravenous carboplatin (day 1) and gemcitabine (day 1 and 8) 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;NICE 2008b). 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 2012), 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 2012;Kitchener 2008)

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). However, even amongst patients with Stage III and IV tumours, whose median OS may be only 2-3 years, between 10 - 20% of patients survive for as long as ten years (du Bois et al. 2009;Heintz et al. 2006), 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. Although up to 70% of patients achieve a response after debulking surgery and first-line chemotherapy, 55-75% of these patients relapse, with recurrent disease within 2 years. Additional chemotherapy in second and subsequent lines can alleviate symptoms and further prolong survival, but as shown above, the prognosis for ovarian cancer patients is, in general, very poor.

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 et al. 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 et al. 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. This was confirmed by early studies of single agent bevacizumab in recurrent ovarian cancer, where an objective response rate of 16-30% was observed, with disease stabilisation in up to 52% of patients (Burger et al. 2007;Cannistra et al. 2007;Smerdel et al. 2010)

Clinical need for improved therapeutic efficacy

For the majority of patients, treatment following recurrence is palliative rather than curative. The type of therapy used in recurrent disease is determined by the time since last platinum therapy. Platinum combination therapy is the preferred option in patients who have recurred more than 6 months after previous platinum therapy (platinum sensitive and partially sensitive patients). This can achieve median progression free survival (PFS) of up to 12 months and overall survival (OS) up to 29 months (Parmar et al. 2003). A number of single-agent non-platinum therapies, such as paclitaxel, gemcitabine, topotecan and pegylated liposomal doxorubicin, are used in platinum-resistant patients, i.e. those who develop recurrence less than 6 months after prior platinum therapy. However, the median PFS and OS for such patients is very much shorter than in the platinum sensitive population.

It has been well-established that the probability of response to platinum-retreatment is directly related to the interval between therapy and relapse (Gore et al. 1990). Therefore, strategies which can prolong the platinum-free interval after both first and subsequent lines of therapy are very important for improving the outlook for ovarian cancer patients.

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.

About 4,300 patients per year receive first-line chemotherapy for ovarian cancer in the UK and at relapse 79% of these patients will have platinum sensitive or partially sensitive disease. Of this population, about 6% are likely to enter into clinical studies, as many as 30% of the remaining patients may be unsuitable for further chemotherapy and about 4% are likely to have contraindications to bevacizumab. This suggests that a total of approximately

2,100 patients should be eligible for second-line bevacizumab therapy in the UK.

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.

Cancer Research UK quote data for women diagnosed in Anglia with ovarian cancer between 2004 and 2008. These statistics show that about 35% of patients were diagnosed with early stage (I and II) disease and for them 5-year overall survival (OS) was greater than 50%. However, for patients diagnosed with advanced stage (III and IV) disease, the prognosis is much poorer. More than 40% of patients were diagnosed with Stage III disease and only about 20% of these patients survived for 5 years. For the 15% of patients with Stage IV disease at diagnosis, 5 year OS was only 6% (Cancer Research UK 2012).

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 (NICE 2003) . Although most patients (70% to 80%) initially respond to first-line chemotherapy, most responders eventually relapse (55% to 75% within 2 years) (NICE 2003).

The timing of relapse after platinum therapy is highly prognostic and determines the therapy for recurrent disease; patients relapsing within 6 months are regarded as platinum resistant and NICE lists subsequent therapeutic options of single-agent treatment with paclitaxel, pegylated liposomal doxorubicin and topotecan (NICE 2008b). Alongside these, other guidelines recommend use of etoposide or gemcitabine (Colombo et al. 2010;NCCN Guidelines 2012). Patients who relapse more than 6 months following platinum-therapy are considered suitable for retreatment with platinum combination therapy, and are deemed either partially platinum-sensitive (6 – 12 months PFI) or platinum-sensitive (≥ 12 months PFI).

Platinum-based therapies are used in subsequent lines of therapy for as long as patients remain sensitive, because of the recognition that platinum compounds are the most effective therapy for a majority of ovarian cancers. Eventually, most patients become platinum resistant and the therapies available to them are then restricted, with very poor outcomes and very short expected survival (< 12 months) (Naumann & Coleman 2011).

A new therapy which can extend PFS for platinum sensitive patients in the second-line setting will not only improve the outcome of second-line therapy, but will also maintain more patients in the ‘platinum sensitive’ group, thereby increasing their choice of therapy and thus improving their outcomes in subsequent lines.

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

The choice of platinum agent 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.

The current NICE-recommended standard of care for platinum-sensitive patients is paclitaxel in combination with platinum-based therapy (NICE TA91). However, this may not always be the preferred option, as patients retreated with a paclitaxel-platinum combination within 12-24 months of front-line therapy are at risk of significant neurotoxicity (Colombo et al. 2010;Pfisterer & Ledermann 2006). For this reason, international guidelines also recommend the combination of carboplatin with gemcitabine, docetaxel or pegylated liposomal doxorubicin (PLD) (Colombo et al. 2010;NCCN Guidelines 2012).

The single-agent therapy of choice in UK clinical practice for partially platinum-sensitive patients is also an issue for consideration. PLD is recommended by NICE, and may be the preferred choice of many clinicians (NICE 2008b).However, due to manufacturing issues, PLD has not been available on the UK market since 2011.

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

Three-weekly therapy with carboplatin plus gemcitabine is the main comparator.

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 £265 per cycle (NHS Reference costs 2010/2011 (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:

3.1.2 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;

3.1.3 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

3.1.4 could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

3.1.5 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.

3.1.6 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.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Women with recurrent platinum sensitive or partially platinum sensitive advanced epithelial ovarian, fallopian tube of primary peritoneal cancer	As per scope	
Intervention	Bevacizumab in combination with platinum based therapy	Bevacizumab in combination with gemcitabine and carboplatin	License is expected to be granted in combination only with gemcitabine and carboplatin
Comparator(s)	Paclitaxel in combination with a platinum compound Gemcitabine in combination with carboplatin Pegylated liposomal doxorubicin hydrochloride in combination with a platinum compound Platinum-based chemotherapy as monotherapy	As per scope	
Outcomes	The outcome measures to be considered include: overall survival progression-free	As per scope	

	survival response rate adverse effects of treatment health-related 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	
Subgroups to be considered	None	Fully platinum sensitive (relapse >12 months after last platinum therapy) and Partially platinum sensitive (relapse 6-12 months after last platinum therapy)	These sub groups arose from a stratification factor in the OCEANS trial
Special considerations, including issues related to equity or equality	None		

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

6.1.1 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 10.2, appendix 2.

A systematic review was conducted to identify any large (n ≥ 200) randomised controlled trials evaluating bevacizumab in combination with carboplatin and gemcitabine for patients with platinum-sensitive recurrent ovarian cancer.

The searches for RCT, and non-RCT data used the same initial search strategy. Searches used index and text words which included *bevacizumab* and *ovarian cancer* as descriptors. The search was restricted to only include documents that were relating to use in women with second-line ovarian cancer, either as part of randomised clinical-trials or non-randomised studies. The pool of results was then further restricted manually according to the eligibility criteria listed later in the document, to identify relevant RCTs (Section**Error! Reference source not found.**) and additionally to identify non-RCTs (Section **Error! Reference source not found.**).

The safety search (Section 6.8) used the same initial search strategy, with the exception that the search was widened to include all studies in the recurrent

ovarian setting. The eligibility criteria for this search are listed in Section **Error! Reference source not found.**.

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.

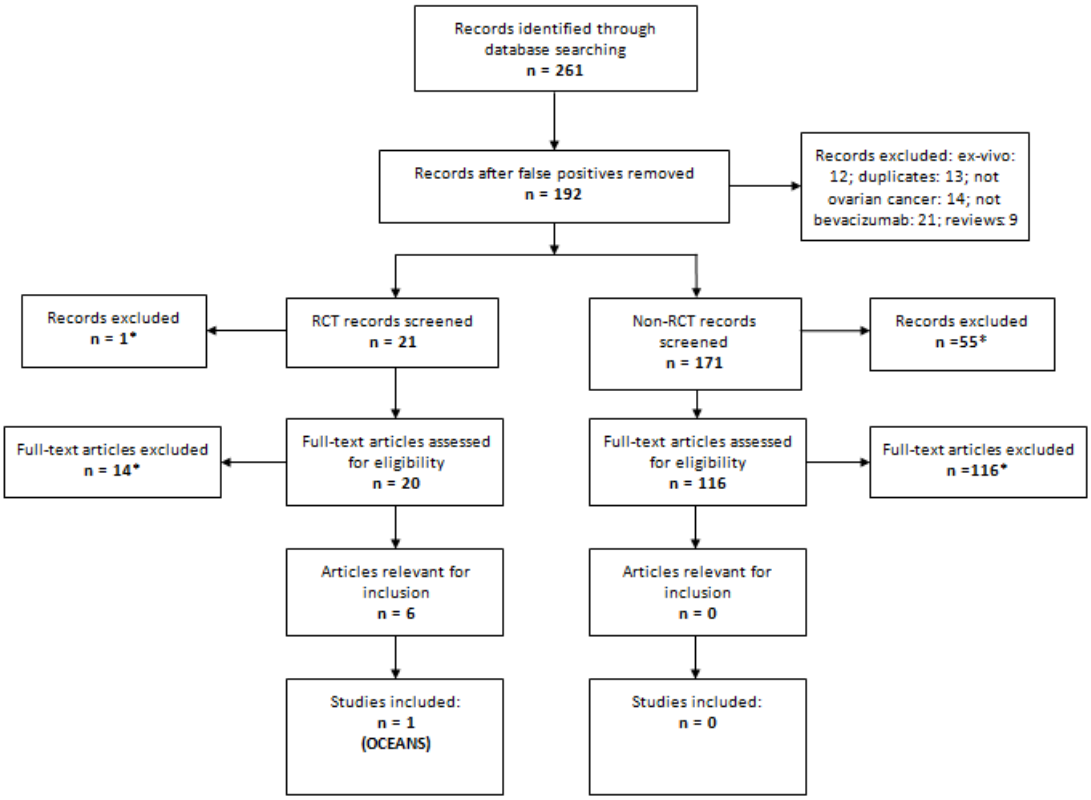
Table B1 Eligibility criteria used in search strategy

	Clinical effectiveness
Inclusion criteria	Population: Platinum-sensitive, second line relapsed/recurrent ovarian cancer Interventions: Bevacizumab in combination with carboplatin and gemcitabine Outcomes: Standard efficacy (eg. PFS, ORR, OS) and safety assessments Study design: Large RCT studies (≥200 patients) Language restrictions: none
Exclusion criteria	Population: Patients with front-line or platinum resistant/refractory ovarian cancer Interventions: Anything other than bevacizumab in combination with carboplatin and gemcitabine Outcomes: None Study design: Small scale (<200 patients) or non-RCT Language restrictions: none

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.

A flow diagram of the numbers of studies included and excluded at each stage is shown in Figure 1.

Figure 1: Systematic review flow diagram



*Reasons for exclusion provided in Appendix**Error! Reference source not found.**. All conference abstracts were reviewed in full-text form.

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.

All relevant publications and abstracts are listed below 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. This should be presented in tabular form. A suggested format is presented below.

Table 1: List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
AVF4095g (OCEANS)	Intravenous carboplatin (AUC 4, day 1) and gemcitabine (1000 mg/m^2, days 1&8) [q3w, 6-10 cycles] plus concurrent and extended intravenous bevacizumab (15 mg/kg, day 1) [q3w until disease progression/ unacceptable toxicity]	Intravenous carboplatin (AUC 4, day 1) and gemcitabine (1000 mg/m^2, days 1&8) [q3w, 6-10 cycles] plus concurrent and extended intravenous placebo (15 mg/kg, day 1) [q3w until disease progression/ unacceptable toxicity]	[n = 484 (ITT)] Patients with platinum-sensitive recurrent ovarian, fallopian tube or primary peritoneal cancer (recurring ≥ 6 months following front line platinum-based therapy) and measurable disease.	Aghajanian et al 2012; J Clin Oncol 30:2039-2045

OCEANS was a multicentre, placebo-controlled, Phase III randomised trial in patients with recurrent platinum sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer. These diseases are histologically equivalent and throughout this document the term ovarian cancer (OC) is used to refer to all three diseases. The OCEANS trial evaluated the efficacy and safety of bevacizumab, when given in combination with carboplatin and gemcitabine followed by bevacizumab maintenance therapy (BV), compared with carboplatin and gemcitabine when given with placebo followed by placebo maintenance (PL).

It was published in the Journal of Clinical Oncology in June 2012:

Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol. 2012 Jun 10;30(17):2039-45. Epub 2012 Apr 23.

The following abstracts have also been published:

Aghajanian C, Blank S, Goff B, et al. An updated safety analysis of OCEANS, a randomized, double-blind, phase III trial of gemcitabine (G) and carboplatin (C) with bevacizumab (BV) or placebo (PL) followed by BV or PL to disease progression (PD) in patients with platinum-sensitive (Plat-S) recurrent ovarian cancer. ASCO 2012 [5054]

Aghajanian C, Makhija S, Rutherford T, et al. Independent radiologic review of OCEANS, a phase III trial of carboplatin, gemcitabine, and bevacizumab or placebo for the treatment of platinum-sensitive, recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. SGO 2012 [68]

Aghajanian C, Blank S, Goff B, et al. Efficacy in patient subgroups in OCEANS, a randomised, double-blinded, placebo-controlled, Phase 3 trial of chemotherapy ± bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian cancer (OC), primary peritoneal cancer (PPC) or fallopian tube cancer (FTC). ECCO/ESMO 2011 Late breaking abstracts (5LBA)

Aghajanian C, Finkler N, Rutherford T, et al. OCEANS: a randomized, double-blinded, placebo-controlled, phase III trial of chemotherapy ± bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian cancers (EOC). ESGO 2011

Aghajanian C, Finkler N, Rutherford T, et al. OCEANS: a randomized, double-blinded, placebo-controlled phase III trial of chemotherapy with or without bevacizumab (BEV) in patients with platinum-sensitive recurrent epithelial ovarian (EOC), primary peritoneal (PPC), or fallopian tube cancer (FTC). ASCO 2011 [LBA5007]

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.

OCEANS compared the intervention directly with the standard treatment of carboplatin plus gemcitabine.

Please see Section 6.7 for an indirect comparison to the other NICE-recommended standard treatments.

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.

OCEANS (AVF4095g) is the only study which compares the intervention with the appropriate comparators.

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 non-RCTs were identified as relevant to the decision problem.

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

6.3.2 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. The following tables provide a suggested format for when there is more than one RCT.

The study design of OCEANS (AVF4095g) is described below in Table 2.

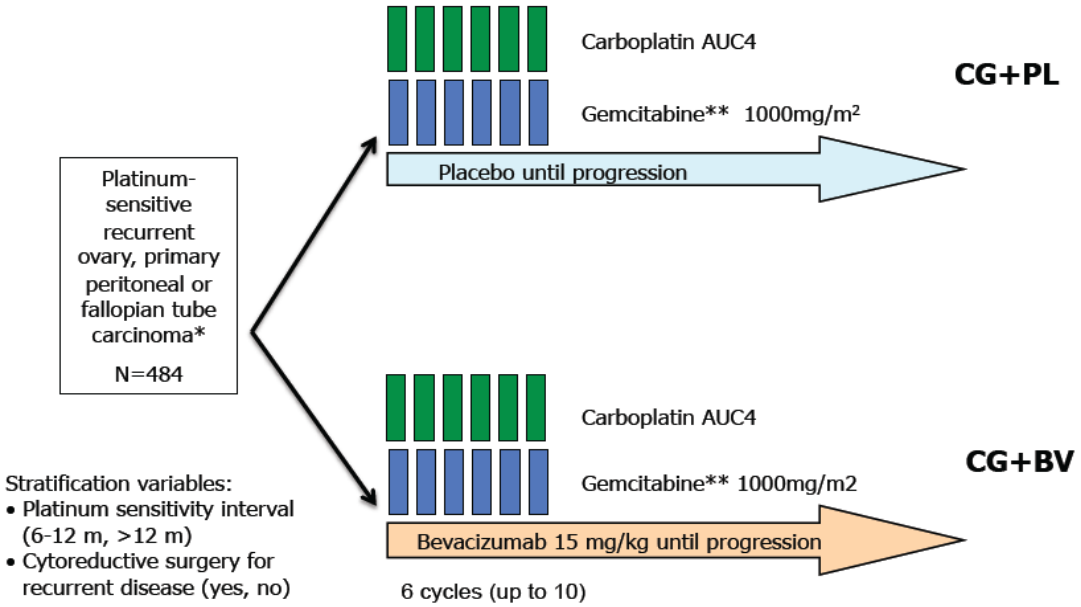
Table 2: Summary of the methodology of OCEANS

Trial no. (acronym)	**AVF4095g (OCEANS)**
Location	A total of 96 investigative sites in the United States participated in the study. The study was sponsored by Genentech.
Design	Phase III, randomized, double-blind, placebo-controlled, multicenter study. See Figure 2 for the study schema.
Duration of study	17th April 2007 (1st patient enrolment) to 17th September 2010 (clinical data cut-off)
Method of randomisation	484 patients were randomised in a 1:1 ratio into one of the two treatment arms (BV or PL). Randomisation was performed using an IVRS (Interactive Voice Response System). At randomization, patients were stratified by two factors: Time to recurrence since the last platinum therapy (recurrence 6–12 months after platinum-based treatment vs. recurrence > 12 months after platinum-based treatment) Cytoreductive surgery for recurrent OC, (surgery performed vs. surgery not performed). Two randomization audits were performed by an external data coordinating centre to ensure that the randomization had been carried out correctly: one after approximately 30 patients and one after approximately 200 patients were enrolled in the study.
Method of blinding (care provider,	The Sponsor's personnel, the Clinical Research Organisation (CRO), investigators, and patients were

Trial no. (acronym)	AVF4095g (OCEANS)
patient and outcome assessor)	blinded to treatment assignment of BV or PL. The Sponsor's personnel remained blinded until the database lock for the final PFS analysis. Subsequent to this database lock, patient treatment assignments were unblinded and provided to the treating investigator. The protocol offered the option of unblinding at progression; therefore, investigators and patients may have been unblinded to treatment assignment of BV or PL at the time of investigator-determined disease progression.
Intervention(s) (n =) and comparator(s) (n =)	OCEANS was a two-armed trial. BV (n=242): Carboplatin AUC 4 q3w (Day 1), gemcitabine 1000 mg/m2 q3w (Days 1 & 8) and bevacizumab 15 mg/kg q3w (Day 1) for 6 – 10 cycles, followed by extended bevacizumab 15 mg/kg q3w (Day 1). PL (n=242): Carboplatin AUC 4 q3w (Day 1), gemcitabine 1000 mg/m2 q3w (Days 1 & 8) and placebo 15 mg/kg q3w (Day 1) for 6 – 10 cycles, followed by extended placebo 15 mg/kg q3w (Day 1). Patients received treatment until disease progression or unacceptable toxicity, whichever came first. All drugs were administered intravenously. Post-progression therapy (including bevacizumab) was not controlled by the study protocol.
Primary outcomes (including scoring methods and timings of assessments)	The primary efficacy outcome measure for this study was investigator-determined PFS. The primary objective of this trial was to evaluate the efficacy of the combination of carboplatin and gemcitabine with concomitant and extended bevacizumab (BV) compared with carboplatin and gemcitabine and concomitant and extended placebo (PL) in patients with platinum-sensitive recurrent OC. The primary efficacy outcome measure was investigator-assessed PFS according to the Response Evaluation Criteria for Solid Tumors (RECIST modified v1.0) Scans for progression were performed at baseline and every 9 weeks until progression.
Secondary outcomes (including scoring methods and timings of assessments)	Secondary outcome measures were: Objective response rates (partial response or complete response as defined by the investigator, per RECIST) Overall survival Duration of objective response

Trial no. (acronym)	AVF4095g (OCEANS)
	Safety assessments evaluated the incidence of all adverse events (AEs) (according to NCI CTCAE v3), serious AEs, and selected AEs. Scans for response were performed at baseline and every 9 weeks until progression. Assessment of AEs was conducted predose at each study visit (days 1 and 8 during the chemotherapy phase, day 1 during the bevacizumab/placebo extension phase) and at the termination of carboplatin-gemcitabine and bevacizumab or placebo. Survival was assessed at follow-up.
Duration of follow-up	Patients were followed for survival every 3 months until death, withdrawal of consent, loss to follow-up or study termination.

Figure 2: OCEANS study schema



*Only patients with measurable disease at baseline are enrolled

**Gemcitabine was given on Day 1 and Day 8

Participants

6.3.3 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 3 - Eligibility criteria of RCTs

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
AVF4095g (OCEANS)	Patients who met the following criteria were eligible for study entry: Age ≥ 18 years Histologically documented OC that had recurred > 6 months after platinum-based chemotherapy This must have been the first recurrence of OC. No prior chemotherapy in the recurrent setting Measurable disease according to RECIST with at least one lesion that could be accurately measured Greater than 28 days from and recovered from prior radiation therapy or surgery Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1	Patients who met any of the following criteria were excluded from study entry. Disease-specific exclusions Concomitant anti-neoplastic anti-hormonal therapy was not allowed. History of abdominal fistula, GI perforations, or intra-abdominal abscess Patients with clinical symptoms or signs of GI obstruction or who required parenteral hydration, parenteral nutrition, or tube feeding Patients with evidence of abdominal free air not explained by paracentesis or recent surgical procedure. General Medical Exclusions Life expectancy of < 12 weeks Screening clinical laboratory values outside of defined ranges History of other malignancies within 5 years of Day 1 Cycle 1, Any other diseases, metabolic dysfunction, that contraindicated the use of an investigational drug or rendered the patient at high risk for treatment complications Bevacizumab-Specific Exclusions Prior bevacizumab or other VEGF/VEGF receptor–targeted agent use Inadequately controlled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg on

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
		antihypertensive medications) History of hypertensive crisis or hypertensive encephalopathy New York Heart Association Class II or greater congestive heart failure (CHF) History of myocardial infarction or unstable angina within 6 months prior to Day 1 Cycle 1 (day of the first BV/PL infusion) History of stroke or transient ischemic attack within 6 months prior to study enrollment Known CNS disease except for treated brain metastasis History of significant vascular disease (e.g. aortic aneurysm, aortic dissection) peripheral arterial thrombosis within 6 months prior to Day 1 Cycle 1 History of hemoptysis (≥ 1/2 teaspoon of bright red blood per episode) within 1 month prior to Day 1 Cycle 1 Evidence of bleeding diathesis or significant coagulopathy Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to Day 1 Cycle 1 Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to Day 1 Cycle 1 Serious, non-healing wound; active ulcer; or untreated bone fracture Proteinuria, as demonstrated by a UPCR of ≥ 1.0 at screening Known hypersensitivity to any component of bevacizumab

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
		Pregnancy (positive pregnancy test) or lactation
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		

6.3.4 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.

The baseline and disease characteristics of patients in OCEANS are summarised in Table 4. Overall, these were comparable between treatment arms. The median age was 61, with just over a third of patients (36.8%) 65 years or older. Median patient weight was 73kg and comparable between the two arms. Almost all patients were of good performance status at baseline (ECOG 0: 75.8%; ECOG 1: 24.0%). Only one patient, in the bevacizumab arm, had an ECOG status of 2. The primary site of cancer in the majority of patients was the ovary (84.1%); most patients had serous adenocarcinoma (80.8%). The proportion of patients with histological subtypes associated with a worse prognosis (mucinous and clear cell) was small and similar between the two arms (mucinous: BV: 1.2%; PL: 0.4%; clear cell: BV: 3.7%; PL: 2.5%).

Less than half the patients in each arm were classified as partially platinum-sensitive (BV: 41.3%; PL: 42.1%). A minority of patients in both arms received cytoreductive surgery following disease recurrence (BV: 12.4%; PL: 9.9%). Tumour sizes and CA-125 (cancer antigen 125, a marker of ovarian tumour burden) levels were comparable between the arms at baseline. Nearly three-quarters of patients had CA125 levels > 35 U/ml (BV: 75.0%;PL 72.6%).The median sum of longest diameters of lesions was 59.0 mm (BV: 60.0 mm [10.0 – 285.0]; PL: 58.0 mm [11.0 – 307.8]).

Table 4: Baseline characteristics of patients in OCEANS

Characteristic	PL (n = 242)	BV (n = 242)	All Patients (n = 484)

Characteristic	PL (n = 242)	BV (n = 242)	All Patients (n = 484)
Age, years			
Mean (SD)	61.6 (10.2)	60.5 (9.8)	61.0 (10.0)
Median	61.0	60.0	61.0
25th and 75th percentiles	55.0, 68.0	53.0, 68.0	54.0, 68.0
Range	28.0–86.0	38.0–87.0	28.0–87.0
No. (%) of patients by age, years			
< 40	2 (0.8)	2 (0.8)	4 (0.8)
40–64	147 (60.7)	155 (64.0)	302 (62.4)
≥ 65	93 (38.4)	85 (35.1)	178 (36.8)
No. (%) of patients by race			
American Indian or Alaska Native	0 (0.0)	2 (0.8)	2 (0.4)
Asian	6 (2.5)	9 (3.7)	15 (3.1)
Black or African American	7 (2.9)	8 (3.3)	15 (3.1)
Native Hawaiian/other Pacific Islander	1 (0.4)	1 (0.4)	2 (0.4)
White	222 (91.7)	218 (90.1)	440 (90.9)
Not Available	6 (2.5)	4 (1.7)	10 (2.1)
No. (%) of patients by ECOG at baseline			
0	185 (76.4)	182 (75.2)	367 (75.8)
1	57 (23.6)	59 (24.4)	116 (24.0)
2	0 (0.0)	1 (0.4)	1 (0.2)
Weight, in kg, at baseline			
Mean (SD)	75.8 (19.1)	75.5 (17.9)	75.7 (18.5)
Median	73.5	71.5	73.0
25th and 75th percentiles	62.1, 84.0	64.0, 84.5	63.0, 84.0
Range	43.6–163.9	41.9–159.6	41.9–163.9
No. (%) of patients by primary site			
Fallopian tube carcinoma	15 (6.2)	14 (5.8)	29 (6.0)
Ovarian carcinoma	207 (85.5)	200 (82.6)	407 (84.1)
Primary peritoneal carcinoma	20 (8.3)	28 (11.6)	48 (9.9)
No. (%) of patients by histology subtype			
Serous	202 (83.5)	189 (78.1)	391 (80.8)
Mucinous	1 (0.4)	3 (1.2)	4 (0.8)
Endometrioid	16 (6.6)	13 (5.4)	29 (6.0)
Transitional cell	2 (0.8)	2 (0.8)	4 (0.8)
Clear cell	6 (2.5)	9 (3.7)	15 (3.1)
Other	10 (4.1)	20 (8.3)	30 (6.2)
Serous, clear cell	1 (0.4)	2 (0.8)	3 (0.6)
Serous, endometrioid	4 (1.7)	2 (0.8)	6 (1.2)
Serous, transitional cell	0 (0.0)	2 (0.8)	2 (0.4)
No. (%) of patients by cytoreductive surgery for recurrent disease			
Yes	24 (9.9)	30 (12.4)	54 (11.2)
No	218 (90.1)	212 (87.6)	430 (88.8)
No. (%) of patients by time to recurrence since the last platinum-based therapy			

Characteristic	PL (n = 242)	BV (n = 242)	All Patients (n = 484)
6–12 months	102 (42.1)	100 (41.3)	202 (41.7)
> 12 months	140 (57.9)	142 (58.7)	282 (58.3)
Baseline SLD of target lesions (mm)			
Mean (SD)	72.4 (52.4)	73.8 (53.0)	73.1 (52.7)
Median	58.0	60.0	59.0
25th and 75th percentiles	34.0, 95.0	36.0, 100.0	35.0, 98.0
Range	11.0–307.8	10.0–285.0	10.0–307.8
No. (%) of patients by baseline SLD category			
≤ Median (59.0 mm)	126 (52.1)	118 (48.8)	244 (50.4)
< Median	116 (47.9)	124 (51.2)	240 (49.6)
No. (%) of patients by baseline CA125			
≤ 35 U/mL	63 (27.4)	57 (25.0)	120 (26.2)
> 35 U/mL	167 (72.6)	171 (75.0)	338 (73.8)

PL = placebo; BV = bevacizumab; ECOG = Eastern Cooperative Oncology Group; SD = standard deviation; SLD = sum of longest diameters.

Outcomes

6.3.5 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.

OCEANS

6.3.5.1 Primary outcome(s) and measures

Progression-free survival

The primary outcome measure in OCEANS was progression-free survival (PFS), determined by the investigators. PFS was assessed using radiologic evaluation according to the modified Response Evaluation Criteria for Solid Tumors (RECIST v1.0). Progression could also be determined by symptomatic progression, but not by CA-125 elevation alone.

PFS was defined as time from randomization to progressive disease or death by any cause.

Primary analysis of PFS was based on the ITT population, censoring for patients without disease-progression or death at time of last tumour assessment, or patients receiving non-protocol-specified therapy.

6.3.5.2 Secondary outcomes

Overall survival

Duration of overall survival (OS) was defined as the time from randomisation to death by any cause. Interim analyses of OS were planned for the time of initial PFS data cut-off, and additionally when approximately 214 deaths had been observed. Final OS analysis will be conducted when 353 patients have died. OS analysis is based on the ITT population.

Objective response

Objective response is defined as the occurrence of a complete (CR) or partial (PR) response (assessed using RECIST), confirmed by a repeat assessment performed ≥ 4 weeks after the criteria for response are first met. Randomised patients not meeting these criteria, including patients without a post-baseline tumor assessment, were considered to be non-responders in the analysis of objective response. The study enrolled only patients with measurable disease at baseline; as a result, the ITT population was used for the analysis of objective response.

Duration of objective response

Duration of objective response was analysed for the subset of patients who achieved an objective response. The duration of objective response was the time from the time of initial CR or PR until documented disease progression or death.

Safety analyses

Safety assessments consisted of monitoring and recording protocol-defined adverse events (AEs) and serious adverse events (SAEs); measurement of biochemistry variables; measurement of vital signs; and other protocol-specified tests deemed critical to the safety evaluation of the study drugs.

Safety assessment was conducted based on the categories below.

- Incidence of all adverse events, graded according to the NCI-CTCAE, version 3.

- Incidence of all serious adverse events.
- Incidence of selected adverse events relevant to bevacizumab.

All the safety analyses were based on the primary safety population (all patients who received any amount of carboplatin, gemcitabine or study drug).

The selected adverse events assessed were those that have previously been identified with bevacizumab across indications: hypertension (Grade ≥ 3); proteinuria (Grade ≥ 3); neutropenia (Grade ≥ 4); febrile neutropenia (all grades); thrombocytopenia (Grade ≥ 4); arterial thromboembolic events (all grades); gastrointestinal perforation (all grades); wound dehiscence (Grade ≥ 3); pulmonary or CNS bleeding (all grades); bleeding other than pulmonary or CNS bleeding (Grade ≥ 3); left ventricular systolic dysfunction (Grade ≥ 3); and RPLS (reversible posterior leukoencephalopathy syndrome) (all grades).

6.3.5.3 Exploratory outcome measures

IRC-assessment of PFS, overall response and duration of response

To evaluate the robustness of the primary endpoint of investigator-determined PFS, an independent-review committee conducted an analysis of PFS using RECIST v1.0. IRC-determined PFS was defined as the time from randomization to disease progression, as defined by the IRC, or on-study death. On-study death was defined as death occurring within 9 weeks of the last dose of chemotherapy or study drug.

Objective response and duration of objective response were also assessed by the IRC using RECIST.

6.3.5.4 Reliability/validity/current use in clinical practice

Progression-free survival

PFS is a valid endpoint for OCEANS, which evaluated the efficacy of second-line treatment. Patients presenting with recurrent ovarian cancer generally have clinical symptoms and measurable deposits of disease. Shrinkage of this disease and alleviation of symptoms is the primary aim of therapy for

recurrent ovarian cancer and PFS is a reasonable measurement of this treatment efficacy. Moreover, the measurement of PFS is not confounded by post-progression cross-over or additional 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 the therapy of recurrent ovarian cancer by international groups involved in clinical research, such as the Gynecologic Cancer InterGroup (GCIG).

OCEANS 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, and are recommended as such by the GCIG.

CA-125 may also be used as a measure of progression in ovarian 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, 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 will have probably decreased any use of CA-125 alone as a marker for further treatment in UK clinical practice as no survival benefit was demonstrated for early treatment based on rising CA-125 alone (Rustin et al. 2010). In the OCEANS study, rising Ca-125 alone, without confirmation by RECIST criteria, was not used as indicating progressive disease.

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.

Overall survival

OS is often regarded as a meaningful standard for determining the efficacy of potential life-extending drugs. However, it is often difficult to reliably and ethically determine in clinical studies. In second-line trials in recurrent platinum-sensitive ovarian cancer, OS results may be confounded as patients may go on to receive several additional lines of life-prolonging treatments. The OCEANS protocol did not restrict post-progression therapies for either treatment arm; therefore patients in both study arms could receive bevacizumab in third or subsequent lines of therapy and at least 34% of PL and 18% of BV patients received post-progression bevacizumab.

Objective response rate

Objective response rate (ORR) was defined according to the modified RECIST criteria, which are the standard method of evaluating ORR. In the OCEANS study all patients had measureable disease and so the ORR measurement reflected therapeutic efficacy across the entire study population. 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).

Safety

The NCI CTCAE (v3.0) criteria were used to analyse safety. This is the current, standard assessment of safety. Adverse events of special interest for 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

6.3.6 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.

The following information is extracted from the most recent SAP (statistical analysis plan) for OCEANS, which outlines the statistical methodology used.

6.3.6.1 Primary efficacy endpoint

The primary efficacy analysis is the comparison of PFS between the two treatment arms (Arm A: carboplatin + gemcitabine + bevacizumab; Arm B: carboplatin + gemcitabine + placebo). PFS is defined as the time from randomisation to disease progression based on the investigator assessment, or death due to any cause.

Significance level

The overall Type I error rate for the two-sided test for the primary endpoint of PFS will be controlled at $\alpha = 0.05$. Only one futility interim analysis is planned for the primary endpoint PFS. As a result, the total $\alpha = 0.05$ is reserved for the final PFS analysis.

Methodology

The primary analysis of PFS will be a two-sided stratified log-rank test comparing Arms A and B. The stratification factors used for the primary analysis will be time to recurrence since the last platinum-based therapy (6−12 months, > 12 months), and presence of cytoreductive surgery for recurrent disease (surgery was performed, surgery was not performed). Results from an unstratified log-rank test will also be presented.

The Kaplan−Meier curves will be constructed to provide a visual description of the difference between the treatment arms. Kaplan−Meier methodology will be

used to estimate median PFS for each treatment arm. Brookmeyer−Crowley methodology will be used to construct the 95% confidence interval (CI) for the median PFS for each treatment arm (BROOKMEYER & CROWLEY 1982).

The null and alternative hypotheses regarding PFS can be phrased in terms of the hazard ratio function, $\lambda_{ArmA} / \lambda_{ArmB}$, where λ_{ArmA} represents the hazard function of progression for Arm A (BV) and λ_{ArmB} represents the hazard function of progression for Arm B (PL). A hazard ratio of < 1 indicates that PFS is prolonged for patients randomized to carboplatin + gemcitabine + bevacizumab compared with those randomized to carboplatin + gemcitabine + placebo. The null and alternative hypotheses, respectively, can be written as follows:

$$H_0: \frac{\lambda_{ArmA}}{\lambda_{ArmB}} = 1 \quad \text{and} \quad H_A: \frac{\lambda_{ArmA}}{\lambda_{ArmB}} \neq 1.$$

The hazard ratio, $\lambda_{ArmA} / \lambda_{ArmB}$, will be estimated using a stratified Cox regression model with the same two stratification factors used in the stratified log-rank test. The unstratified hazard ratio will also be presented.

If the estimate of $\lambda_{ArmA} / \lambda_{ArmB} < 1$ and the results from the stratified log-rank test lead to the rejection of H_0 in favor of H_A, then it will be concluded that the regimen of carboplatin + gemcitabine + bevacizumab prolongs PFS compared with a regimen of the carboplatin + gemcitabine + placebo in patients with platinum-sensitive recurrent ovary, primary peritoneal, or fallopian tube carcinoma.

Censoring

Data for patients who do not have investigator-determined disease progression and who have not died will be censored at the time of the last tumor assessment. If no tumor assessments were performed after the baseline visit, PFS will be censored at the date of randomization plus 1 day. PFS data for patients receiving non-protocol cancer therapy prior to

documented disease progression will also be censored at the time of the last tumor assessment prior to therapy initiation.

Determination of sample size

The sample size for the study was calculated based on the following assumptions:

• 80% power to reject the null hypothesis

• Two-sided log-rank test at α = 0.05

• A hazard ratio of 0.73

• Median PFS in the control group of 8.6 months

The sample size calculation was performed using the S-PLUS, seqtrial module versions 7.0 and 3.0, respectively. On the basis of these assumptions, a total of 317 events are needed at the time of the final analysis. On the basis of an enrollment rate of 20 patients per month, a ramp-up period of approximately 3 months, and an exponential drop-out rate of 0.019575, Genentech estimated that a total of 480 patients are required to achieve this goal in an acceptable time frame. Complete enrollment is expected approximately 2.5 years and full information of the primary endpoint is expected approximately 3.5 years after study initiation.

The final analysis of OS is planned when 353 deaths are observed. Median OS is assumed to be 18 months in the control group. If the experimental arm truly decreases the death rate by 25.9% (i.e., a hazard ratio of 0.741), 353 deaths will provide 80% power for a two-sided test conducted at level α = 0.048 to correctly classify that the experimental arm is superior to the control arm.

6.3.6.2 Secondary efficacy endpoints

Final analyses of objective response and duration of objective response as well as an interim analysis of OS will occur at the time of full PFS information as specified by the protocol. An additional OS interim analysis will be conducted when approximately 214 deaths have been observed. The final analysis of OS is planned when 353 deaths are observed.

Duration of objective response is based on a non-randomized subset of patients (specifically, patients who achieve an objective response); therefore, formal hypothesis testing will not be performed for this endpoint. To protect the experiment-wise error rate among objective response and OS, a hierarchical procedure will be used for testing the hypotheses associated with the two endpoints.

Specifically, objective response will be tested at the α = 0.05 level. If the active arm is declared superior to the control arm with respect to objective response, then OS will be tested at the α = 0.05 level.

Objective Response Rate

The ITT population is used for the analysis of objective response. Objective response rates will be formally compared between Arms A and B using the Cochran-Mantel-Haenszel test, with the following stratification factors: time to recurrence since the last platinum-based therapy (6−12 months, > 12 months), and presence of cytoreductive surgery for recurrent disease (surgery was performed, surgery was not performed). For each treatment arm, an estimate of the objective response rate and its 95% CI will be determined; the 95% CI will be constructed using the normal approximation to the binomial distribution. Specifically, CIs will be computed using the following formula:

$$95\%\ \mathrm{CI} = \hat{p} \pm 1.96\sqrt{\frac{\hat{p} \times (1-\hat{p})}{n}},$$

where n denotes the number of patients in the ITT population and pˆ is the proportion of these n patients who achieved an objective response.

CIs for the difference in objective response rates between Arms A and B will also be determined using the normal approximation to the binomial distribution:

$$95\%\ \mathrm{CI} = \hat{p}_{ArmB} - \hat{p}_{ArmA} \pm 1.96\sqrt{\frac{\hat{p}_{ArmA} \times (1-\hat{p}_{ArmA})}{n_{ArmA}} + \frac{\hat{p}_{ArmB} \times (1-\hat{p}_{ArmB})}{n_{ArmB}}}$$

In addition to the above analysis of objective response rates, best overall confirmed response will be summarized by treatment arm. The summary will include the four RECIST categories: complete response, partial response, stable disease, and progressive disease. The summary will also include a category for unevaluable patients, if applicable.

Duration of objective response

Duration of objective response is based on a non-randomized subset of patients (specifically, patients who achieve an objective response), therefore formal hypothesis testing will not be performed for this endpoint. Comparisons between treatment arms will be made for descriptive purposes.

Data for patients with an objective response who do not experience disease progression or who have not died by the time of analysis will be censored at the time of the last tumor assessment. If no tumor assessments were performed after date of the first occurrence of a complete or partial response, duration of objective response will be censored at the date of the first occurrence of a complete or partial response plus one. Duration of objective response for patients receiving non-protocol cancer therapy prior to documented disease progression will also be censored at the time of the last tumor assessment prior to therapy initiation.

Overall survival

OS is defined as the time from randomization to death from any cause. An OS data sweep and formal OS interim analysis will be conducted at the time of the final PFS analysis. It was projected that at the time of the full PFS

analysis, 214 deaths would have been observed. If the number of deaths observed at the final PFS assessment is substantially smaller than the original event projection, an additional OS analysis will occur when approximately 214 death events have been observed. The decision of having a second interim OS analysis is based on input from the FDA meeting in February 2008 and July 2011 and is not influenced by the results upon PFS unblinding. OS data summaries including OS Kaplan−Meier curves, median OS for each arm, confidence interval for median OS for each arm using Brookmeyer−Crowley methodology, stratified hazard ratio using stratified Cox regression model and its confidence interval, will be provided (BROOKMEYER et al. 1982).

The final analysis of OS will be performed when 353 deaths are observed with the following specifications.

Significance Level

The overall Type I error rate for the two-sided stratified log-rank test for OS will be controlled at α = 0.05. Testing OS will follow a hierarchical procedure. Specifically, objective response will be tested at the α = 0.05 level. If the active arm is declared superior to the control arm with respect to objective response, then OS will be tested at the α = 0.05 level.

At the interim OS analysis conducted at the time of the final PFS analysis, OS will be tested at the α = 0.001 level. An additional interim OS analysis will be performed when approximately 214 deaths have been observed and tested at the α = 0.001 level. The remaining α of 0.048 will be allocated for the final OS analysis.

Censoring

OS for patients who have not died (or are not known to have died, or are lost to follow-up) at the time of analysis will be censored at the date the patient was last known to be alive.

6.3.6.3 Exploratory efficacy endpoints

IRC-determined analyses

To evaluate PFS based on the IRC assessment as a sensitivity analysis, the same methodology as the primary efficacy endpoint will be applied. For this analysis, PFS is defined as the time from randomization until disease progression as determined by the IRC, or on-study death, whichever occurs first. On-study death is defined as death occurring within 9 weeks from the date of the last study treatment (chemotherapy or study drug) or from the date of the last tumor assessment, whichever occurs later. Data for patients without documented disease progression as determined by the IRC or on-study death will be censored at the time of the last IRC tumor assessment. For those patients who do not receive a post-randomization IRC tumor assessment and do not die on study, the date of randomization plus one will be used as the censor date. PFS data for patients receiving non-protocol cancer therapy prior to documented disease progression based on the IRC assessment will also be censored at the time of the last IRC tumor assessment prior to therapy initiation.

IRC-analysis of ORR and duration of response

IRC assessment of ORR and duration of objective response will be assessed using the methodology outlined for investigator-assessed ORR and duration of response.

Safety

Safety analyses will include summaries of deaths and all adverse events by treatment arm. The following subset of adverse events will also be summarized: serious adverse events, adverse events leading to study treatment discontinuation, and selected adverse events.

Adverse events, graded using NCI−CTCAE v3.0, will be coded using the most recent version of the Medical Dictionary for Regulatory Activities. The proportion of patients experiencing at least one adverse event will be reported by toxicity term and treatment arm. Patients will be tabulated into system

organ class and preferred toxicity term categories according to the maximum reported severity.

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

A number of pre-specified subgroup analyses were conducted to evaluate whether individual demographic or baseline characteristics had an impact on prognosis. The following baseline characteristics were analysed as subgroups:

- Platinum-sensitivity (6 – 12 vs > 12 months);
- Occurrence of cytoreductive surgery (Yes vs No);
- Age (< 65 vs ≥ 65 years);
- Race (white vs non-white);
- ECOG performance status (0 vs 1);
- Histopathological cell type (fallopian tube vs ovarian vs primary peritoneal);
- SLD of target lesions at baseline (≤ median (59.0 mm) vs > median);
- Baseline CA125 (≤ 35 vs > 35 U/ml)
- Prior biologic therapy (yes vs no);
- Prior hormonal therapy (yes v no)
- Prior myeloablative therapy (no).

Participant flow

6.3.8 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.

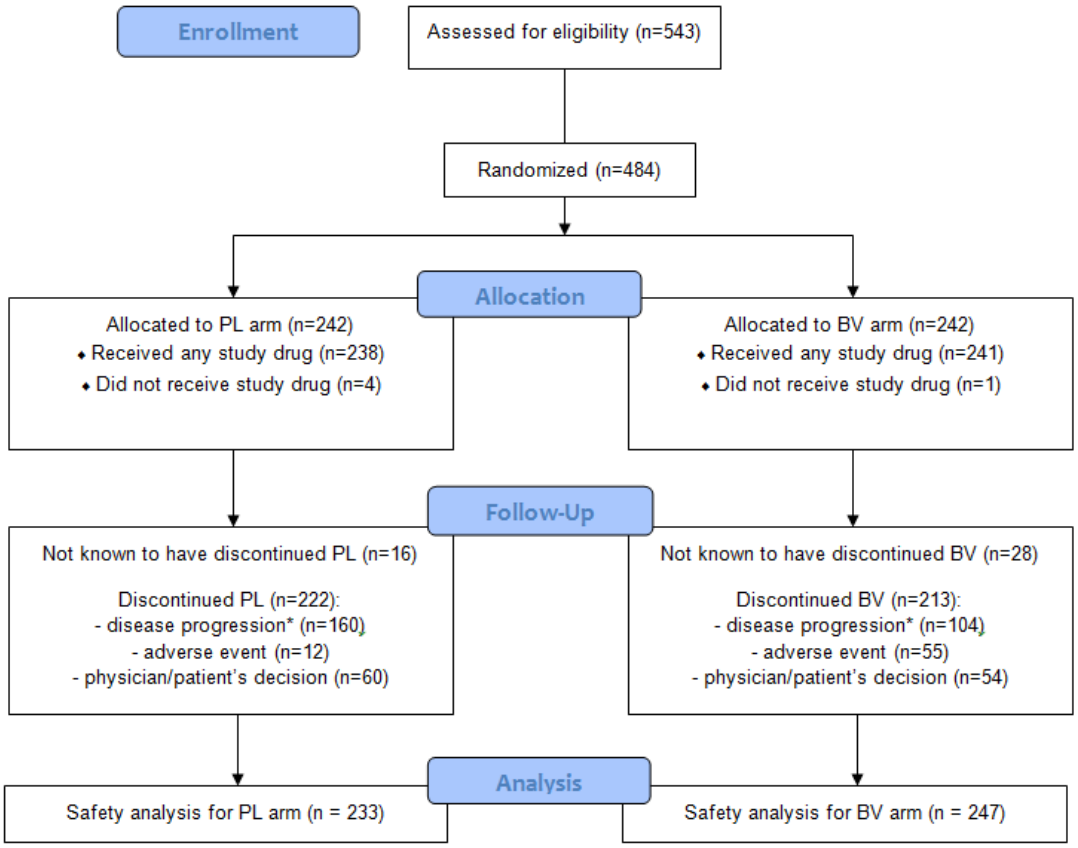
The CONSORT flow chart for all patients in OCEANS is shown in Figure 3. Of the 582 patients assessed for eligibility, 484 patients were randomised in a 1:1 ratio to the PL and BV arms.

Five patients didn't receive any study treatment (carboplatin, gemcitabine, bevacizumab or placebo): four in the PL arm and one in the BV arm. One further patient in the BV arm received study treatment, but not bevacizumab.

A comparable number of patients discontinued treatment in the BV arm compared to the PL arm. The major reason for discontinuing therapy in both arms was due to disease progression; a greater number of these occurred in the placebo arm (BV: 104 patients [43.0%]; PL: 160 patients [66.1%]). A similar proportion of patients discontinued due to physician or patient choice (BV: 22.3%; PL: 20.7%). However, the number of discontinuations due to adverse events was higher in the BV arm (BV: 22.7%; PL: 5.0%). At time of data cutoff, more patients were still receiving treatment in the BV arm (11.6%) than in the PL arm (6.6%) and no patients were receiving chemotherapy.

Five patients from the PL arm received bevacizumab in error before disease progression; three of these received one dose, and two received two doses. After the protocol violation was discovered, these patients resumed their assigned treatment for the remainder of the study. None of these patients were excluded from the efficacy or safety analyses.

Figure 3: CONSORT flow diagram for OCEANS



Study drug= carboplatin, gemcitabine, bevacizumab or placebo. *disease progression or death by any cause

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.

See **Error! Reference source not found.** (Section**Error! Reference source not found.**) for a complete quality assessment of OCEANS.

In summary, randomisation was carried out appropriately and confirmed by audit of the process. Concealment of the treatment allocation was adequate as all study personnel, investigators and patients were blinded to treatment assignment of BV or PL. The two study groups were similar at the outset of the study in terms of prognostic factors. There were no unexpected imbalances in drop-outs between the groups.

There is no evidence to suggest that the authors measured more outcomes than they reported. An appropriate intention-to-treat analysis was included.
Results of the relevant RCTs

6.4.4 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.

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

6.4.6 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.

OCEANS: Progression free survival

6.4.6.1 Primary PFS endpoint

The final investigator-assessed PFS analysis was conducted once 338 events had occurred, at a data cut-off date of 17th September 2010. The median follow-up was 24 months.

The results of analysis of the primary endpoint of investigator-determined PFS are shown in Table 5 and Figure 4.

A total of 338 patients had experienced disease progression or death at the time of data cutoff, exceeding the total of 317 events required for the final analysis of PFS. The proportion of patients with disease progression or death was higher in the PL arm than the BV arm (BV: 62.4%; PL: 77.3%).

Table 5 – Primary PFS analysis[1]

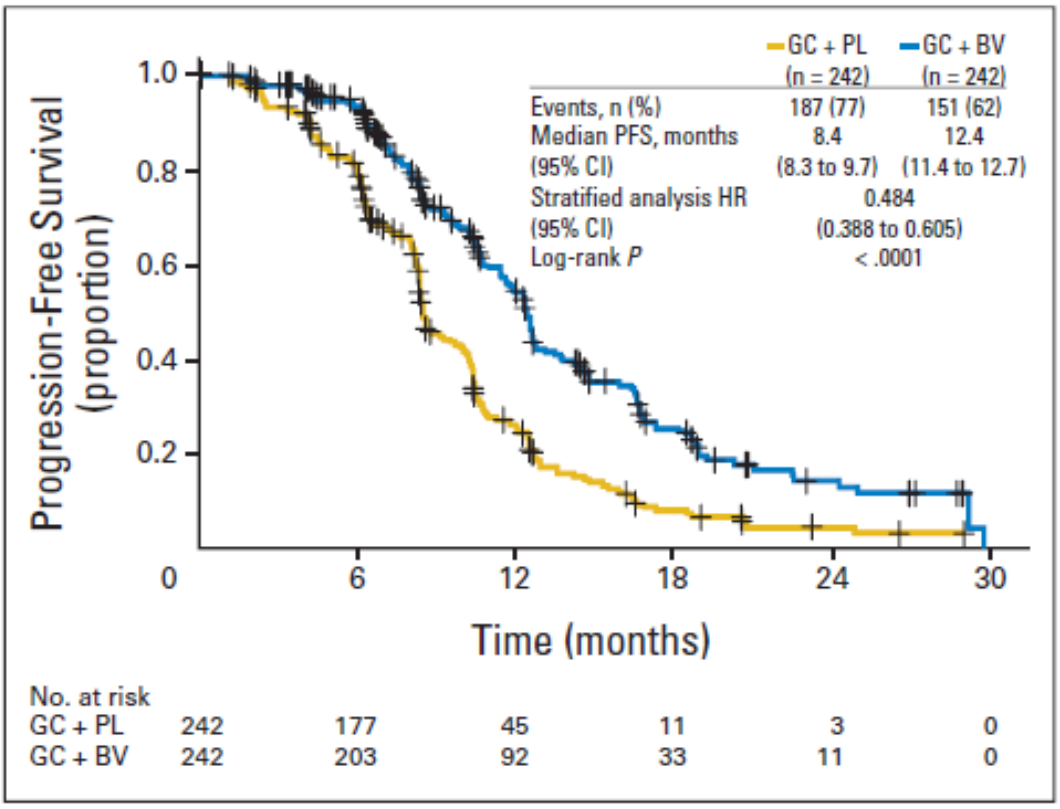
	PL (n = 242)	BV (n = 242)
No. (%) of patients with an event	187 (77.3)	151 (62.4)
Disease progression	185 (76.4)	146 (60.3)
Death	2 (0.8)	5 (2.1)
No. (%) of patients not known to have an event	55 (22.7)	91 (37.6)
Progression-free survival, months		
Median	8.4	12.4
95% CI	8.31, 9.66	11.40, 12.71
Stratified analysis		
Hazard ratio (relative to PL)		0.484
95% CI		0.388, 0.605
p-value (log-rank)		< 0.0001
Unstratified analysis		
Hazard ratio (relative to PL)		0.492
95% CI		0.396, 0.613
p-value (log-rank)		< 0.0001

1Based on investigator-assessment of randomly-assigned patients, censoring for non-protocol-specified cancer therapies. BV: carboplatin + gemcitabine + bevacizumab; PL: carboplatin + gemcitabine + placebo; CI = confidence interval.

Summaries of progression-free survival (median, percentiles) were estimated from Kaplan-Meier curves. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. The strata are the time to recurrence since the last platinum therapy (6–12 months, > 12 months) and cytoreductive surgery for recurrent disease (yes, no).

There was a significant increase in median PFS of 4.0 months for patients in the BV arm compared to those in the PL arm (BV: 12.4 months; PL: 8.4 months [$p < 0.001$]). Additionally, the stratified analysis yielded a hazard ratio in favour of BV (HR: 0.484; 95% CI: 0.388 – 0.605; $p < 0.0001$), showing that the risk of disease progression or death was reduced by 51.6% for patients in the BV arm relative to the PL arm. Therefore, the null hypothesis of no difference between the BV and PL treatment arms was rejected. The Kaplan-Meier plot showed a separation of the curves after approximately 1 month, which was then maintained until the time of data cut-off.

Figure 4: Kaplan-Meier estimates of investigator-assessed PFS[1]



1Censoring for non-protocol specified therapy (randomly-assigned patients). GC+PL: gemcitabine + carboplatin + placebo arm; GC+BV: gemcitabine + carboplatin + bevacizumab arm.

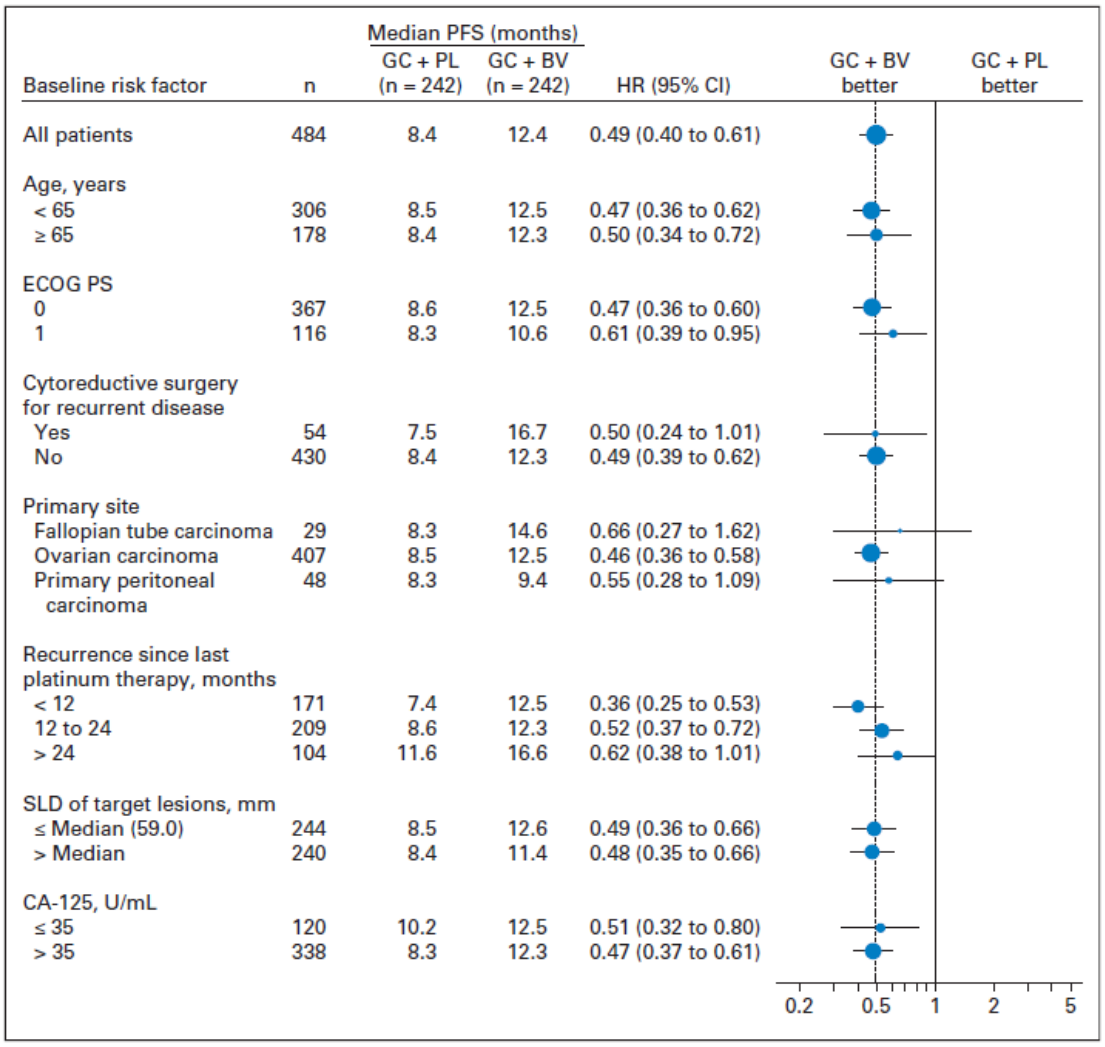
6.4.6.2 Subgroup analysis of PFS

Subgroup analyses of the important prognostic factors are shown in Figure 5, as published in the Journal of Clinical Oncology in 2012 (Aghajanian et al. 2012).

There was an approximate halving of the risk of progression or death for the BV arm versus the PL arm for both younger and older patients, whether or not cytoreductive surgery had been performed and whatever the baseline size of target lesions or CA-125 levels. The hazard ratio for patients with an ECOG performance status of 1 (HR: 0.65; 0.39 – 0.95; n = 116) was slightly higher than the ITT population. This was also the case for the small proportion of patients whose primary cancer was fallopian tube carcinoma (HR: 0.66; 0.27 – 1.62; n = 29) or primary peritoneal carcinoma (HR: 0.55; 0.28 – 1.09; n=48).

Subgroup analysis of the predefined stratification factor of platinum-sensitivity suggested that patients with the shortest platinum free interval might gain the greatest benefit with bevacizumab therapy. The stratified subgroup of 202 patients with a 6-12 months platinum-free interval (partially platinum-sensitive) had a median PFS of 11.9 months with BV versus 8.0 months with PL (HR=0.41; 95% CI 0.29-0.58). For the stratified subgroup of 282 patients with >12 months since last platinum exposure, the median PFS was 12.4 months with BV and 9.7 months with PL (HR=0.55; 95% CI 0.41-0.73). Figure 4 shows a further breakdown of the patients according to platinum-free interval; those with disease recurring < 12 months following previous platinum therapy in the BV treatment arm were 64% less likely to experience progression or death compared to patients in the PL arm (HR: 0.36; 0.25 – 0.53; n=171). Patients with disease recurrence between 12 – 24 months after platinum therapy had a similar risk of progression or death to the ITT population (HR: 0.52; 0.37 – 0.72; n = 209), while the benefit for those whose disease recurred more than 24 months following prior platinum therapy was slightly reduced. For this patient subgroup, the upper limit of the 95% CI just crossed the significance threshold (HR: 0.62; 0.38 – 1.01; n = 104).

Figure 5: PFS by baseline risk factors



Vertical dashed line indicates the hazard ratio (HR) for all patients. The diameter of a circle is proportional to the square root of the number of events. GC+BV: gemcitabine + carboplatin + bevacizumab; GV+PL: gemcitabine + carboplatin + placebo; CA-125: cancer antigen 125; ECOG PS: Eastern Cooperative Oncology Group performance status; SLD: sum of longest diameters.

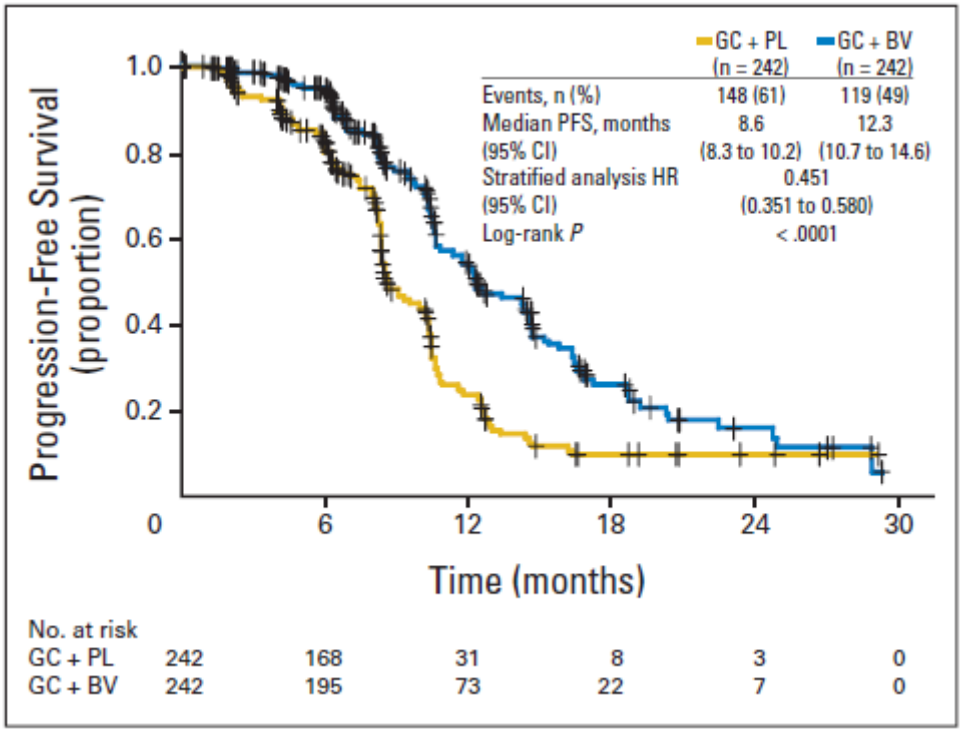
6.4.6.3 Independent review committee assessment of PFS

An independent review committee (IRC) determined the reliability of the Investigator-determined progression. Figure 6 shows the Kaplan-Meier curves for PFS, assessed by the IRC.

This PFS analysis was consistent with the primary endpoint analysis. It reported a 3.7 month increase in median PFS for patients in the BV arm versus the PL arm (BV: 12.3 months; PL: 8.6 months). The stratified hazard ratio also favoured the BV arm (HR: 0.451; 0.351 – 0.580; p<0.0001), with a

reduction in risk of disease progression or death of 54.9% for patients in the BV arm relative to the PL arm.

Figure 6: Kaplan-Meier estimates of IRC-assessed PFS[1]

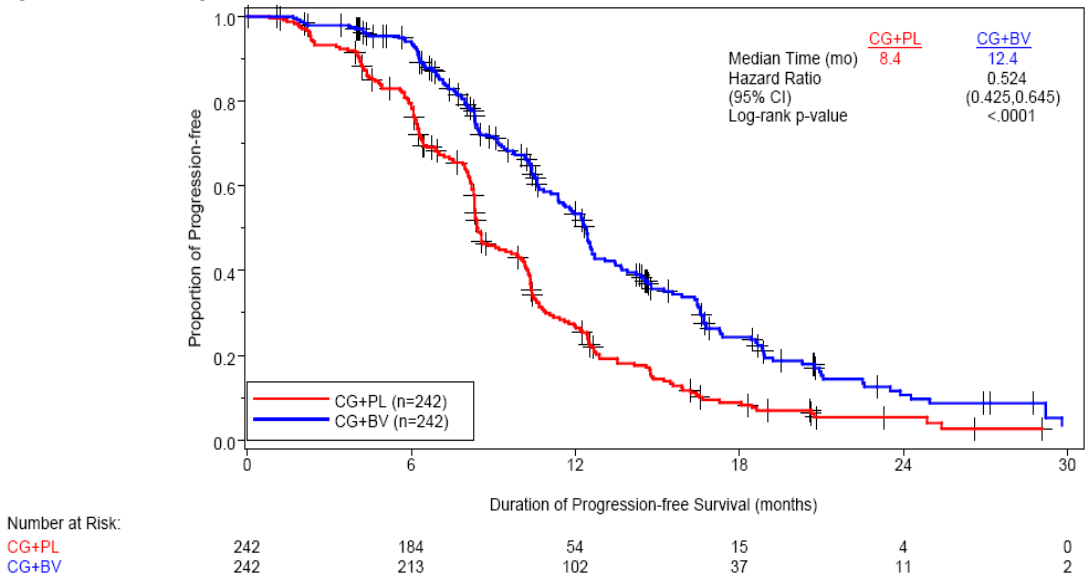


[1]*Censoring for non-protocol-specified cancer therapy (randomly assigned patients).*

6.4.6.4 Sensitivity analysis for PFS not censored for NPT

A sensitivity analysis of the investigator-determined PFS was conducted, without censoring for non-protocol therapies (Figure 7). These results were consistent with those of the primary endpoint.

Figure 7: Investigator-assessed PFS[1]



BV = bevacizumab; CG = carboplatin+gemcitabine; PL = placebo.

1Not censoring for non-protocol specified therapy.

6.4.6.5 Objective Response Rate and Duration of Response

Investigator-assessed Objective Response Rate

Table 6 shows the investigator-assessed Objective Response Rates (ORRs) for patients in the BV and PL treatment arms. There was a significant increase of 21.1% in ORR for the BV arm relative to the PL arm (BV: 78.5% [95% CI: 73.3 – 83.7]; PL: 57.4% [95% CI: 51.2 – 63.7]; p<0.0001). The proportion of patients achieving complete response was also higher in the BV arm than in the PL arm (BV: 17.4%; PL: 9.1%).

Table 6: Investigator-assessed Objective Response Rate

	PL (n = 242)	BV (n = 242)
No. (%) of patients with objective response	139 (57.4)	190 (78.5)
Best objective confirmed response:		
Complete Response	22 (9.1)	42 (17.4)
Partial Response	117 (48.3)	148 (61.2)
95% CI for objective response rate	(51.2%, 63.7%)	(73.3%, 83.7%)
Difference in objective response rates (%)		
Relative to PL	21.1%	
95% CI	13.0%, 29.2%	
Stratified analysis		
p-value	< 0.0001	
Unstratified analysis		
p-value	< 0.0001	

BV = carboplatin + gemcitabine + bevacizumab; PL: carboplatin + gemcitabine + placebo; CI = confidence interval; RECIST = Response Evaluation Criteria for Solid Tumors.
Objective response was defined as a complete or partial best overall confirmed response per RECIST.
95% CIs for response rate and for the difference in response rates were computed using the normal approximation to the binomial distribution.
p-value for the unstratified analysis is from the Pearson`s $\chi 2$ test; p-value for the stratified analysis is from the Cochran-Mantel-Haenszel test.
The strata are the time to recurrence since the last platinum therapy (6–12 months, > 12 months) and cytoreductive surgery for recurrent disease (yes, no).

Investigator-assessed duration of response

Of the patients achieving objective response, those in the BV arm had a longer median duration of response than those in the placebo arm (BV: 10.4 months [95%CI: 9.36 – 11.83]; PL: 7.4 months [95% CI: 6.31 – 8.31]). Additionally patients in the BV arm who achieved a response had a 46.6% reduction in the risk of disease progression versus patients in the PL arm (HR: 0.534; 0.408 – 0.698; p<0.0001). This was reflected by a greater percentage of responders in the BV arm not known to have experienced progressive disease or death (BV: 37.4%; PL: 24.5%) by the time of data cutoff.

Table 7: Investigator-assessed duration of objective response

	PL (n = 139)	BV (n = 190)
No. (%) of patients with an event	105 (75.5)	119 (62.6)
No. (%) of patients not known to have an event	34 (24.5)	71 (37.4)
Duration of response, months		
Median	7.4	10.4
95% CI	6.31, 8.31	9.36, 11.83
Stratified analysis		
Hazard ratio (relative to PL)	0.534	
95% CI	0.408, 0.698	
p-value (log-rank) a	< 0.0001	
Unstratified analysis		
Hazard ratio (relative to PL)	0.537	
95% CI	0.412, 0.700	
p-value (log-rank) a	< 0.0001	

BV: carboplatin + gemcitabine + bevacizumab; PL: carboplatin + gemcitabine + placebo; CI: confidence interval.

Summaries of duration of objective response (median, percentiles) were estimated from Kaplan-Meier curves. 95% CI for duration of objective response was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. Only responders with measurable disease at baseline were included for this analysis.

aTreatment arms were compared for descriptive purposes.

IRC-assessed Objective Response Rate and Duration of Response

The IRC assessed best overall confirmed response using RECIST criteria. ORR was consistent with the investigator-assessed ORR analysis, with a 28.9% improvement in ORR for the BV arm compared with the PL arm (BV: 74.8% vs PL: 53.7%; P < 0.0001). The overall rate of complete responses was higher by investigator assessment (BV: 17.4%; PL: 9.1%) when compared to IRC assessment (BV: 0.8%; PL: 1.2%).

IRC-assessed duration of response was consistent with investigator-assessed duration of response.

6.4.6.6 Overall survival

Overall survival data are still immature, with the final analysis expected in late 2013. Three interim analyses of overall survival have been conducted, two of which were protocol-specified. The third, using a data cut-off of 30th March

2012, was conducted at the request of the European Medicines Association. Table 8 summarizes the results of the interim analyses conducted to date.

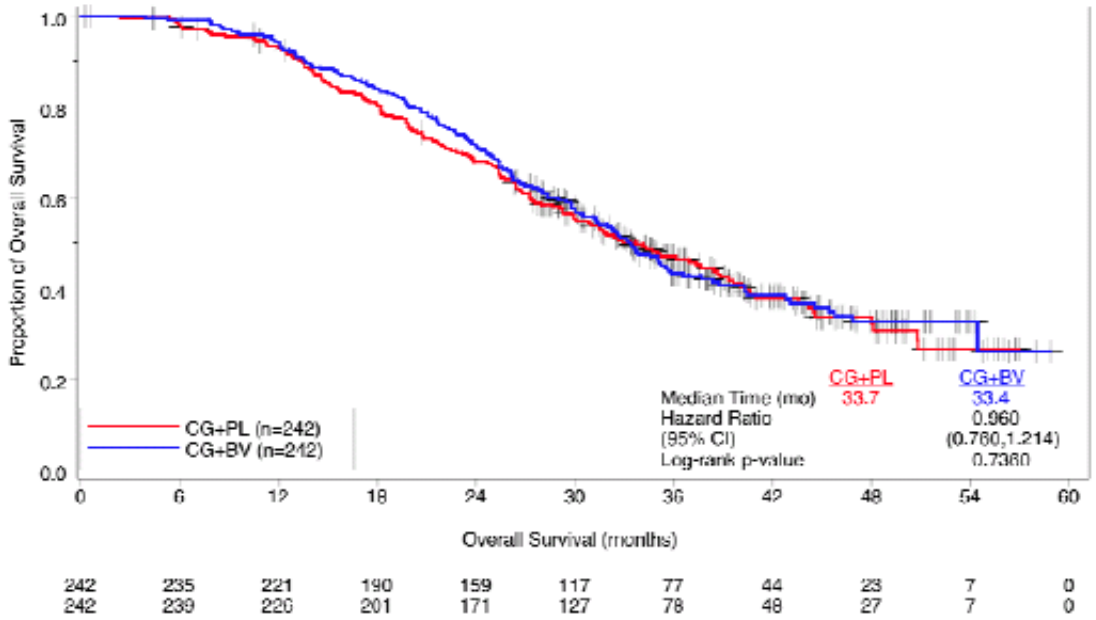
Table 8: Overall survival interim analyses[1]

	First interim OS analysis		Second interim OS analysis		Third interim OS analysis	
	PL n = 242	BV n = 242	PL n = 242	BV n = 242	PL n = 242	BV n = 242
No. of events	78 (32.2%)	63 (26.0%)	112 (46.3%)	123 (50.8%)	142 (58.7%)	144 (59.5%)
Median OS, months	29.9	35.5	35.2	33.3	33.7	33.4
95% CI	26.4 – NE	30.0 – NE	29.9 – 40.3	29.8 – 35.5	29.27 – 38.67	30.32 – 35.84
HR	0.751		1.027		0.960	
95% CI	0.537 – 1.052		0.792 – 1.331		0.760 – 1.214	

[1]Cut-off dates: first interim analysis: 17th September 2010 (final PFS analysis); second interim analysis: 29th August 2011; third interim analysis: 30th March 2012.

A Kaplan-Meier curve for the most recent overall survival analysis, conducted when 286 patients had died, is shown in Figure 8. It shows a comparable median overall survival for the BV and PL treatment arms (BV: 33.4 months; PL: 33.7 months), with no significant difference in the risk of death between the two treatment arms (HR: 0.960; 0.760 – 1.214; P = 0.7360).

Figure 8: Third interim analysis of overall survival[1]



[1]As requested by the European Medicines Association. Based on a data cut-off 30th March 2012. CG+PL: carboplatin + gemcitabine + placebo; CG+BV: carboplatin + gemcitabine + bevacizumab.

6.4.6.7 Subsequent therapies received following disease progression

The post-progression therapies received were analysed from the data-set for the 2nd interim OS analysis.

Table 9 shows that the vast majority of patients in the ITT population received subsequent anticancer therapy following disease progression (BV: 84.3%; PL: 88.0%). Of note, more than a third of patients in the PL arm received subsequent bevacizumab (34.7%), compared with less than a fifth of patients in the BV arm (18.1%). Additionally, more patients in the BV arm received subsequent retreatment with a platinum agent (BV: 40.7%; PL: 34.3%), possibly reflecting the longer PFS of these patients. Other therapies received post-progression were comparable between the two treatment arms.

Table 9: Post-progression therapy by treatment arm[1]

Type of therapy	PL (n = 242)	BV (n = 242)
Any subsequent anticancer therapy	213 (88.0%)	204 (84.3%)
Subsequent bevacizumab	74 (34.7%)	37 (18.1%)
Subsequent chemotherapy2	208 (97.7%)	199 (97.5%)
Pegylated liposomal doxorubicin	157 (73.7%)	144 (70.6%)
Paclitaxel	98 (46.0%)	95 (46.6%)
Platinum agent	73 (34.3%)	83 (40.7%)
Other chemotherapy	123 (57.7%)	110 (53.9%)

[1]Analysis conducted at the same data cut-off as the second interim OS analysis (29th August 2011). [2]Many patients received more than one type of subsequent anticancer therapy, therefore percentage does total 100%.

Table 10 shows the total number of lines of anti-cancer therapies received by patients in each treatment arm. Each line of subsequent therapy was given to fewer patients in the BV than in the PL treatment arm.

Table 10: Exposure to chemotherapy by treatment arms in OCEANS

Total lines of anti-cancer therapy	PL (n=242)	BV (n=242)
3 or more	215 (88.8%)	204 (84.3%)
4 or more	156 (64.5%)	144 (59.5%)
5 or more	111 (45.9%)	93 (38.4%)
6 or more	67 (27.7%)	52 (21.5%)
7 or more	42 (17.4%)	26 (10.7%)
8 or more	16 (6.6%)	16 (6.6%)

Summary of Efficacy, OCEANS study

OCEANS assessed the efficacy of adding bevacizumab to a chemotherapy regimen of carboplatin + gemcitabine in 484 patients with platinum-sensitive relapsed ovarian cancer.

There was a significant improvement in the primary endpoint of progression free survival, with a 4 month increase in median PFS (BV: 12.4 months; PL: 8.4 months). Additionally, the risk of progression was more than halved for the BV arm relative to the PL arm (HR: 0.484; 95% CI: 0.388 – 0.605; p<0.0001). These benefits were confirmed by an independent review committee assessment of response, and additionally a sensitivity analysis of PFS without censoring for non-protocol therapy.

Analysis of PFS across a variety of subgroups showed a benefit consistent with that of the ITT population. Patients with partially platinum-sensitive disease appeared to have the greatest benefit with BV relative to PL (HR: 0.36; 95% CI: 0.25 – 0.53).

Significantly more patients achieved a complete or partial response with BV than with PL (BV: 78.5%; PL: 57.4%). Of those who achieved a response, the duration of response was 3 months longer for BV than PL (BV: 10.4 months [9.36 – 11.83]; PL 7.4 [6.31 – 8.31]).

Data for overall survival are currently immature. The most recent analysis shows no significant difference in OS between the treatment arms (BV: 33.4 months; PL: 33.7 months; HR: 0.960; 95% CI: 0.760 – 1.214). However, more patients in the PL arm than the BV arm have received post-progression bevacizumab, which may confound the results (BV: 18.1%; PL: 34.7%). Fewer patients receiving BV were treated with subsequent lines of therapy than those receiving PL.

6.5 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.

6.5.1 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).

As only one study was available, it was not appropriate to conduct a meta-analysis.

6.5.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

N/A

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.

In order to better understand the relevance of OCEANS to UK clinical practice, a literature search was conducted to allow a network analysis against the current NICE-recommended standards of care. The search was conducted to identify any large RCTs evaluating the efficacy of any of the comparators listed in the decision problem (paclitaxel, carboplatin, cisplatin, PLDH or gemcitabine) in recurrent platinum-sensitive ovarian cancer. The full search strategy is provided in Section **Error! Reference source not found.**.

6.6.2 Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

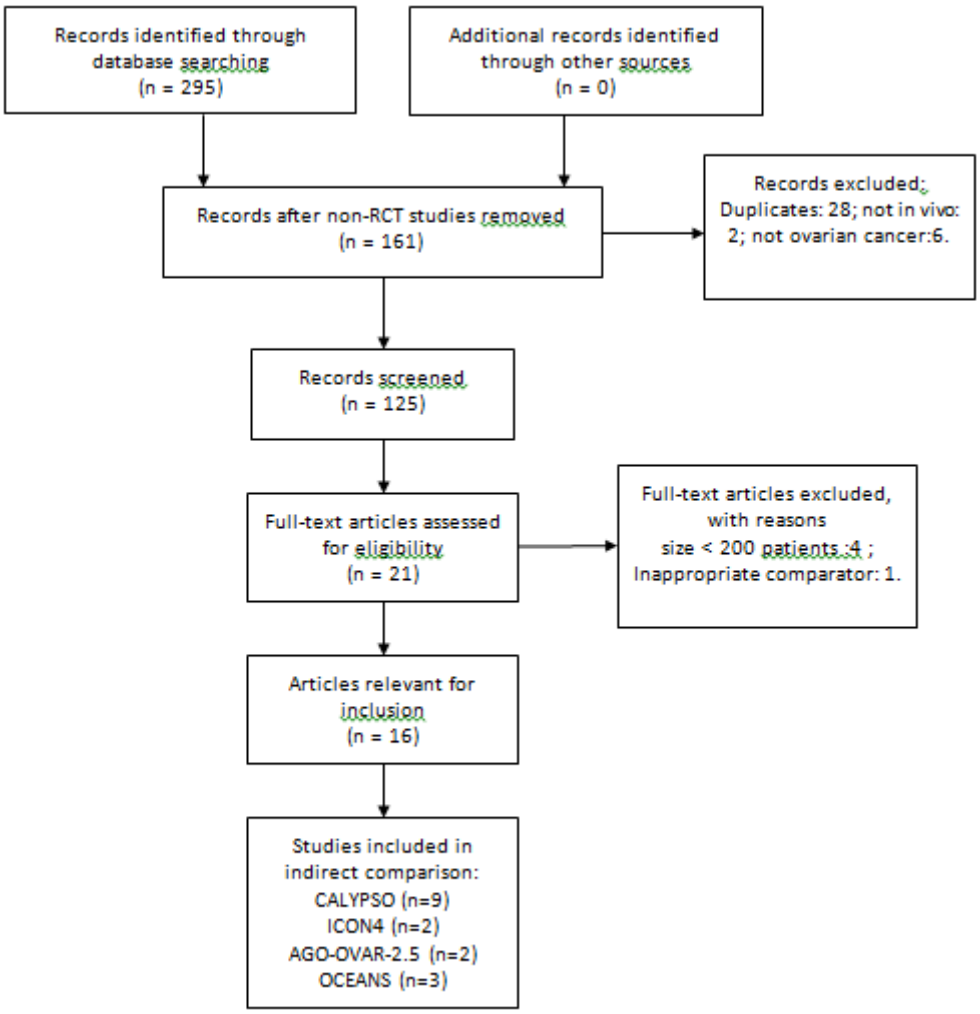
The inclusion and exclusion criteria for studies in the indirect treatment comparison are described in Table 11.

Table 11: Eligibility criteria for indirect comparison

	Clinical effectiveness
Inclusion criteria	Population – Patients with platinum-sensitive, recurrent ovarian cancer. Interventions – Studies evaluating any of: paclitaxel, platinum-based therapy (carboplatin or cisplatin), gemcitabine or PLD. Outcomes – Assessment of PFS Study design – Large, randomised controlled trial (n ≥ 200) Language restrictions – None.
Exclusion criteria	Population – Patients with any other disease than platinum-sensitive, recurrent ovarian cancer. Interventions – Any study not evaluating any of the interventions specified in the inclusion criteria (in either experimental or control arms) Outcomes – No assessment of PFS Study design – non-RCTs or small RCTs (n < 200).

Figure 9 shows the QUORUM statement flow diagram for the indirect comparison search. Further details are provided in Appendix **Error! Reference source not found.**

Figure 9: Flow diagram for indirect comparison search



6.6.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

6.6.3.1 Trials included in the indirect comparison

Alongside OCEANS, the systematic review identified three additional randomised controlled trials for inclusion in the indirect comparison: AGO-OVAR-2.5, ICON4 (ICON4/AGO-OVAR-2.2) and the GCIG-run CALYPSO study. These trials are summarised in Table 12 and Table 13.

Table 12: Summary of the trials used to conduct the indirect comparison

No. trials	References of trials	Platinum + PLD	Platinum + paclitaxel	Platinum	Platinum + gemcitabine	Platinum + gemcitabine+ bevacizumab
1	CALYPSO	✓	✓			
1	ICON4		✓	✓		
1	AGO-OVAR-2.5			✓	✓	
1	OCEANS				✓	✓
Adapted from Caldwell et al. (2005) Simultaneous comparison of multiple treatments combining direct and indirect evidence. BMJ 331: 897–900						

*Due to changes in standard of care therapy, "standard platinum therapy" in CALYPSO was carboplatin + paclitaxel, while in ICON4 it was a variety of platinum-based regimens.

Table 13: Summaries of the trials in the indirect comparison

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
AVF4095g (OCEANS)	Intravenous carboplatin (AUC 4, day 1) and gemcitabine (1000 mg/m2, days 1&8) [q3w, 6-10 cycles] plus concurrent and extended intravenous bevacizumab (15 mg/kg, day 1) [q3w until disease progression/ unacceptable toxicity]	Intravenous carboplatin (AUC 4, day 1) and gemcitabine (1000 mg/m2, days 1&8) [q3w, 6-10 cycles] plus concurrent and extended intravenous placebo (15 mg/kg, day 1) [q3w until disease progression/ unacceptable toxicity]	[n = 484 (ITT)] Patients with platinum-sensitive recurrent ovarian cancer (recurring ≥ 6 months following front line platinum-based therapy) and measurable disease.	Aghajanian et al 2012; J Clin Oncol 30:2039-2045
AGO-OVAR-2.5	Intravenous carboplatin (AUC 4, day 1) and gemcitabine (1000 mg/m2, days 1&8) [q3w, 6-10 cycles]	Intravenous carboplatin (AUC 5, day 1) [q3w, 6 – 10 cycles]	[n = 356 (ITT)] Patients with platinum-sensitive recurrent ovarian cancer (recurring ≥ 6 months following front line platinum-based	Pfisterer et al 2006; J Clin Oncol 24:4699-4707

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
			therapy) and measurable disease.	
ICON4 (ICON4/AGO-OVAR-2.2)	Intravenous conventional platinum-based therapy (various regimens which included carboplatin [AUC 5-6] or cisplatin [50 mg/m2]) plus paclitaxel (ICON4: 175mg/m2;AGO : 185 mg/m2) [day 1, q3w, ≥ 6 cycles*]	Intravenous conventional platinum-based therapy (various regimens which included carboplatin [AUC 5-6] or cisplatin [75 mg/m2]) [day 1, q3w, ≥ 6 cycles]	[n = 802 (ITT)] Patients with platinum-sensitive recurrent ovarian cancer (disease recurrence ≥ 6 months following platinum-based therapy [≥ 12 months in the Italian group])	Parmar et al 2003; The Lancet 361:2099-2106
CALYPSO (AGO-OVAR 2.9)	Intravenous PLD (30 mg/m2, day 1) and carboplatin (AUC5, day 1), [q4w, ≥ 6 cycles]	Intravenous paclitaxel (175 mg/m2, day 1) and carboplatin (AUC5, day 1), [q3w, ≥ 6 cycles]	[n=976 (ITT)] Patients with platinum-sensitive recurrent ovarian cancer (recurring ≥ 6 months following first- or second- line platinum-based therapy) and measurable disease.	Pujade-Lauraine et al 2010; JCO 28:3323-3329

6.6.3.2 Eligibility criteria

Eligibility criteria were reasonably similar to those in OCEANS, and all patients had platinum-sensitive relapsed ovarian cancer, with a platinum-free interval of ≥ 6 months. The notable differences in eligibility criteria amongst the 3 studies, as compared with OCEANS, are described below:

AGO-OVAR-2.5

No notable differences from the OCEANS study population were identified.

ICON4

- Patients in the Italian ICON4 group (n=213) were required to have a platinum-free interval of >12 months. This resulted in a lower proportion of patients with partially platinum-sensitive disease (23-29%) than in the other trials (35-42%) (Table 14)

- Patients in the MRC CTU protocol section of ICON4 were eligible for inclusion if they had ≥1 line of previous chemotherapy. A small proportion of patients (n=67 [8.4%]) had received ≥ 2 lines of previous chemotherapy.

- Eighteen patients (2.2%) in the MRC CTU were diagnosed to have relapsed disease based on raised CA125 levels alone. All other patients in the study were diagnosed as having recurrent disease by clinical or radiological criteria.

CALYPSO (AGO-OVAR2.9)

- Patients in CALYPSO were considered eligible if they had received 1-2 lines of previous platinum-based chemotherapy. One hundred and forty six patients (15%) had received two previous lines of chemotherapy.

Numerous baseline characteristics were reported in each of the study publications. However, only age, performance status, number of previous chemotherapy lines and the proportions of platinum-sensitive and partially platinum-sensitive patients were reported across all four trials. These characteristics are presented in Table 14.

Table 14: Baseline characteristics reported across the RCTs

	CALYPSO		ICON 4		AGO-OVAR-2.5		OCEANS	
	CPLD n=466	CP n=507	C n=410	CP n=392	GC n=178	C n=178	GC+PL n=242	GC+BV n=242
Age (years)	Median 60.5 (24-82)	Median 61 (27-82)	Median: 59.2*	Median: 60.0*	Median: 59 (36-78)	Median 58 (21-81)	Mean: 61.6 (20-86)	Mean: 60.5 (38-87)
Performance status (%)	ECOG 0: 61.4 1: 33.9 2: 2.8	ECOG 0: 62.5 1: 32.3 2: 23.0	WHO 0: 64 1: 30 2: 6	WHO 0: 63 1: 31 2: 6	ECOG 0: 46.6 1: 44.4 2: 6.2	ECOG 0: 52.2 1: 40.4 2: 5.1	ECOG 0: 76.4 1: 23.6 2: 0	ECOG 0: 75.2 1: 24.4 2: 0.4
Proportion previous CT lines (%)	1: 87.6 2: 12.4	1: 82.6 2: 12.4	1: 93 2: 6 3: 1	1: 90 2: 6 3: 4	1: 100+	1: 100+	1: 100+	1: 100+
Platinum-sensitivity (%)	6-12: 35 >12: 65	6-12: 36.1 >12: 63.9	6-12: 29 >12: 73	6-12: 23 >12: 77	<6: 0.6 6-12: 39.9 >12: 59.6	<6: 0 6-12: 39.9 >12: 60.1	6-12:42.1 >12: 57.9	6-12: 41.3 >12: 58.7

CPLD: carboplatin and PLD; CP: carboplatin + paclitaxel; C: carboplatin; GC: gemcitabine and carboplatin; PL: placebo; BV: bevacizumab; CT: chemotherapy. *range not reported; [+]assumption based on eligibility criteria – data not available.

6.6.3.3 Relevance of the included RCTs to the decision problem and UK clinical practice

The median ages of patients were comparable across the trials. However the distribution of performance status was markedly different in AGO-OVAR-2.5, with fewer than 50% of patients of PS 0, compared with 75% in OCEANS, in terms of previous therapies, only OCEANS and AGO-OVAR-2.5 were consistent with the decision problem, including only patients who had received one previous line of platinum-based therapy. Approximately 10% of patients in ICON4 had received ≥ 2 lines of prior chemotherapy, while 16% of patients in CALYPSO had received two previous lines of therapy.

Due to the Italian study centres of ICON4 only recruiting fully platinum-sensitive patients (> 12 months PFI), the proportion of partially platinum-sensitive patients was significantly different for ICON4 compared to the other trials. Only one quarter of patients in ICON4 were partially platinum-sensitive, versus approximately two-fifths in the other studies. The improved prognosis of these patients is likely to have resulted in the significantly longer PFS and OS for both arms of ICON4 versus the other studies (Ledermann & Raja 2006).

The study drugs considered for inclusion in the indirect comparison were mostly consistent with the decision problem and the NICE-recommended therapies for platinum-sensitive recurrent ovarian cancer(NICE 2008b). However, ICON4 evaluated the efficacy of adding paclitaxel to “conventional” therapy where 20% of patients in the paclitaxel arm and 29% of patients in the control arm did not receive carboplatin and are therefore not comparable with patients in other studies (ICON Collaborators 1998).

After considering the significant differences in important baseline prognostic factors, and seeking statistical advice regarding the feasibility of an indirect comparison, it was deemed that the levels of hetereogeneity between the 4 studies were too high for an indirect comparison to provide relevant results. For this reason, an indirect comparison was not conducted.

6.6.4 For the selected trials, provide a summary of the data used in the analysis.

N/A

6.6.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

N/A

6.6.6 Please present the results of the analysis.

N/A

6.6.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

N/A

6.6.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

N/A

6.6.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

N/A

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 during the systematic review.

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.

The tolerability profile of bevacizumab has been well established from trials in first line ovarian cancer and other therapy areas. However, varying levels of gastrointestinal (GI) perforations were experienced during Phase II trials of bevacizumab in recurrent ovarian cancer. For this reason, a search for prospective trials reporting adverse events with bevacizumab was conducted with the aim of evaluating the incidence of GI perforations. The reported incidences are summarised at the end of the following section.

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 OCEANS – safety analyses

Table 15 shows the exposure to chemotherapy drugs and bevacizumab/placebo for all safety-evaluable patients. The exposure to chemotherapy was comparable between the treatment arms. In terms of carboplatin, patients received a median 2298.6 mg in the BV arm, compared with 2358.0 mg in the PL arm. The median number of carboplatin cycles was 6 in both arms. However, more patients in the PL arm received 7 – 10 cycles of carboplatin than those in the BV arm (BV: 33.3%; PL: 40.3%). The median carboplatin dose intensity was estimated to be just under 90% for both treatment arms (BV: 89.4%; PL: 88.9%).

Exposure to gemcitabine was also comparable. Patients received a median dose of 18,580 mg in the BV arm, versus 20,176 mg in the PL arm. Patients in both arms received a median of 6 cycles of gemcitabine; 41.3% of patients in the BV arm received 7 – 10 cycles versus 45.5% of patients in the PL arm. The median gemcitabine dose intensity was estimated to be approximately three-quarters of the intended dose intensity (BV: 74.0%; PL: 74.2%).

Table 15: Exposure to chemotherapy in OCEANS (safety-evaluable patients)

	PL (n = 233)	BV (n = 247)
Total carboplatin dose, mg		
n	233	246
Mean (SD)	2475.8 (1033.2)	2395.7 (1017.1)
Median	2358.0	2298.6
25th and 75th percentiles	1850.0, 3150.0	1776.0, 3077.2
Range	383.0–6552.0	260.0–5920.0
No. (%) of patients by no. of carboplatin cycles		
n	233	246
1–3	32 (13.7)	34 (13.8)
4–6	107 (45.9)	130 (52.8)
7–10	94 (40.3)	82 (33.3)
No. of carboplatin cycles		
n	233	246
Mean (SD)	6.6 (2.4)	6.3 (2.4)
Median	6.0	6.0
25th and 75th percentiles	6.0, 9.0	5.0, 8.0
Range	1.0–10.0	1.0–10.0
Estimated carboplatin dose intensity, %		
n	233	246
Mean (SD)	89.0 (11.3)	88.5 (11.7)
Median	88.9	89.4
25th and 75th percentiles	82.5, 100.0	80.5, 100.0
Range	57.7–118.6	58.7–111.0
Total gemcitabine dose, mg		
n	233	247
Mean (SD)	20,743.1 (8600.9)	20,317.0 (8802.6)
Median	20,176.0	18,580.0
25th and 75th percentiles	14,421.5, 26,280.0	15,090.0, 24820.0
Range	1780.0–44,800.0	1600.0–46,850.0
No. (%) of patients by no. of gemcitabine cycles		
n	233	247
1–3	19 (8.2)	18 (7.3)
4–6	108 (46.4)	127 (51.4)
7–10	106 (45.5)	102 (41.3)
Number of gemcitabine cycles		
n	233	247
Mean (SD)	7.0 (2.2)	7.0 (2.3)
Median	6.0	6.0
25th and 75th percentiles	6.0, 9.0	6.0, 9.0
Range	1.0–10.0	1.0–10.0
Estimated gemcitabine dose intensity, %		
n	233	247
Mean (SD)	71.8 (16.9)	70.7 (17.1)

	PL (n = 233)	BV (n = 247)
Median	74.2	74.0
25th and 75th percentiles	60.0, 86.0	57.1, 85.7
Range	31.5–95.4	29.3–95.4

BV = carboplatin + gemcitabine + bevacizumab arm; PL = carboplatin + gemcitabine + placebo arm; SD = standard deviation. Estimated dose intensity (%) is the actual dose received divided by the intended dose × 100.

Patient exposure to bevacizumab/placebo in OCEANS is shown in Table 16. The median dose of bevacizumab received in the BV arm was higher than the corresponding ‘dose’ in the placebo arm (BV: 13,220.0 mg; PL: 11,190.0 mg). This is due to the fact that patients received a median 10 cycles of placebo, compared with a median 12 cycles of bevacizumab; this equated to a median duration of treatment of 32.1 weeks in the PL arm and 37.3 weeks in the BV arm. Median estimated dose intensity was 92.3% of the intended dose for both arms.

Table 16: Exposure to bevacizumab/placebo in OCEANS (safety evaluable patients)

	PL (n = 233)	BV (n = 247)
Total dose, mg		
n	233	246
Mean (SD)	12,748.2 (7812.6)	15,332.8 (10,179.1)
Median	11,190.0	13,220.0
25th and 75th percentiles	7640.0, 16353.0	7856.0, 20790.0
Range	750.0–41,910.0	855.0–60,375.0
No. (%) of patients by no. of cycles, categorical		
n	233	246
1–3	19 (8.2%)	17 (6.9%)
4–6	40 (17.2%)	37 (15.0%)
7–10	63 (27.0%)	57 (23.2%)
11–20	93 (39.9%)	90 (36.6%)
21–30	15 (6.4%)	34 (13.8%)
31–40	3 (1.3%)	9 (3.7%)
41–50	0 (0.0%)	2 (0.8%)
No. of cycles		
n	233	246
Mean (SD)	11.2 (6.2)	13.6 (8.5)
Median	10.0	12.0
25th and 75th percentiles	6.0, 14.0	8.0, 18.0
Range	1.0–36.0	1.0–43.0
Estimated dose intensity, %		
n	233	246
Mean (SD)	91.7 (8.4)	91.4 (8.3)
Median	92.3	92.3
25th and 75th percentiles	86.7, 100.0	87.5, 100.0
Range	60.0–108.7	60.0–100.6
Duration of bevacizumab/placebo (weeks)		
n	233	246
Mean (SD)	33.9 (20.0)	42.0 (27.4)
Median	32.1	37.3
25th and 75th percentiles	20.7, 43.6	23.0, 54.1
Range	0.1–123.1	0.1–141.1

BV = carboplatin + gemcitabine + bevacizumab arm; PL = carboplatin + gemcitabine + placebo arm; SD = standard deviation.

The duration of follow-up for the safety population is shown in Table 17. Adverse events were recorded for a longer time period in the BV arm than the PL arm, with a median duration of safety follow-up of 9.6 months in the BV am and 8.4 months in the PL arm.

Table 17: Duration of safety follow-up in OCEANS

Duration of Safety Follow-Up (months)	PL (n = 233)	BV (n = 247)
n	233	247
Mean (SD)	8.8 (4.5)	10.7 (6.2)
Median	8.4	9.6
25th and 75th percentiles	5.9, 11.0	6.4, 13.4
Range	1.0–29.3	1.0–33.5

BV: carboplatin + gemcitabine + bevacizumab; PL: carboplatin + gemcitabine + placebo;
SD = standard deviation. Duration of follow-up for safety assessment was defined as the time from the first dose of study drug or chemotherapy until 30 days after the last dose of study drug or chemotherapy during the treatment period.

Table 18 provides an overview of the adverse events experienced in OCEANS. All safety-evaluable patients experienced an adverse event, while the proportion of patients experiencing a Grade 3-5 adverse event was slightly higher in the BV arm (BV: 89.5%; PL: 82.5%).

More patients in the BV arm experienced a serious adverse event (SAE) than patients in the PL arm (BV: 34.8%; PL: 24.9%); the percentage of patients experiencing Grade 3-5 SAEs was also higher in the BV arm (BV: 29.1%; PL: 20.2%). Additionally, more patients experienced an adverse event leading to discontinuation of study drug in the BV arm (BV: 19.8%; PL: 4.7%).

Fewer deaths occurred in the BV arm than the PL arm (BV: 25.5%; PL: 33.5%). One patient in each arm died from an adverse event. The patient in the PL arm died of a myocardial infarction, while the patient in the BV arm died of an intracranial haemorrhage.

The incidence of any adverse events of special interest (AESIs), that is events previously associated with bevacizumab across indications, was higher in the BV arm (BV: 94.3%; PL: 85.0%); this was also the case for Grade 3-5 AESIs (BV: 73.7%; 61.8%). Of note, the Grade 3-5 AESIs occurring with ≥ 2% higher incidence in the BV arm were hypertension (BV: 17.4%; PL: 0.4%), proteinuria (BV: 8.5%; PL: 0.9%) and non-CNS bleeding (BV: 5.7%; PL: 0.9%). Adverse events known to be related to chemotherapy, specifically neutropenia (BV: 20.6%; PL: 21.9%) and febrile neutropenia (BV: 1.6%; PL: 1.7%), were comparable between the two arms.

Table 18: Summary of the safety analyses from OCEANS (safety-evaluable patients)

Parameter	No. (%) of Patients	
	PL (n = 233)	BV (n = 247)
Any adverse event	233 (100.0)	247 (100.0)
Grade 3–5 adverse event	192 (82.4)	221 (89.5)
Serious adverse event	58 (24.9)	86 (34.8)
Serious adverse event (Grade 3–5)	47 (20.2)	72 (29.1)
Adverse event leading to study drug (BV/PL) discontinuation	11 (4.7)	49 (19.8)
All deaths	78 (33.5)	63 (25.5)
Grade 5 adverse event	1 (0.4)	1 (0.4)
Adverse events of special interest (any grade)	198 (85.0)	233 (94.3)
Adverse events of special interest (Grade 3–5)	144 (61.8)	182 (73.7)
Arterial Thromboembolic Event (any grade)	2 (0.9)	7 (2.8)
Bleeding (CNS) (any grade)	1 (0.4)	2 (0.8)
Bleeding (Non-CNS) (Grade ≥ 3)	2 (0.9)	14 (5.7)
LV systolic dysfunction/CHF (Grade ≥ 3)	2 (0.9)	3 (1.2)
Febrile neutropenia (any grade)	4 (1.7)	4 (1.6)
Fistula/abscess (any grade) a	1 (0.4)	4 (1.6)
GI perforation (any grade)	0 (0.0)	0 (0.0)
Hypertension (Grade ≥ 3)	1 (0.4)	43 (17.4)
Neutropenia (Grade ≥ 4)	51 (21.9)	51 (20.6)
Proteinuria (Grade ≥ 3)	2 (0.9)	21 (8.5)
RPLS (any grade)	0 (0.0)	3 (1.2) b
Wound healing complication (Grade ≥ 3)	0 (0.0)	2 (0.8)
Venous thromboembolic event (Grade ≥ 3)	6 (2.6)	10 (4.0)

BV = carboplatin + gemcitabine + bevacizumab arm; PL = carboplatin + gemcitabine + placebo arm; CNS = central nervous system; LV = left ventricular; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; GI = gastrointestinal; RPLS = reversible posterior leukoencephalopathy syndrome.

a Includes all fistula/abscess events: anal fistula, female genital tract fistula, pelvic abscess, perirectal abscess, rectal abscess (narratives provided only for GI-related events [anal fistula, perirectal abscess, and rectal abscess) b Two were MRI-confirmed RPLS cases

The adverse events (all grade) which occurred with a ≥ 5% incidence in the BV arm are summarised in Table 19. The adverse events for which there was the largest difference (≥ 10%) were hypertension (BV: 40.5%; PL: 8.6%), epistaxis (BV: 54.3%; PL: 14.2%), headache (BV: 48.6%; PL: 30.0%) and proteinuria (BV: 16.6%; PL: 3.9%).

Table 19: Adverse Events with ≥ 5% Higher Incidence in the BV arm versus the PL arm (safety-evaluable patients)

MedDRA System Organ Class MedDRA Preferred Term	No. (%) of Patients	
	PL (n = 233)	BV (n = 247)
Any adverse events	233 (100.0)	247 (100.0)
Blood and lymphatic system disorders		
Thrombocytopenia	119 (51.1)	143 (57.9)
Gastrointestinal disorders		
Diarrhea	67 (28.8)	92 (37.2)
Gingival bleeding	1 (0.4)	17 (6.9)
Nausea	153 (65.7)	177 (71.7)
Stomatitis	15 (6.4)	37 (15.0)
General disorders/administration site conditions		
Fatigue	175 (75.1)	201 (81.4)
Mucosal inflammation	22 (9.4)	38 (15.4)
Infections and infestations		
Sinusitis	20 (8.6)	36 (14.6)
Injury, poisoning, and procedural complications		
Contusion	21 (9.0)	42 (17.0)
Musculoskeletal/connective tissue disorders		
Arthralgia	44 (18.9)	68 (27.5)
Back pain	30 (12.9)	49 (19.8)
Nervous system disorders		
Dizziness	39 (16.7)	55 (22.3)
Headache	70 (30.0)	120 (48.6)
Psychiatric disorders		
Insomnia	35 (15.0)	50 (20.2)
Renal and urinary disorders		
Proteinuria	9 (3.9)	41 (16.6)
Respiratory, thoracic, mediastinal disorders		
Cough	42 (18.0)	62 (25.1)
Dysphonia	8 (3.4)	32 (13.0)
Dyspnea	56 (24.0)	72 (29.1)
Epistaxis	33 (14.2)	134 (54.3)
Oropharyngeal pain	23 (9.9)	40 (16.2)
Rhinorrhea	8 (3.4)	23 (9.3)
Sinus congestion	4 (1.7)	19 (7.7)
Vascular disorders		
Hypertension	20 (8.6)	100 (40.5)

BV = carboplatin + gemcitabine + bevacizumab arm; PL = carboplatin + gemcitabine + placebo arm; MedDRA = Medical Dictionary for Regulatory Activities;

All reported events were included regardless of relationship to study drug. Only those adverse events occurring within 30 days after last study drug and on or before the 17 September 2010 (final PFS analysis) cutoff date were included in this analysis.

Table 20 shows all Grade 3-5 AEs occurring with ≥ 2% higher incidence in the BV arm than the PL arm. The majority of patients experienced a Grade 3-5 adverse event (BV: 89.5%, PL: 82.4%), most of which were Grade 3 (BV: 42.5%; PL: 42.1%) or Grade 4 (BV: 46.6%; PL: 39.9%). In terms of Grade 4 reactions, thrombocytopenia was the only AE with a significantly higher incidence in the BV arm than in the PL arm (BV: 28.3%; PL: 18.9%). One patient in each arm died from an AE.

Table 20: AEs (grade 3 - 5) with ≥ 2% higher incidence in the BV arm vs the PL arm (safety-evaluable patients)

MedDRA System Organ Class MedDRA Preferred Term	NCI CTCAE Grade	No. (%) of Patients PL (n = 233)	 BV (n = 247)
Any adverse events	Total	192 (82.4)	221 (89.5)
	5	1 (0.4) [a]	1 (0.4) [b]
	4	93 (39.9)	115 (46.6)
	3	98 (42.1)	105 (42.5)
Blood and lymphatic system disorders			
Thrombocytopenia	Total	79 (33.9)	99 (40.1)
	4	44 (18.9)	70 (28.3)
	3	35 (15.0)	29 (11.7)
Gastrointestinal disorders			
Nausea	Total	3 (1.3)	10 (4.0)
	4	0 (0.0)	1 (0.4)
	3	3 (1.3)	9 (3.6)
General disorders and administration site conditions			
Fatigue	Total	10 (4.3)	16 (6.5)
	3	10 (4.3)	16 (6.5)
Nervous system disorders			
Headache	Total	2 (0.9)	9 (3.6)
	4	0 (0.0)	1 (0.4)
	3	2 (0.9)	8 (3.2)
Renal and urinary disorders			
Proteinuria	Total	1 (0.4)	20 (8.1)
	4	0 (0.0)	1 (0.4)
	3	1 (0.4)	19 (7.7)
Respiratory, thoracic, and mediastinal disorders			
Dyspnoea	Total	4 (1.7)	11 (4.5)
	3	4 (1.7)	11 (4.5)
Epistaxis	Total	1 (0.4)	12 (4.9)
	3	1 (0.4)	12 (4.9)
Vascular disorders			
Hypertension	Total	1 (0.4)	40 (16.2)
	4	0 (0.0)	2 (0.8)
	3	1 (0.4)	38 (15.4)

BV = carboplatin + gemcitabine + bevacizumab arm; PL = carboplatin + gemcitabine + placebo arm; MedDRA = Medical Dictionary for Regulatory Activities; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events. NCI CTCAE Grades are only shown for those in which adverse events were reported.

[a] Acute myocardial infarction.

[b] Intracranial hemorrhage.

The number and causes of deaths in the safety population are summarised in Table 21. At the time of data cutoff a higher proportion of patients had died in the PL arm than in the BV arm (BV: 25.5%; PL: 33.5%). The majority of deaths were due to disease progression in both arms (BV: 24.3%; PL: 33.0%); one patient died due to an adverse event in the PL arm, while two patients in the BV arm died of adverse events, only one of which was related to treatment.

Table 21: summary of causes of death (safety-evaluable patients)

	No. (%) of Patients	
	PL (n = 233)	BV (n = 247)
No. of deaths	78 (33.5)	63 (25.5)
Due to disease progression	77 (33.0)	60 (24.3)
Due to adverse event	1 (0.4)	2 (0.8) a
Unknown	0 (0.0)	1 (0.4)

BV = carboplatin + gemcitabine + bevacizumab arm; PL = carboplatin + gemcitabine + placebo arm. aOne adverse event was not treatment emergent.

The results of an updated safety analysis, conducted 11 months after the primary data cut-off, are provided in Table 22. This updated analysis focused on AESIs. An additional three patients had proteinuria (grade ≥3) and one extra patient had hypertension in the bevacizumab arm.

Table 22: Updated safety analysis (11 months after primary data cut-off)

Adverse event, n (%)	PL (n=233)	BV (n=247)
Bleeding (non-CNS), all grade Bleeding (non-CNS), grade ≥3 Epistaxis, grade ≥3	64 (27.5) 2 (0.9) 1 (0.4)	158 (64.0) 14 (5.7) 12 (4.9)
Hypertension, all grade Hypertension, grade ≥3	20 (8.6) 1 (0.4)	107 (43.3) 44 (17.8)
Fistula/abscess, all grade	1 (0.4)	4 (1.6)
Gastrointestinal perforation, all grade	0 (0)	0 (0)
Proteinuria, grade ≥3	2 (0.9)	24 (9.7)
RPLS, all grade	0 (0)	2 (0.8)a
Thrombocytopenia, grade ≥3	79 (34.0)	99 (40.0)

BV = carboplatin + gemcitabine + bevacizumab arm; PL = carboplatin + gemcitabine + placebo arm.[a]MRI-confirmed

The time to discontinuation of study drug due to AEs is shown in Table 23. Most discontinuations occurred during the initial chemotherapy phase (BV: 14.6%; PL:

3.4%), with the majority of patients who did discontinue their study drug doing so within the first 6 cycles (BV: 10.5%; PL: 3.0%).

Table 23: time of study drug discontinuation due to AEs

	No. (%) of Patients	
Protocol Treatment Phase	PL (n = 233)	BV (n = 247)
Total patients discontinued because of AE	11 (4.7)	49 (19.8)
Concurrent chemotherapy plus bevacizumab or placebo	8 (3.4%)	36 (14.6)
Cycles 1–6	7 (3.0%)	26 (10.5)
Cycles 7–10	1 (0.4%)	10 (4.0)
Single-agent bevacizumab or placebo	3 (1.3%)	13 (5.3)
Cycles 7–10	2 (0.9%)	2 (0.8)
Cycles 11–20	1 (0.4)	8 (3.2)
Cycles 20 +	—	3 (1.2)

BV: carboplatin + gemcitabine + bevacizumab; PL: carboplatin + gemcitabine + placebo.

6.8.2.2 Previous experience of GI perforations with bevacizumab in recurrent ovarian cancer

The OCEANS study was originally designed to re-evaluate the safety of bevacizumab in recurrent ovarian cancer, with respect to the incidence of gastrointestinal perforations. The studies which raised a concern about the incidence of GI perforations with bevacizumab in recurrent ovarian cancer are shown below.

A safety literature search identified ten prospectively designed trials of bevacizumab which reported the incidences of adverse events, including GI perforations. The key details of these studies are summarised in Table 24.

Table 24: Incidence of GI perforations in previous prospective trials

Lead author, year	n	Intervention	Population	Incidence of GI perforations
Del Carmen M, 2012	54	Bevacizumab + PLD	Platinum-sensitive ROC	1.9%
Kudoh K, 2011	30	Bevacizumab+PLD	ROC	3.3%
McGonigle K, 2011	40	Bevacizumab + topotecan	Platinum-resistant ROC	0%
Chambers S, 2010	40	Bevacizumab + erlotinib	Heavily pretreated ROC	2.5%
Smerdel, M	38	Bevacizumab	Multiresistant ROC	5.3%
Garcia A, 2008	70	Bevacizumab + cyclophosphamide	ROC	5.7%+
Nimeiri H, 2008	13	Bevacizumab + erlotinib	ROC	15.4%
Chura J, 2007	15	Bevacizumab + cyclophosphamide	Heavily pretreated ROC	0%
Burger R, 2007	62	Bevacizumab	Platinum-sensitive (58.1%) and –resistant (41.9%) ROC	0%
Cannistra S, 2007	44	Bevacizumab	Platinum-resistant ROC	11%

Number of previous chemotherapy lines not included due to insufficient data. +Reported as "gastrointestinal perforation or fistula".

Bevacizumab was used in combination with a variety of cytotoxic agents, with one trial evaluating the efficacy and safety of single-agent bevacizumab. All patients had recurrent ovarian cancer, however most trials did not specify the number of previous chemotherapy lines or the proportion of platinum-sensitive patients. The incidence of gastrointestinal perforations ranged from 0 – 15.4%. The highest incidence (15.4%) occurred in a very small study, where 2 of 13 patients experienced a GI perforation. However, in the larger study of Cannistra, amongst 44 patients with platinum-resistant disease treated with bevacizumab monotherapy, there were 5 GI perforations (11%) and also 5 cases (11%) of bowel obstruction.

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

The tolerability profile of the bevacizumab in the OCEANS study in recurrent platinum-sensitive ovarian cancer was consistent with previous experience of

bevacizumab in other cancer types (Miller et al. 2007;Sandler et al. 2006), and with the safety profile of bevacizumab in front-line ovarian cancer(Burger et al. 2011;Perren et al. 2011). No new safety concerns were identified.

Exposure to chemotherapy was comparable between the study arms, although more patients in the PL arm received 7 – 10 doses of carboplatin than in the BV arm. This may be a reflection of the significantly higher ORR in the BV than in the PL arm of the study. The Grade 3-5 AEs occurring more frequently in the BV arm than the PL arm (≥ 2% difference) were thrombocytopenia, nausea, fatigue, headache, proteinuria, dyspnoea, epistaxis and hypertension. While Grade 3-5 hypertension occurred in 17.4% of patients in the BV arm, only two patients (0.8%) experienced life-threatening (Grade 4) hypertension.

One hundred and forty one patients had died at the time of primary data cut-off, with more deaths in the PL arm than the BV arm. The majority of deaths in both treatment arms were due to disease progression. One death in each arm was due to a Grade 5 AE (BV: intracranial haemorrhage; PL: acute myocardial infarction), with one further death in the BV arm due to an AE which was not related to treatment.

The Grade 3 – 5 adverse events of special interest occurring more commonly (≥ 2% difference) in the BV arm than in the PL arm were hypertension, proteinuria and non-CNS bleeding.

As mentioned in Section6.8.2.2, previous Phase II trials of bevacizumab in recurrent ovarian cancer showed that 0 – 15.4% of patients with recurrent ovarian cancer treated with BV experienced gastrointestinal perforations (Burger et al. 2007;Nimeiri et al. 2008). In response to this safety concern, OCEANS was initially designed to evaluate the risk of GI perforations in forty patients without recognizable risk factors at baseline. However, after no GI perforations were seen the study was expanded to a full Phase III design. Throughout the course of the OCEANS study, no patients experienced gastrointestinal perforations.

More patients in the BV arm discontinued study-drug treatment than in the PL arm. The majority of discontinuations were due to individual adverse events; the only AEs

leading to discontinuation in ≥ 2% of patients in the BV arm were hypertension (BV: 3.6%; PL: 0.0%) and proteinuria (BV: 2.4%; PL: 0.0%).

In summary, the safety data reported in this study are consistent with the established safety profile of bevacizumab in other cancer indications. Importantly, bevacizumab does not appear to increase the risk of gastrointestinal perforations in patients without prior risk factors. 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.

The OCEANS trial was a rigorously conducted double-blind, placebo-controlled trial in 484 patients receiving second-line therapy for platinum sensitive recurrent ovarian cancer. The patients had epithelial ovarian, fallopian tube, or primary peritoneal cancer and were treated with placebo (PL) or bevacizumab (BV) at 15mg/kg every 3 weeks to progression, in combination with 6-10 cycles of carboplatin and gemcitabine. The patients in the 2 study arms were well matched, with regards to baseline characteristics which might affect prognosis. Patients with partially platinum sensitive disease (relapse 6-12 months after prior platinum therapy) made up 42% of the study population while the remainder were fully platinum sensitive, with relapse more than 12 months after previous platinum therapy.

At the time of the primary analysis for PFS, fewer patients in the BV arm had progressed or died (62.4%) versus the PL arm (77.3%). The trial demonstrated a clinically meaningful and statistically significant increase in PFS with the addition of BV to GC. Median PFS was 12.4 months with BV versus 8.4 months with PL (HR 0.484, 95% CI 0.388, 0.605; $p<0.0001$). There was also a highly significant increase in ORR with BV (78.5%) compared to PL (57.4%; $p<0.0001$). The IRC-determined PFS and ORR confirmed these significant improvements in efficacy, thereby adding weight to the results.

Subgroup analysis showed that all groups of patients gained significantly more benefit from BV compared with PL. The results suggest that patients with a shorter

platinum-free interval may have gained the greatest benefit. However, there was no significant difference between the HR for partially platinum sensitive and fully platinum sensitive patients.

The overall survival data are as yet immature (final OS data are expected at the end of 2013) and interim analyses have not shown any difference in OS between the two study arms. However, the estimates for median OS are in the region of 33 months, far in excess of the 18 months postulated in the statistical plan and consequently the median time from progression to death was 21-25 months. Extended statistical modelling has shown that for clinical trials with a PFS benefit, lack of a statistically significant OS benefit does not imply a lack of improvement in OS, especially for diseases with more than 12 months between progression and death. For a trial with an observed p value for improvement in PFS of 0.001 such as OCEANS, there is a less than 20% probability for statistical significance in OS if the median time between progression and death is 24 months. (Broglio & Berry 2009).

More than half the study patients received at least 4 lines of therapy for their disease and a quarter of patients received at least 6 lines of therapy. Moreover, 35% of PL patients and 18% of BV patients received bevacizumab in their subsequent therapy. It may be that the large number of subsequent therapies, including bevacizumab given to patients in both arms of the study have also confounded the ability of the study to show an OS benefit following the increased PFS in the BV arm in second-line therapy.

However, examination of subsequent treatment patterns does show that fewer BV than PL patients were in receipt of every subsequent line of therapy. Thus after progression, patients given PL in the OCEANS study underwent more disease relapses and more subsequent chemotherapy than patients given BV, with all the toxicities associated with chemotherapy and consequent negative impacts on quality of life. (due to adverse events and hospital visits associated with administration of treatments, for example).

Exposure to chemotherapy in the OCEANS study was comparable between treatment arms, although a higher percentage of patients in the PL arm received 7 –

10 doses of carboplatin than in the BV arm, possibly reflecting the lower ORR with PL. The safety profile of BV in combination with carboplatin and gemcitabine was consistent with previous studies of BV in both ovarian cancer and other disease settings. Grade 3-5 AEs occurring more frequently in the BV arm than the PL arm (≥ 2% difference) were thrombocytopenia, nausea, fatigue, headache, proteinuria, dyspnoea, epistaxis and hypertension.

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

Strengths

The OCEANS trial was a large double-blind, randomised, controlled trial that was conducted in centres throughout the United States. This patient population is genetically similar to the demographic in the UK.

The study was adequately powered to measure the primary outcome of PFS. An independent review of PFS, ORR and Duration of Response supported the investigator assessed results and exploratory subgroup analyses also supported the ITT analysis.

Disease progression in the OCEANS trial was evaluated using RECIST criteria alone, which is relevant to UK practice. In the UK, clinical criteria, rather than CA-125, have a dominant role in determining disease progression and change of therapy in ovarian cancer.

Limitations

Once patients had progressed after their second-line therapy they were allowed to receive therapy of the Investigator's choice, including bevacizumab. This may have helped to confound the OS data, as at least 34% of PL patients received subsequent bevacizumab therapy.

Carboplatin and gemcitabine is generally not the most preferred chemotherapy in the UK for the treatment of recurrent ovarian cancer. Many UK clinicians might prefer to use carboplatin plus pegylated liposomal doxorubicin (Caelyx®) in this

setting, or even to rechallenge recurrent patients with the first-line standard of care, carboplatin and paclitaxel. However, Caelyx® is currently unavailable and rechallenge with paclitaxel may not be possible because of tolerability problems such as neuropathy and alopecia. However, due to good manufacturing practice issues, Caelyx® is currently unavailable to new patients until approximately December 2014 (EMA 2012) and rechallenge with paclitaxel may not be possible because of tolerability problems such as neuropathy and alopecia.

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.

The evidence base reviewed in section 6 is relevant to the decision problem, which highlights the need for effective treatment in patients with recurrent ovarian cancer. A relevant, large randomised controlled trial has been reviewed, examining the effects of bevacizumab and chemotherapy (carboplatin and gemcitabine) versus chemotherapy alone.

The primary outcome of OCEANS was to evaluate PFS in patients receiving bevacizumab and chemotherapy versus chemotherapy alone. Patients presenting with recurrent ovarian cancer generally have clinical symptoms and measurable deposits of disease. Shrinkage of this disease and alleviation of symptoms is the primary aim of therapy for recurrent ovarian cancer and PFS is a reasonable measurement of this treatment efficacy. 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 then maintain disease remission for as long as possible and so PFS is a meaningful outcome from the perspective of both treating clinician and the patient.

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?

Patients entered into the OCEANS study are representative of the population presenting with recurrent ovarian cancer in routine UK clinical practice. The disease-specific and bevacizumab-specific exclusion criteria for recruitment to the study reflect the contraindications and special warnings in the Avastin SPC. The population entering the study should therefore reflect the patients for whom therapy with bevacizumab would be considered in routine practice.

The subgroup analyses of PFS in the OCEANS study suggest that bevacizumab provided benefit across all subgroups of patients recruited to the study, irrespective of age, performance status, lesion size, tumour marker level or time since last platinum therapy. The results should therefore be applicable to patients with platinum sensitive recurrent ovarian cancer in routine UK clinical practice.

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 in relapsed or recurrent 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), Medline (MEYY) as well as health economic databases, EconLIT and NHS EED. In addition TUFTS CEA registry was searched using ovarian cancer and recurrent, the search was restricted to ratios, this produced no additional results. 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 and 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 relapsed or recurrent 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 and 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:

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

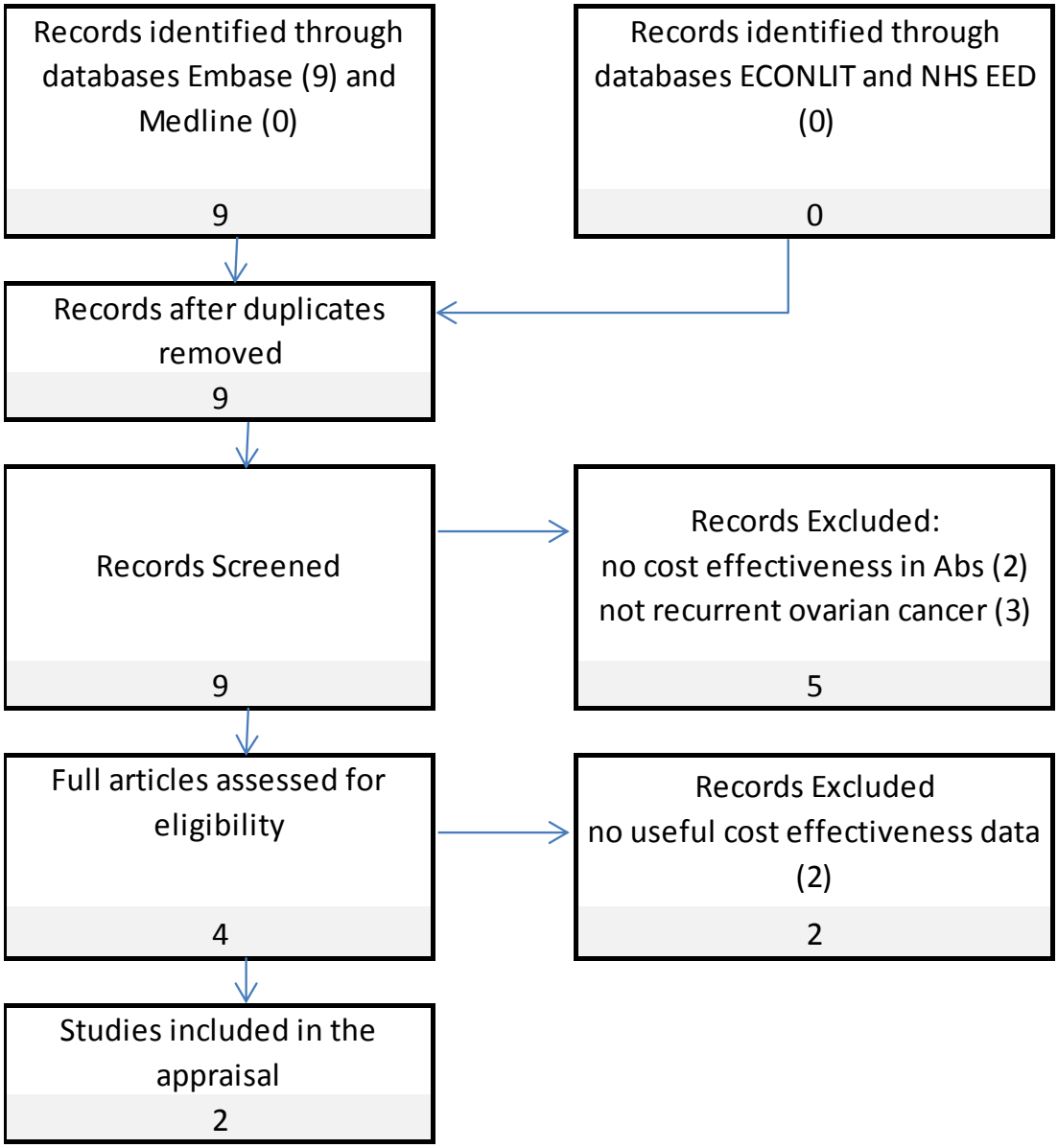
If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria in Table 25 below.

Table 25: Inclusion/exclusion criteria for Cost Effectiveness

INCLUSION	EXCLUSION
Intervention: Bevacizumab	
Disease: recurrent/relapsed ovarian cancer	Disease is not recurrent/relapsed 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 10 for the full flow of documents and rationale for exclusions. From the 9 results, 2 were excluded as they did not include cost effectiveness terms in the abstract, 3 were excluded since it did not relate to ovarian cancer. The remaining 4 papers were found to be relevant and were retrieved and read in full. 2 of these papers contained no useful cost effectiveness data. The remaining 2 papers were included

Figure 10: 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. If more than one study is identified, please present in a table as suggested below.

2 papers were identified, as detailed in Figure 10. Refer to appendix 11 section 7.1 for the detailed quality assessment of these 2 studies. An overview of the 2 papers is provided below.

1. Is it more cost-effective to use bevacizumab in the primary treatment setting or at recurrence? An economic analysis Fuh et al. 2011 (abstract only) (Fuh et al. 2011)

Aim: To compare the cost effectiveness of bevacizumab in the primary versus recurrent setting.

Methods: Drugs costs, rates of complication and PFS were taken from published data. Costs were based on Medicare payments for administration of chemotherapy, drug costs: Paclitaxel, carboplatin and bevacizumab plus maintenance bevacizumab (PCB + mB) and costs of potential complications

Results:

	Cost	Incremental PFS	ICER per LYS
Primary setting: addition of B plus mB	$140.29k	6 months	$270.9k
Recurrent setting: addition of B plus mB	$92.94k	3 months	$361.1k

2. An economic analysis of bevacizumab in recurrent treatment of ovarian cancer. J Chan et al 2011(Chan et al. 2011)

Aim: To determine if the addition if bevacizumab to chemotherapy for the recurrent treatment of advanced ovarian cancer is cost effective.

Methods: Based on OCEANS data, gemcitabine, carboplatin (GC) compared to gemcitabine, carboplatin with concurrent and maintenance bevacizumab (GCB + mB).Costs based on Medicare payment for the administration of chemotherapy, drug costs and costs of potential complications. Recurrence rates determined from published data.

Results:

	Cost for 240 patients	Incremental Cost for 240 patients	PFS per patient	Incremental PFS for 240 patients	ICER per LYG
GC	$4m		8.6 months		
GCB + mB	$36.5m	$32.5m	Scenario 1 11 months Scenario 2 15 months	2.4months x 240 = 576 months = 48 LYG 6.4months x 240 = 1536 months =128 LYG	$677.25k $253.97k

Table 26 shows a tabulated summary of the 2 papers.

Table 26: Summary of included Cost Effectiveness Papers

Study	Cost Year (Discount Rate)	Country study was performed	Summary of the model	Patient population	Costs considered	QALY's (incremental)	Costs (incremental)	ICER per QALY gained	Relevance
Fuh et al. 2011 (abstract only) (Fuh et al. 2011)	Not stated	USA	Based on GOG - 0218 (1st line OC) – maintenance bevacizumab (mB) plus plactitaxel, carboplatin and bevacizumab (B) Compared cost and effect of this treatment in 1st and 2nd line setting	1L and recurrent ovarian cancer	Drug costs, rates of complications	2nd line - 0.26 LYS	2nd line - $47.4k	2nd line +$90.2k per LYS Using B abstract concludes that in the primary setting B + mB may be more cost effective than use in the recurrent setting	Not relevant since analysis is based entirely on data in 1st line setting Assumptions on additional PFS from addition of B plus mB are not explained, nor are the basis of costs of complications.
Chan et al 2011 - abstract only (Chan et al. 2011)	Not stated	USA	Based on OCEANS gemcitabine + carboplatin =GC compared to gemcitabine + carboplatin + concurrent and maintenance bevacizumab =GCB + B	Recurrent ovarian cancer 240 patients per arm	Chemotherapy administration and costs of complications	Base: +2.4 months GCB+B x 240 patients = 48 LYS Second assumption: +6.4 months GCB+B x 240 patients = 128 LYS	For 240 patients in each arm GCB+B = $32.5m	Base:$677.2m GCB+B per LYS for total 240 population 2nd assumption $253.9m for total population	Not relevant – cost based on US setting, no details of the costs are provided or basis of the assumption regarding increase of PFS to 15 months for GCB +B

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.

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.

The model is based on the OCEANS randomised placebo-controlled study and uses survival, safety and treatment duration data from the ITT population. The patients recruited to this study are fully within the limits of the marketing authorization.

The dose of bevacizumab, carboplatin and gemcitabine received by patients is dependent on a number of demographic characteristics (i.e. body weight, body surface area (BSA) and creatinine clearance rates which are influenced by age). The OCEANS study was conducted in North America and it is likely

[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.

that the patients enrolled had baseline demographic characteristics different from counterparts in the UK. Therefore, in order to more accurately model the doses of these drugs likely to be required by UK patients, the base case economic model uses data from a published study reporting the age and BSA of 321 women who were treated for ovarian cancer in 3 UK centres in 2005 (Sacco et al. 2010). The impact of using the characteristics of patients recruited to OCEANS was explored in sensitivity analysis.

Table 27: Demographic characteristics [mean (95% CI)] of ovarian cancer patients in the UK and in the OCEANS study

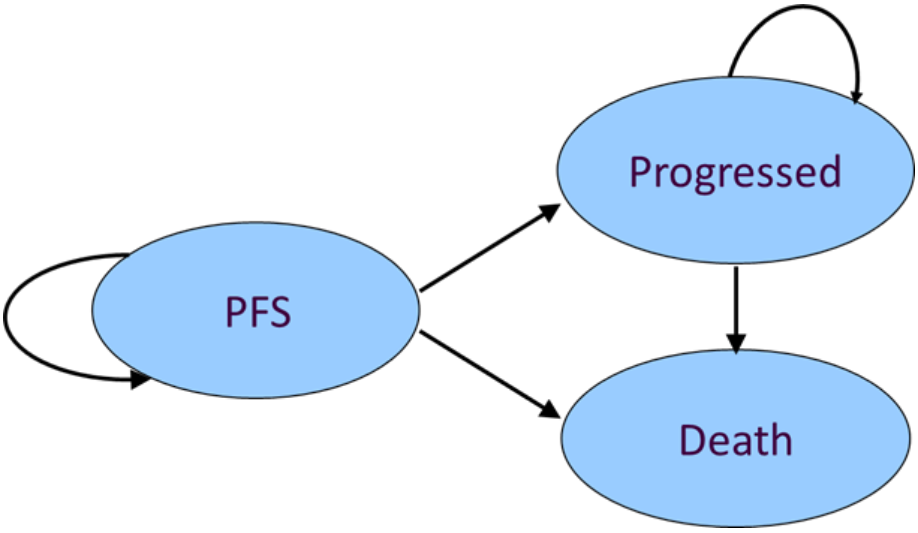
Source of patient data	UK cohort (N=321)	OCEANS (N=484)
Average Age of Cohort (years)	61.37 (37-79)	61.02 (43-81)
Body weight (kg)	69.35* (41.70-107.65)	75.68 (48.91-117.93)
Height (cm)	160.05** (N/A)	161.4 147-175.3)
BSA (Body Surface Area) (m^2)	1.713 (1.39-2.08)	1.789*** (1.397-2.224)
* Body weight was calculated from BSA, ** Height assumed to be 160.05cm for all patients, *** BSA calculated from weight and height data		

Details of the calculations used are provided in Section 7.5.5.

Model structure

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

Figure 11: Model schema



The base case time horizon for both models is 10 years and costs and outcomes were discounted at 3.5% per annum. 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).

A 3-state, Area-Under-the-Curve model, (Figure 11) founded on the PFS and OS endpoints of the OCEANS 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 29th September 2010 clinical cut-off date which corresponded to a median follow-up period of 24 months and 29% of patients had died. This data-cut was chosen as it represents the most recent contemporaneous analysis of all the main outcomes of interest (e.g. PFS, OS, AEs, post-progression therapies etc) and represents the final PFS analysis for the study.

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 model presented is a 3-state model 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 B2 Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	10 years	The base case time horizon allows for more than 97% of the cohort to enter the death state.	(NICE 2008a)
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 2008a)
Half-cycle correction	Yes	As per NICE guide to methods.	(NICE 2008a)
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?

Yes, both intervention and comparators in the base case analysis are implemented in the model as per the relevant marketing authorisations.

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.

PFS

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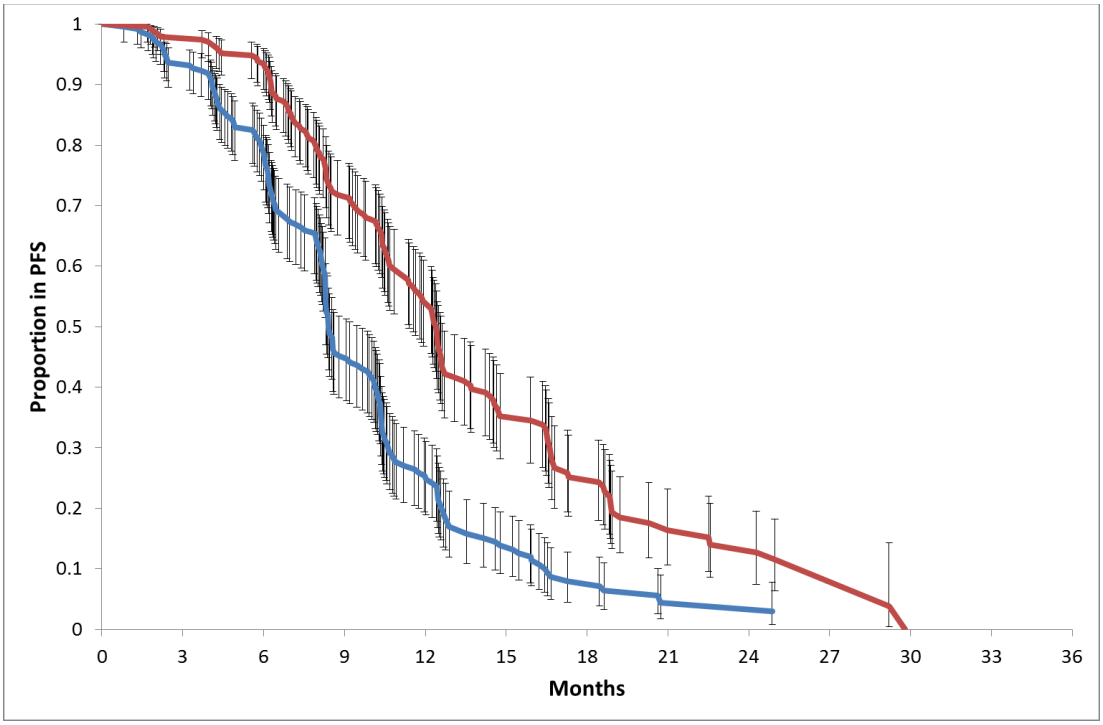
The proportion of patients remaining in the PFS state is calculated directly from the Kaplan-Meier survival curves for bevacizumab + carboplatin/gemcitabine and placebo/carboplatin/gemcitabine arms of the OCEANS study. This data reflected a median PFS gain of 4.0 months, HR=0.484 (95% CI: 0.388 – 0.605) and was included in the study report published in the Journal of Clinical Oncology in June 2012 as well as the marketing authorization application to EMA. As shown in Figure 12, the addition of bevacizumab to carboplatin/gemcitabine combination therapy results in a significant delay in disease progression as evidenced by the non-overlapping 95% confidence intervals for PFS.

Figure 12: Progression-free survival of patients in the OCEANS study receiving bevacizumab (red) or placebo (blue) in combination with carboplatin and gemcitabine with 95% confidence limits

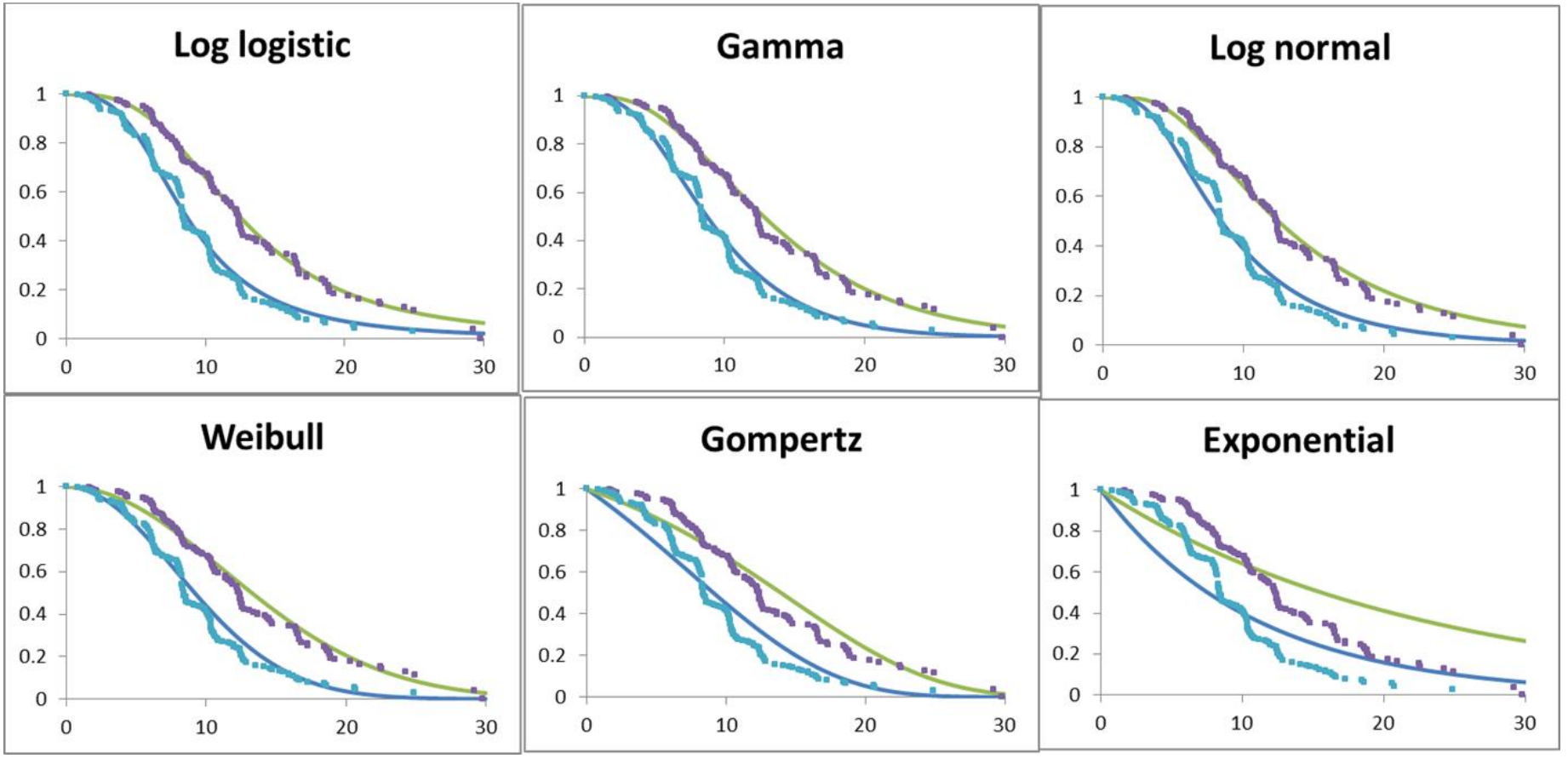


Parametric functions to describe the PFS times observed within the clinical trial period of the OCEANS study (derived using the PROC LIFEREG procedure in SAS v9.2) were assessed for their goodness of fit to the data using Akaike (AIC) and Bayesian Information Criteria (BIC) and graphical assessment of each function (Table 28 and Figure 13).

Table 28: Statistical fit of parametric curves to progression-free survival

Model	BIC	AIC
log logistic	772.509	759.963
gamma	786.915	770.187
log normal	795.127	782.581
Weibull	805.912	789.184
exponential	1001.22	992.858
Gompertz	1173.25	1160.71

Figure 13: Visual comparison of parametric curves describing progression-free survival of patients receiving bevacizumab (green line and purple dots) or placebo (blue line and light blue dots) in addition to carboplatin and gemcitabine

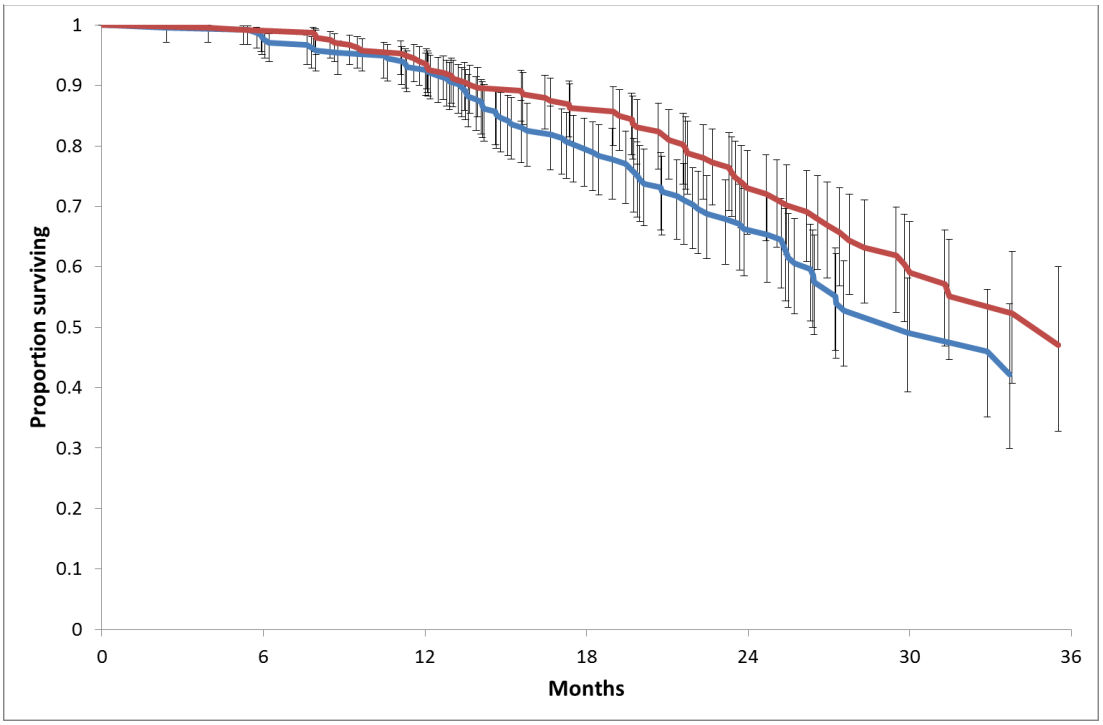


Of the 6 parametric functions tested, 4 (Log logistic, Gamma, Log normal and Weibull) appeared to provide close approximations to the observations from the study and are comparable with each other in terms of statistical and visual fit. In contrast, both the Gompertz and exponential functions provided a much poorer fit to the data and are unlikely to be useful in further analyses.

OS

After disease progression, patients leave the “PFS” health state and enter the “Progressed disease” health state. The proportion of patients in this health state is derived from the difference between patients in the PFS health state and those who have died in the OCEANS study. As shown in Figure 14 (and in contrast to PFS), there was significant overlap of OS curves for patients in either treatment arm of the OCEANS study. However, overall survival data are still immature and results are likely to be confounded by the effects of subsequent lines of therapy (including surgery and radiotherapy as well as disease-modifying treatments) which are outside the control of the study protocol.

Figure 14: Overall survival of patients in the OCEANS study receiving bevacizumab (red) or placebo (blue) in combination with carboplatin and gemcitabine with 95% confidence limits



Statistical and visual comparison of the 6 different parametric functions describing OS reveals similar results to those for PFS, i.e. 4 functions are much better approximations for the data than the other 2 (Table 29 and Figure 15).

Table 29: Statistical fit of parametric curves to overall survival data

Model	BIC	AIC
log logistic	608.929	596.383
gamma	615.061	598.332
log normal	611.487	598.94
Weibull	617.344	600.615
exponential	700.113	691.749
Gompertz	718.44	705.893

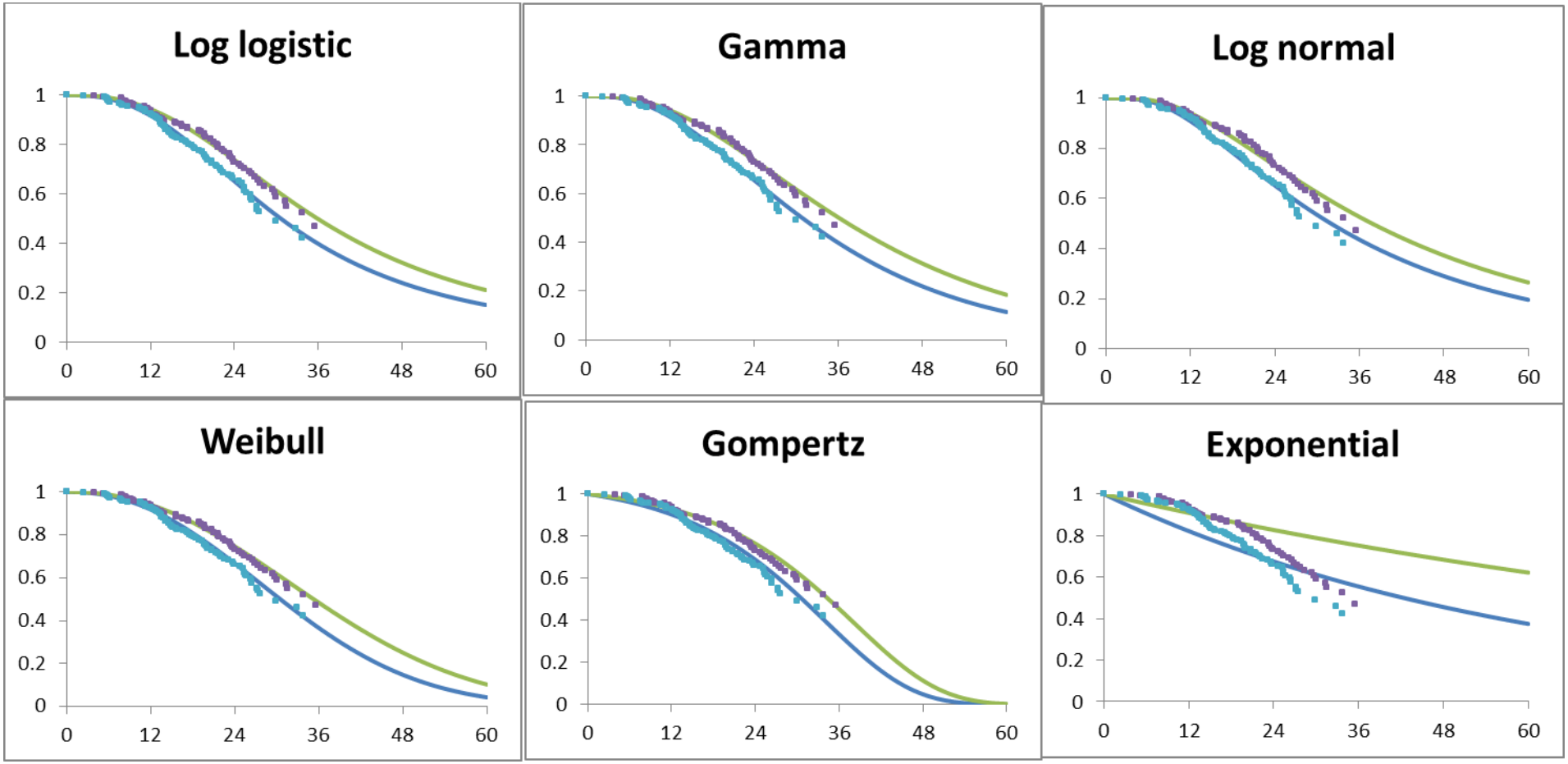
7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

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

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

Figure 15: Visual comparison of parametric curves describing overall survival of patients receiving bevacizumab (green line and purple dots) or placebo (blue line and light blue dots) in addition to carboplatin and gemcitabine



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).

N/A

[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. Please present in a table, as suggested below.

Table B3 Summary of variables applied in the economic model

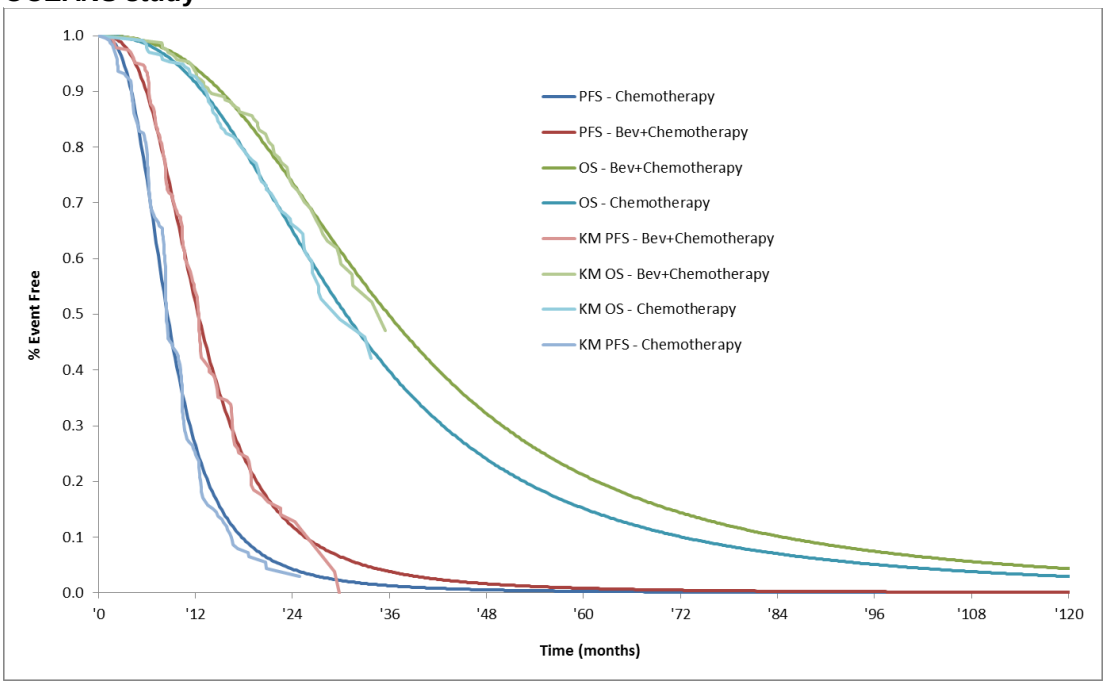
Variable	Value	CI (distribution)	Reference to section in submission
Patient characteristics			
Age	UK Cohort: 61.37 OCEANS: 61.02	37-79 43-80.93	section 6.3.4
Weight	UK Cohort: 69.35 OCEANS: 75.68	41.70-107.65 48.91-117.93	
Height	UK Cohort: 160.05 OCEANS: 161.38	N/A	
BSA	UK Cohort: 1.713 OCEANS: 1.789	1.39-2.08 1.40-2.22	
Utilities			
PFS	0.718	0.699 - 0.737	section 7.4.8
PD	0.649	0.611 – 0.686	
Costs			
Bevacizumab arm drug costs			
Expected cost of bevacizumab per visit	UK Cohort: £2,555 OCEANS: £2,762	£1,652-£3,940 £1,752-£4074	section 7.5.5.1
Expected cost of carboplatin per visit	UK Cohort: £155 OCEANS: £167	£105-£242 £115-£244	section 7.5.5.2
Expected cost of gemcitabine per visit	UK Cohort: £22 OCEANS: £22	£17-£26 £18-£28	section 7.5.5.3
Chemotherapy arm drug costs			
Expected cost of carboplatin per visit	UK Cohort: £155 OCEANS: £166	£105-£242 £112-£256	section 7.5.5.2
Expected cost of gemcitabine per visit	UK Cohort: £22 OCEANS: £22	£17-£26 £18-£28	section 7.5.5.3
Drug administration and preparation costs			
First visit administration and pharmacy costs	£275	upper and lower quartiles from NHS Reference costs	section 7.5.5.4 and section 7.5.5.5

Subsequent visit administration and pharmacy costs	£94	upper and lower quartiles from NHS Reference costs	
Weekly disease management costs			
PFS (£)	£10	+/- 10%	section 7.5.6
PD (£)	£44	+/- 10%	
Cost of post progression therapies			
Chemotherapy arm	£1,553	N/A	section 7.5.8.1
Bevacizumab arm	£2,916	N/A	
Palliative care	£6,727	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.

The base case analysis of the addition of bevacizumab to carboplatin and gemcitabine combination therapy is based on PFS and OS curves described by log logistic functions since these were found to have the best statistical fit to the data (Table 28 and Table 29 and Figure 16). The effect of alternative functions is explored in sensitivity analyses.

Figure 16: PFS and OS curves used in the base case economic analysis of the OCEANS study



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 OCEANS would hold in clinical practice.
- The base case assumed that outcomes from OCEANS 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 model assumed that costs of disease management and the utility of patients in progression-free and progressed

disease states were similar to those described in a previous appraisal of ovarian cancer (Papaioannou et al. 2010).

- It was assumed that the treatments received by patients after disease progression in the OCEANS study are similar to those received by patients in the UK healthcare system and the average costs associated with these treatments was incurred by all patients at the beginning of the model time horizon.

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).

HRQL data derived from clinical trials

7.4.2 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.

No QoL data was gathered in the OCEANS trial.

Mapping

7.4.3 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.

Not applicable as no QoL data was gathered during the OCEANS trial

HRQL studies

7.4.4 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 recurrent or relapsed 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) and 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, relapsed and recurrent.

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 recurrent or relapsed ovarian cancer? If No – Exclude

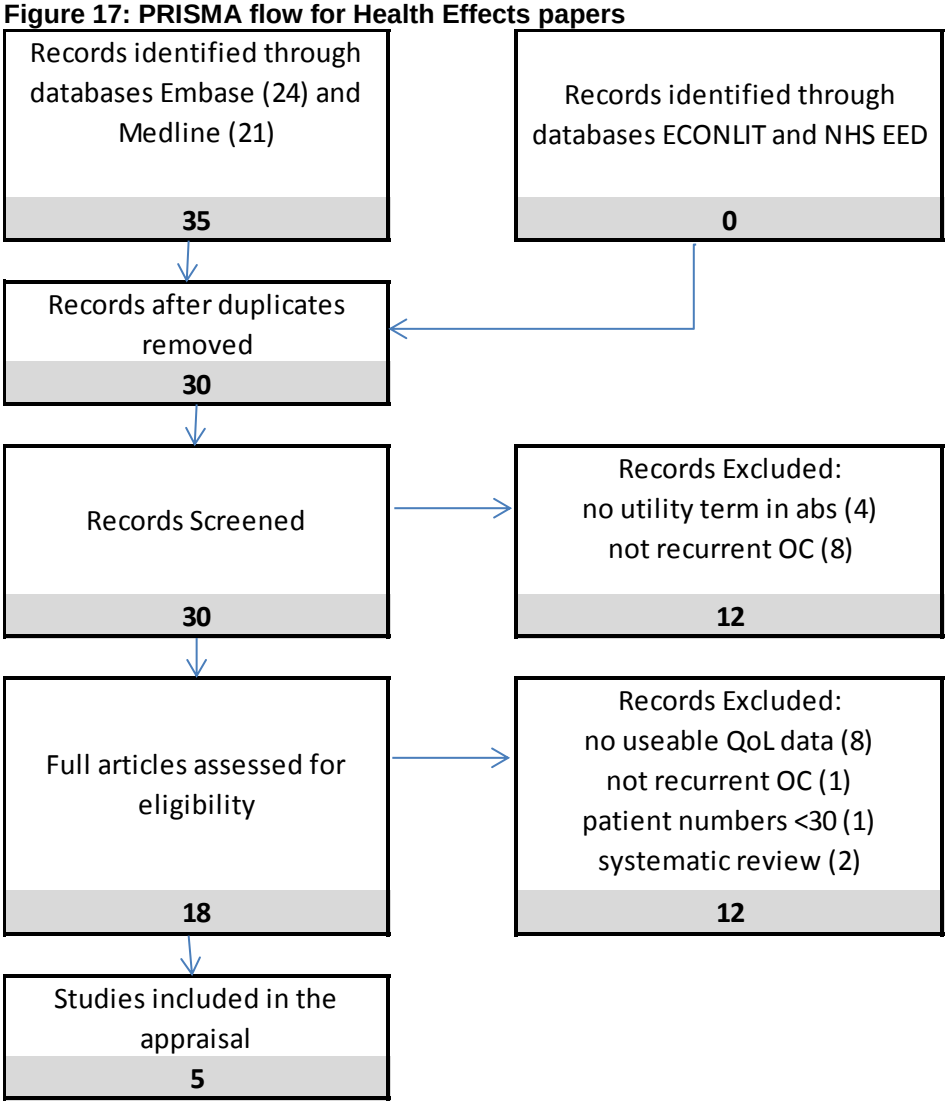
If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria in Table 30 below.

Table 30: 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 recurrent/relapsed Ovarian Cancer	Disease is not recurrent/relapsed Ovarian Cancer
	Literature review

Results: In total 35 individual records were identified via the four databases, 5 of these were duplicates. At initial screening of the abstract and title 12 studies were excluded .The PRISMA diagram Figure 17 shows the document selection and rationale for these exclusions. 18 records were deemed potentially relevant. These 18 results were then retrieved and assessed more comprehensively against the inclusion/exclusion criteria, 5 were found to be relevant.

Figure 17: PRISMA flow for Health Effects papers



7.4.5 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 31 to Table 35 below provide a summary of the 5 papers found to be appropriate.

Table 31: summary of health effects papers: Brundage et al 2012

	Brundage et al. 2012 (Brundage et al. 2012)			
Population in which health effects were measured.	Age: >18 years, confirmed diagnosis of ovarian, fallopian tube or extra-ovarian papillary serous cancer. Disease progression >6 months after treatment with 1st (85%) or 2nd line platinum based chemotherapy regimen. EGOG status 2 or less (95% have 0 or 1).Stage III/ IV 85% Life expectancy at least 12 weeks			
Recruitment	Recruited into CALYPSO trial			
Interventions and comparators.	• PLD (day 1) and carboplatin at 4 week intervals (CD) • paclitaxel (day 1) and carboplatin at 3 week intervals (CP)			
Sample size.	976 patients: 476 randomised to PLD and carboplatin (CD), 509 to carboplatin and paclitaxel (CP)			
Response rates		CP (n)	CD (n)	total
	Baseline	90% 458	90.1% 421	90%
	3 months	73.5%	79.3%	76%
	6 months	60.3%	68.3%	64%
	12 months	49.7%	50.6%	57%
	% with baseline + min 1 other	79%	84%	

Description of health states.	EORTC-QLQ C30: Physical, role, emotional, cognitive and social. Global health state and symptom scales (fatigue, nausea, vomiting and pain and dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties) OV28: 28 items including abdominal/ gastrointestinal symptoms, peripheral neuropathy, other chemotherapy side effects, hormonal symptoms, body image, attitudes to disease/treatment and sexuality.
Adverse events.	As described above
Health states appropriate?	Appropriate
Method of elicitation / Method of valuation	Patients completed ,EORTC-QLQ core instrument and OV28 ovarian cancer specific model data gathered at randomisation and then at 3, 6, 9 and 12 month assessments. Data on compliance to complete the questionnaires shown in response rates above. Baseline compliance 90% overall.
Mapping.	N/A
Uncertainty around values.	Missing data is likely to bias the estimate of mean improvement in HRQoL over time.
Consistency with reference case.	No EQ-5D data wasreported
Appropriateness for CE analysis.	No EQ-5D scores have been mapped from the EORTC QoL-QC30 or OV28 results, meaning there are no utility values presented.
Results with confidence intervals.	Table 1 of the paper shows baseline HRQoL mean scores and change in mean scores across time points. Global health status scores were broadly similar across both treatment arms and showed minor variation across 3 and 6 month reports. The main differences from base line were in symptom scales where variations between treatment arms could be seen, with neuropathy and other chemotherapy side effects showing the widest variation.

Table 32: Summary of health effects papers - Kranser et al

	Krasner et al.2012 (Krasner et al. 2012)
Population in which health effects were measured.	Age >18 years, diagnosis of epithelial ovarian, epithelial fallopian tube or primary peritoneal cancer Previously treated with 1 platinum based chemotherapy regimen Excluded were refractory disease (progression within 6months of 1st treatment of platinum therapy)

Recruitment	Patients recruited into clinical trial
Interventions and comparators.	• trabectedin and PLD at 3 weekly intervals (T + PLD) • PLD at 4 weekly intervals
Sample size.	672 patients: 335 PLD and 337 T + PLD. 663 patients completed patient reported outcome questionnaires.
Response rates	T + PLD PLD Overall 85.6% 84.8% Rates varied across cycles. All at 90% or more with exception of cycle 11 and 15 (83%), cycle 21(67%) and end of treatment (66%). This data is not broken down by arm
Description of health states.	EORTC-QLQ C30: Physical, role, emotional, cognitive and social. Global health state and symptom scales (fatigue, nausea, vomiting and pain and dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties) OV28: 28 items including abdominal/ gastrointestinal symptoms, peripheral neuropathy, other chemotherapy side effects, hormonal symptoms, body image, attitudes to disease/treatment and sexuality. EQ-5D: mobility, self-care, usual activities, pain/discomfort, anxiety/depression.
Adverse events.	As described above
Health states appropriate?	Appropriate
Method of elicitation / Method of valuation	Patients completed, EORTC-QLQ C30 core instrument, OV28 ovarian cancer specific model and EQ-5D Data gathered at screening and on day 1 of every other treatment cycle (before treatment of any other study evaluation)
Mapping.	N/A
Uncertainty around values.	N/A
Consistency with reference case.	EQ-5D data available from patients perspective.
Appropriateness for CE analysis.	EQ-5D scores are available but are not converted to utilities in this paper
Results with confidence intervals.	Table 1 from the paper shows mean changes from baseline to end of treatment in EQ-5D scores.Mean score of QLQ Q30 across time points from baseline to end of treatment was similar across the two treatment groups. The largest difference between

	treatment arms was seen in the global fatigue scale where trabectedin/PLD scored a mean increase (worsening) from baseline of 15.28 compared to PLD of 12.73.

Table 33: Summary of health effects papers - Pokrzywinski et al

	Pokrzywinski et al. 2011 (Pokrzywinski et al. 2011)
Population in which health effects were measured.	Recurrent platinum sensitive ovarian, peritoneal or tubal cancer, 1 prior platinum based regimen and may have received consolidation therapy or 1 prior biologic therapy as a single agent for recurrent disease, no prior treatment with docetaxel, performance status 0 (73.6%) 1 (22.3%) 2 (2.02%), >18 years
Recruitment.	Enrolled onto Phase II clinical trial
Interventions and comparators.	• Weekly docetaxel (days 1 and 8) and carboplatin 3 weekly (cDC) • Docetaxel (days 1 and 8) every 3 weeks for 6 cycles, followed by carboplatin every 3 weeks for 6 cycles or until progression (sDC)
Sample size.	148 randomised equally between the 2 treatment arms
Response rates.	<table><tr><td></td><td>cDC</td><td>sDC</td></tr><tr><td>Baseline + at least one follow up HRQoL</td><td>88%</td><td>89%</td></tr><tr><td>End of study assessment</td><td>51%</td><td>48.7%</td></tr></table>
Description of health states.	FACT-O: physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), functional well-being (FWB), and ovarian cancer specific module (OCS)
Adverse events.	N/A
Health states appropriate?	Appropriate
Method of elicitation /. Method of valuation	Patients completed Functional Assessment of Cancer Therapy ovarian (FACT-O) including (FACT-G) cancer therapy general. Trial outcome index (FACT-O TOI) constructed by combining FACT-O scores
Mapping.	N/A
Uncertainty around values.	N/A
Consistency with reference case.	EQ-5D has not been collected
Appropriateness for CE analysis.	No utility values are presented. Not appropriate
Results with confidence	<table><tr><td>Baseline</td><td>(n)</td><td>cDC (SD)</td><td>(n)</td><td>sDC (SD)</td></tr></table>

intervals.	PWB	65	23.2 (5.1)	64	23.3 (5.0)
	SWB	65	24.2 (4.7)	64	24.9 (4.5)
	EWB	65	17.8 (4.9)	66	16.7 (4.3)
	FWB	65	20.7 (6.0)	65	21.3 (5.6)
	OCS	65	32.3 (6.0)	64	34.1 (5.3)
	TOI	65	76.3 (14.0)	66	76.6 (16.1)
	FACT-G	65	85.9 (15.2)	63	86.0 (13.8)
	FACT-O	65	118.2 (19.3	66	117.4 (21.0)
	Baseline FACT-O scores showed no statistically significant differences between treatment arms .Mean scores for baseline and by cycle are shown in table 3 of the paper. sDC group showed statically significant changes in FACT-O TOI scores compared with cDC. Treatment had less impacton FACT-O TOI scores on the sDC group than cDC.				

Table 34: Summary of health effects papers - Havrilesky et al.

	Havrilesky et al.2012 (Havrilesky et al. 2012)
Population in which health effects were measured.	Recurrent platinum sensitive ovarian cancer
Recruitment.	Enrolled onto Phase II clinical trial
Interventions and comparators.	• Docetaxel (days 1 and 8) combined with carboplatin 3 weekly (cDC) • Docetaxel (days 1 and 8) every 3 weeks followed by carboplatin every 3 weeks for 6 cycles or until disease progression (sDC)
Sample size.	Not stated
Response rates.	Not reported
Description of health states.	Not reported
Adverse events.	AEs with no difference between the arms were not included in the

	cDC (range)	sDC (range)
Probability of GCSF support	0.221 (0.1 – 0.5)	0.141 (0.1 – 0.3)
Probability of EPO support	0.5 (0.1 – 0.8)	0.338 (0.2 – 0.5)
Probability of severe neurologic toxicity	0.029 (0.0 – 0.1)	0.0

<table>
<tr><td></td><td>model</td></tr>
<tr><td>Health states appropriate?</td><td>Not reported</td></tr>
<tr><td>Method of elicitation /. Method of valuation</td><td>Patients completed Functional Assessment of Cancer Therapy (FACT)
Utility calculated at 4 time points: study entry, before cycle 4, before cycle 6 and at the end of the study. FACT – G used to calculate utility value</td></tr>
<tr><td>Mapping.</td><td>N/A</td></tr>
<tr><td>Uncertainty around values.</td><td>N/A</td></tr>
<tr><td>Consistency with reference case.</td><td>EQ-5D has not been collected</td></tr>
<tr><td>Appropriateness for CE analysis.</td><td>Utility values are presented but are not valued using EQ-5D. Costs not collected during the trial, but obtained subsequently using national reimbursement data (USA). Discounting was not applied. Not appropriate</td></tr>
<tr><td>Results with confidence intervals.</td><td><table><tr><td></td><td>cDC (range)</td><td>sDC (range)</td></tr><tr><td>Randomisation</td><td>0.87 (0.84 – 0.89)</td><td>0.87 (0.85 – 0.89)</td></tr><tr><td>Cycle 4</td><td>0.79 (0.75 – 0.83)</td><td>0.85 (0.82 – 0.87)</td></tr><tr><td>Cycle 6</td><td>0.82 (0.79 – 0.84)</td><td>0.87 (0.84 – 0.90)</td></tr><tr><td>End of study</td><td>0.83 (0.0 – 0.86)</td><td>0.84 (0.81 – 0.87)</td></tr></table>Results comparable across both treatment arms. Slight decrease in scores from baseline to end of study</td></tr>
</table>

Table 35: Summary of health effects papers - Vergote et al.

	Vergote et al. 2011 (Vergote et al. 2011)
Population in which health effects were measured.	Partially platinum sensitive recurrent ovarian cancer
Recruitment	Recruited to clinical trial OVA-301
Interventions and comparators.	• trabectedin + PLD (T+D) • PLD
Sample size.	214 patients
Response rates.	90% at baseline, with 83% at 21 cycles
Description of health states.	Appetite loss, dyspnoea, nausea/vomiting, pain, peripheral neuropathy
Adverse events.	As above
Health states	Appropriate

<table>
<tr><td>appropriate?</td><td></td></tr>
<tr><td>Method of elicitation / Method of valuation</td><td>EORTC-QLQ C30 and OV28
Completed at screening and on day 1 over every other treatment cycle and at the end of treatment</td></tr>
<tr><td>Mapping.</td><td>N/A</td></tr>
<tr><td>Uncertainty around values.</td><td>N/A</td></tr>
<tr><td>Consistency with reference case.</td><td>EQ-5D has not been collected</td></tr>
<tr><td>Appropriateness for CE analysis.</td><td>No utility scores are reported</td></tr>
<tr><td>Results with confidence intervals.</td><td>Mean score changes from baseline of the functional symptoms and global health status (GHS) at various timepoints:
<table>
<tr><th>Item/Domain</th><th colspan="3">C3</th><th colspan="3">C5</th><th>C7</th></tr>
<tr><th></th><th>PLD</th><th>T+P</th><th>p[a]</th><th>PLD</th><th>T+P</th><th>p[a]</th><th>PLD</th></tr>
<tr><td>Appetite loss[1]</td><td>2.5</td><td>16.7</td><td>0.054</td><td>−1.4</td><td>7.0</td><td>0.975</td><td>−1.6</td></tr>
<tr><td>Dyspnea[1]</td><td>−1.3</td><td>4.3</td><td>0.024</td><td>1.4</td><td>5.0</td><td>0.195</td><td>−1.6</td></tr>
<tr><td>Nausea/ Vomiting[1]</td><td>1.6</td><td>13.8</td><td>0.003</td><td>0.7</td><td>7.2</td><td>0.022</td><td>1.6</td></tr>
<tr><td>Pain[1]</td><td>−3.4</td><td>−2.7</td><td>0.862</td><td>−0.4</td><td>−5.3</td><td>0.054</td><td>−1.6</td></tr>
<tr><td>Peripheral Neuropathy[1]</td><td>7.9</td><td>4.4</td><td>0.666</td><td>10.8</td><td>3.1</td><td>0.229</td><td>9.1</td></tr>
<tr><td>GHS/QoL[2]</td><td>−2.4</td><td>−6.6</td><td>0.352</td><td>−0.6</td><td>−3.1</td><td>0.909</td><td>0.9</td></tr>
<tr><td colspan="8">[1]Lower is better; [2]Higher is better; [a]T-test p-values comparing r</td></tr>
</table></td></tr>
</table>

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

N/A

Adverse events

7.4.7 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

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

7.4.8 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 B4 Summary of quality-of-life values for cost-effectiveness analysis

State	Utility value	95% Confidence interval	Reference in submission	Justification
PFS	0.718	0.699 - 0.737	N/A	Used in TA222 Trabectedin in treatment for relapsed OC
PD 2	0.649	0.611 – 0.686	N/A	Used in TA222 – Trabectedin in treatment for relapsed OC

Utilities are taken from TA222 – Trabectedin in treatment for relapsed ovarian cancer. This data is from the OVA-301 study where HRQoL was captured using EQ-5D. The OVA-301 HRQoL data is for the combined treatment group across all platinum sensitive women. Although QoL data was provided in TA222 by platinum sensitivity, the ERG was concerned with the validity of this

data and recommended the use of the utilities for the combined treatment group as shown above.

Comparison of the OCEANS study and OVA-301 in terms of adverse events showed very little overlap in the types of adverse events, with only neutropenia appearing in both trials. Therefore the use of the utility data from TA222 should be used with caution in this analysis.

7.4.9 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
- 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

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

[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.

Patients with stable disease may be relatively asymptomatic (unless their disease is causing bowel obstruction and/or pain). Patients with progressed disease have any combination of the following symptoms: fatigue, distension, bloating, constipation, anorexia, urinary frequency, pain and bowel obstruction. Recurrent ascites also occurs in patients, which require drainage and, in a smaller proportion, recurrent pleural effusions.

Bowel obstruction in those with disease progression is probably the most impactful event and symptoms include loss of appetite, nausea, vomiting, constipation and pain and, more rarely, perforation. HRQoL would also be influenced by the adverse events the patient may experience during treatment.

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

N/A

7.4.12 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

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

HRQoL is assumed to be constant over time during PFS. The HRQoL reduces once disease progression has occurred but remains constant.

7.4.14 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 described in NICE CG122 (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), 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 and 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 relapsed or recurrent, ovary cancer or carcinoma.

NHS EED and ECONLIT

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

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 relapsed or recurrent 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 36Table 36: inclusion/exclusion criteria for resource search of the 4 databases. PRISMA diagram Figure 18 shows the full flow of documents and reason for exclusion

Table 36: inclusion/exclusion criteria for resource search of the 4 databases

INCLUSION	EXCLUSION
Recurrent/relapsed Ovarian cancer	Disease is not recurrent/relapsed Ovarian Cancer
Resource utilitisation from an NHS perspective	Resource utilisation from outside of UK
	Literature review
Cost Estimation or Cost Collection included in abstract	No useful cost values

Results: In total 110 records were identified via the four databases, 9 were duplicates. Of the remaining 101 papers, 98 studies were excluded upon initial screening of title and abstract (PRISMA diagram Figure 18 shows for the rationale for these exclusions). The remaining 3 were deemed potentially relevant. These 3 results were then retrieved and assessed more comprehensively against the inclusion/exclusion criteria in Table 36, 2 were found to be relevant. These are summarized in Table 37

Figure 18: PRISMA flow showing resource studies identified through searching of the 4 databases

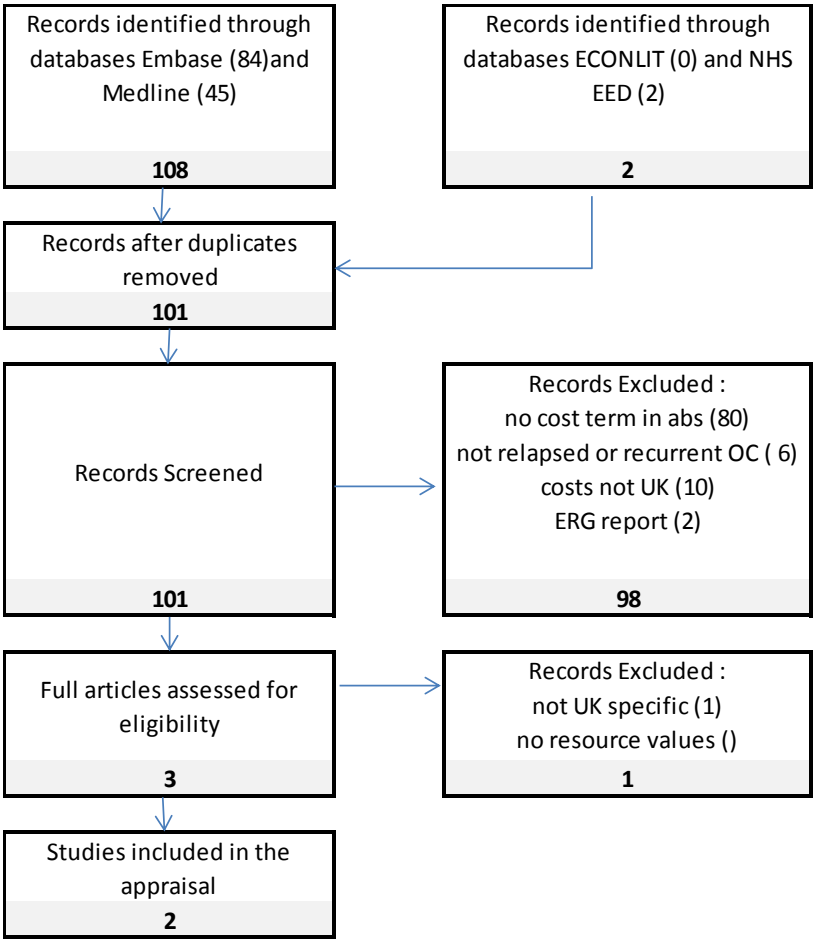


Table 37: Summary of resource papers identified via systematic review

<table>
<tr><td>Title</td><td>A comparative economic analysis of pegylated liposomal doxorubicin versus topotecan in ovarian cancer in the USA and the UK
DH Smith et al. 2002(Smith et al. 2002)</td></tr>
<tr><td>Country of study</td><td>USA and UK</td></tr>
<tr><td>Date of study</td><td>1997 – 1999</td></tr>
<tr><td>Applicability to UK clinical practice</td><td>Study included European sites of which 40% were UK.
Interventions : PLD every 29 days or topotecan for 5 consecutive days every 21 days</td></tr>
<tr><td>Cost valuations used</td><td>Drug costs from British National Formulary (BNF), Blood products from National Blood Authority 2000 tariff, Inpatient stays from The new 1999 National reference costs, Intensive care unit from Edbrooke et al. 1999(Edbrooke et al. 1999), Outpatient clinic visit and chemotherapy administration from tariffs at UK cancer centre
All costs reported in US$ converted at a rate of $1.4 = £1
Table 1. Estimates of resource cost (in US$)
<table>
<tr><th></th><th>North America</th><th>Sensitivity analysis value</th><th>Europe</th><th>Sensitivity analysis value</th></tr>
<tr><td>Pegylated liposomal doxorubicin (per mg)</td><td>33</td><td>NV</td><td>29</td><td>NV</td></tr>
<tr><td>Topotecan (per mg)</td><td>151</td><td>NV</td><td>109</td><td>NV</td></tr>
<tr><td>Study drug administration (per dose + pre-meds)</td><td>295</td><td>136</td><td>185</td><td>139</td></tr>
<tr><td>Erythropoietin (per 10000 U)</td><td>120</td><td>NV</td><td>116</td><td>NV</td></tr>
<tr><td>Colony stimulating factors (per 300 µg)</td><td>165</td><td>NV</td><td>108</td><td>NV</td></tr>
<tr><td>Platelets (per unit)</td><td>601</td><td>NV</td><td>223</td><td>NV</td></tr>
<tr><td>Packed red cells (per unit)</td><td>79</td><td>NV</td><td>136</td><td>NV</td></tr>
<tr><td>Blood product administration</td><td>310</td><td>36</td><td>410</td><td>206</td></tr>
<tr><td>Hospital stays (per day)</td><td>1000</td><td>500</td><td>410</td><td>206</td></tr>
<tr><td>Oncologist office visit</td><td>140</td><td>70</td><td>126</td><td>63</td></tr>
</table>
NV, not varied in sensitivity analysis.</td></tr>
</table>

Table 4. Estimates of quantities of resources used per person (base case)

	Topotecan (T)		Pegylated liposomal doxorubicin (P)		Difference (P–T)	
	North America	Europe	North America	Europe	North America	Europe
Cycles of therapy	5.75	5.75	4.87	4.87	−0.88[a]	−0.88[a]
Units of platelets	1.10	0.30	0.05	0.02	−1.05[a]	−0.28[a]
Units of packed red cells	1.56	4.15	0.26	0.65	−1.30[a]	−3.49[a]
Units of erythropoietin	291 091	20 786	25 670	690	−265 421[a]	−20 096[a]
Colony stimulating factor (μg)	3520	1494	762	31	−2758[a]	−1463[a]
Hospital stays	0.24	0.53	0.08	0.12	−0.17[a]	−0.41[a]
Office visits	12.7	4.2	4.6	3.2	−8.1[a]	−1.0[a]

[a]P <0.001 from t-test.

Costs for use in economic analysis

Study drug: dose taken from trial data
Drug administration: ambulatory visit per dose, pre-medication and specialist visit at start of each cycle
Management of AE's: 8 AE's evaluated. Quantities of resource partly from trial data and partly from panel of oncologists in USA and UK. Average hospital stay 5.5 days in UK (estimated based on weighted average using frequency of AE occurrence in the trial)

Table 3. European cost analysis per person (costs expressed in US$)

	Topotecan (T)	Pegylated liposomal doxorubicin (P)	Difference (P – T)
Study drug	7286	11 381	4095
Administration	5701	1513	−4187
Total study drug + administration	**12 986**	**12 894**	**−92**
Stomatitis/pharyngitis	**70**	**175**	**105**
PPE	**1**	**189**	**188**
Nausea and vomiting	**298**	**151**	**−147**
Diarrhea	**60**	**36**	**−24**
Colony stimulating factors	538	11	−526
Neutropenia office visits and other medication	218	25	−193
Total neutropenia	**756**	**36**	**−720**
Sepsis and fever	**105**	**46**	**−59**
Erythropoietin	242	8	−234
Transfusions	1190	181	−1009
Anemia and thrombocytopenia office visits and medication	0	0	0
Total anemia and thrombocytopenia	**1432**	**189**	**−1243**
Hospital stays	**1197**	**280**	**−917**
Total cost	**16 906**	**13 997**	**−2909**
95% CI on total cost	15 617 to 18 847	12 863 to 15 392	−779 to −3415

£1 = US$1.4; CI, confidence interval.

Technology Costs	Topotecan $10,058 per person, PLD $12.962 per person
Title	Cost-effectiveness of Trabectedin in combination with pegylated liposomal doxorubicin hydrochloride for the treatment of women with relapsed platinum sensitive ovarian cancer in the UK – Analysis based on final survival data M Gore et al. 2011 (poster) (Gore et al. 2011)
Country of study	UK
Date of study	2005 -2010 (OVA-301)
Applicability to UK clinical practice	Study carried out in the UK. Interventions: Trabectedin in combination with PLDH compared to PLDH alone in patients with relapsed platinum sensitive ovarian cancer
Cost valuations used	Drug Administration Medical management AE costs Costs valued using British National Formulary and UK healthcare resource group codes. No detail provided in the poster
Costs for use in economic analysis	Trabectedin plus PLDH £41,657 PLDH £23,579 No further detail provided in the poster
Technology Costs	Not reported

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.

[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.

Table B5 Unit costs associated with the technology in the economic model

Items	Bevacizumab + chemotherapy (confidence interval)	Chemotherapy alone (confidence interval)	Ref. in submission
Expected cost of bevacizumab per visit	UK Cohort: £2,555 (£1,652-£3,940) OCEANS: £2,762 (£1,752-£4074)	N/A	Section 7.5.5.1
Expected cost of carboplatin per visit	UK Cohort: £155 (£105-£242) OCEANS: £167 (£115-£244)	UK Cohort: £155 £105-£242 OCEANS: £166 £112-£256	Section 7.5.5.2
Expected cost of gemcitabine per visit	UK Cohort: £22 (£17-£26) OCEANS: £22 (£18-£28)	UK Cohort: £22 (£17-£26) OCEANS: £22 (£18-£28)	Section 7.5.5.3
First visit administration and pharmacy costs	£275 (upper and lower quartiles from NHS Reference costs)		Section 7.5.5.4
Subsequent visit administration and pharmacy costs	£94 (upper and lower quartiles from NHS Reference costs)		Section 7.5.5.4

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

7.5.5.1 Assumptions regarding bevacizumab preparation

No vial sharing of bevacizumab

In order to more accurately model the amount of drug required by UK patients, the base case scenario of the economic 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 for ovarian cancer in 3 centres in 2005. It should be noted that this study did not provide the weight and height of individuals and so these parameters must be imputed 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:

Individual body weight = 68.15kg * (individual BSA / mean BSA)$^{(1/0.425)}$

A consequence of this approach is to assume all patients are of equal height (160.05cm).

Table 38: 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		Average number of vials used		Cost
			Mean	SD	400mg	100mg	
UK	Sacco*	321	69.35kg	17.52kg	2.081	2.604	£2,556
USA	OCEANS	484	75.68kg	18.47kg	2.364	2.376	£2,762

*** 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 OCEANS is more than 5kg heavier 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 weight is calculated and used to estimate the average cost of drug per visit (Table 39). The actual effect of this change is relatively small, resulting in a reduction in costs of between £120 and £130 per patient or approximately 5% of base case drug costs (compare Table 38 and Table 39).

Table 39: 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
			Mean	SD		
UK	Sacco*	321	69.35kg	17.52kg	1040.29mg	£2,428
USA	Oceans	484	75.68kg	18.47kg	1133.16mg	£2,640

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

7.5.5.2 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 4 mg/ml/min (according to well established formulae (Calvert et al. 1989;Cockcroft & Gault 1976)). 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 inTable 40 and this is applied to all patients remaining on treatment every 3 weeks of the model.

Table 40: Calculation of carboplatin dose and cost per patient cohorts considered in the economic evaluation

	N	Age (years)	Weight (kg)	CrCl (ml/min)	Total dose (mg)	Cost (£)
Sacco	321	61.37	69.35	76.09	359	155.43
OCEANS	484	61.02	75.67	83.50	384	166.36

Underlined values are used in the base case scenario.

7.5.5.3 Gemcitabine drug costs

In the model, gemcitabine is administered by intravenous infusion on days 1 and 8 of a 3 week cycle at 1000mg/m^2 as described in the OCEANS study.

Since gemcitabine is a popular chemotherapy agent, it is reasonable to assume that unused material from vials is re-allocated to other preparations. Gemcitabine can be purchased in vials of 1000 mg at £12.57 (standard deviation of average price, £12.13) (Commercial Medicines Unit 2012). The cost per cycle of gemcitabine for patient cohorts considered in the economic evaluation is presented in and this is applied to all patients remaining on treatment for 2 weeks every 3 weeks of the model.

Table 41: Calculation of gemcitabine dose and cost per patient cohorts considered in the economic evaluation

	N	BSA (m^2)	Total dose (mg)	Cost (£)
Sacco	321	1.713	1713	21.53
OCEANS	484	1.789	1789	22.49

Underlined values are used in the base case scenario.

7.5.5.4 Chemotherapy administration and pharmacy costs

Carboplatin and gemcitabine are both administered by intravenous infusion in a hospital on the first day of every third week in the model for a maximum of 10 cycles according to the OCEANS study protocol. In addition, patients receive a second infusion of gemcitabine on day 8 of every 3-week cycle. There is a cost associated with both the pharmacy preparation of the infusion and the administration of the drugs themselves (typically within a hospital setting).

The cost of administering 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 gemcitabine 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).

Therefore, the total 'per cycle' administration and pharmacy cost of carboplatin and gemcitabine for the first cycle is £274.57 while subsequent cycles cost £94.27. Similarly, on visits where gemcitabine is administered as monotherapy (i.e. in week 2 of the chemotherapy cycle), the total cost is £89.67.

7.5.5.5 Bevacizumab administration and pharmacy costs

In cycles where bevacizumab is administered in addition to carboplatin and gemcitabine, 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 chemotherapy combination treatment phase is £4.60, 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 £4.60 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 £89.67.

7.5.5.6 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 OCEANS study (Table 42, Figure 19, Figure 20 and Figure 21).

Table 42: Mean treatment duration for patients in OCEANS according to treatment arm

	bevacizumab		carboplatin		gemcitabine	
Treatment arm	**weeks**	**months**	**weeks**	**months**	**weeks**	**months**
bevacizumab + chemotherapy	50.74	11.71	20.11	4.64	22.93	5.29
chemotherapy	-	-	20.50	4.73	22.50	5.19

Figure 19: Proportion of patients in OCEANS remaining on bevacizumab (solid line) compared to progression (dotted line)

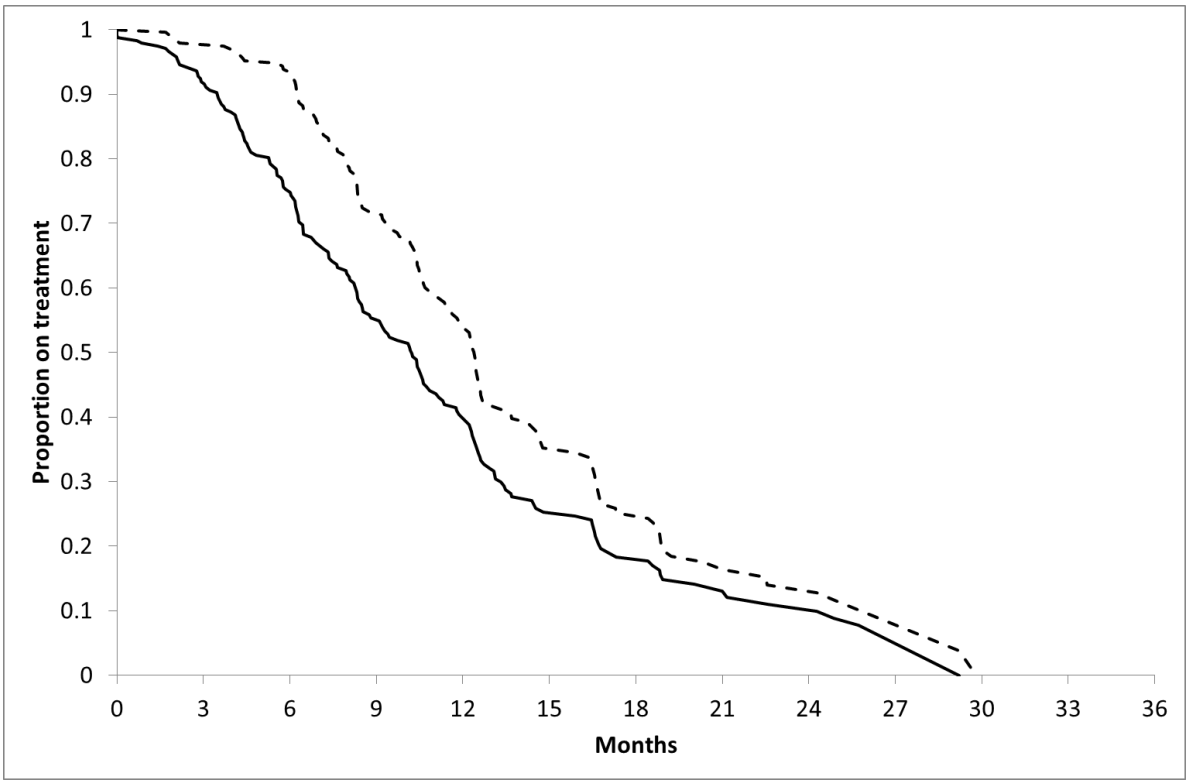


Figure 20: Proportion of patients receiving treatment with carboplatin in the bevacizumab (black line) and chemotherapy alone (grey line) arms of the OCEANS study

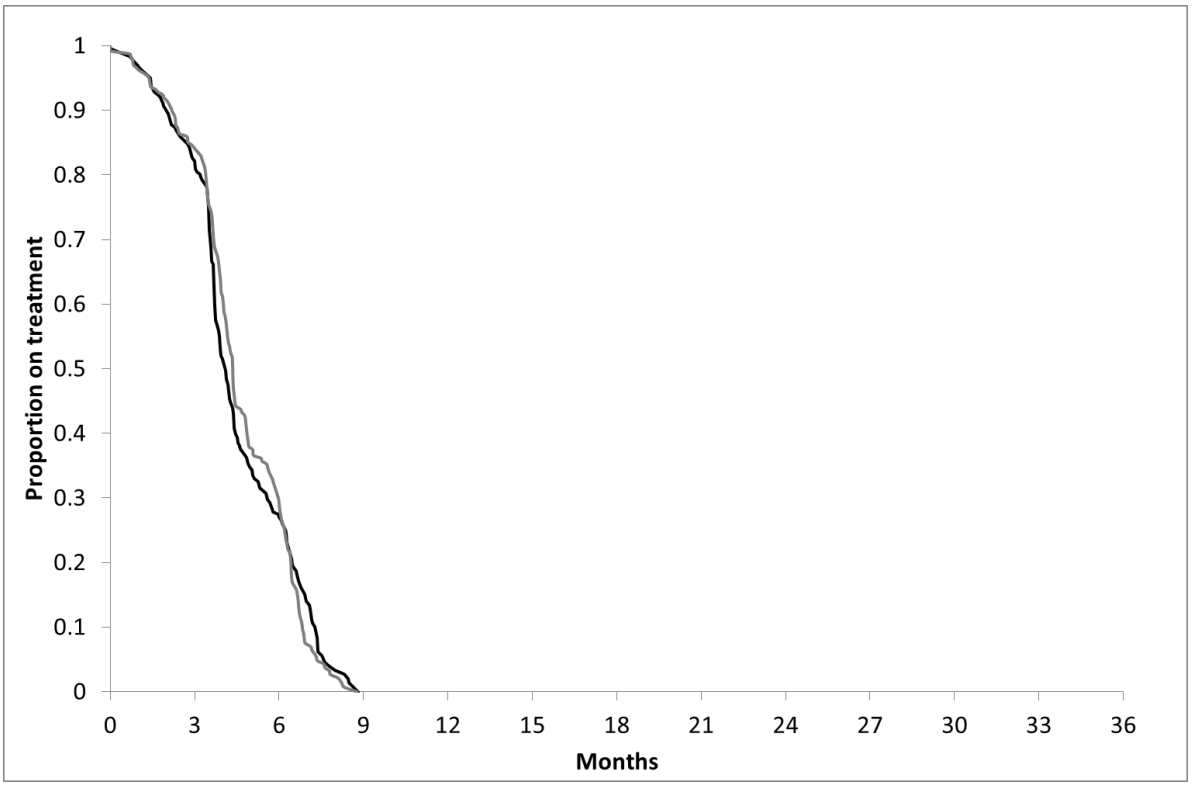
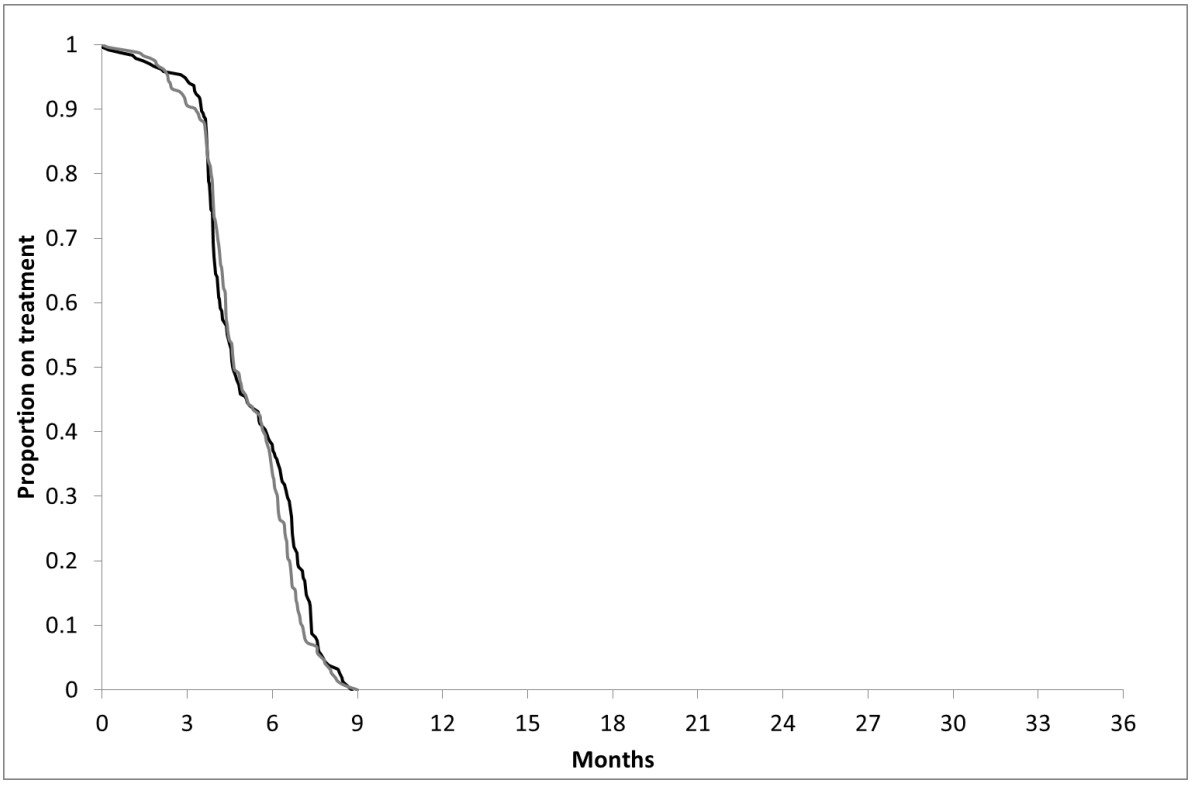


Figure 21: Proportion of patients receiving treatment with gemcitabine in the bevacizumab (black line) and chemotherapy alone (grey line) arms of the OCEANS study



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, platinum-sensitive patients are assessed by a consulting physician 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)).

Patients with progressed disease (PD) are assumed to have an outpatient review by a consultant oncologist approximately every 3 months, in line with the expected duration of subsequent chemotherapy treatments (clinical expert opinion). The total weekly costs of supporting patients in either PFS or PD health states are shown in Table 43.

Table 43: List of health states and associated costs in the economic model

Health states	Items	Frequency	Unit cost	Average weekly Value	Reference Cost Source (Department of Health 2011)
PFS	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**	
PD	Outpatient visit to consultant oncologist	once every 3 months	£134	£10.31	Outpatient attendance data (503; Gynaecological Oncology)
				£10.31	

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 44). 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. the usual treatment for epistaxis/fatigue/proteinuria 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. Episodes of decreased neutrophil/white blood cell counts as a result of cytotoxic chemotherapy were 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. The expected cost of treating adverse events in patients receiving bevacizumab in addition to carboplatin and gemcitabine is £224, compared to £146 for treating patients receiving carboplatin and gemcitabine alone.

Table 44: List of adverse events and summary of costs included in the economic model (>2% incidence in either arm)

Adverse Event	Chemotherapy	Bevacizumab + chemotherapy	Cost per episode	NHS Reference Costs 2010/11, (Department of Health 2011)
Epistaxis	1 (0.4%)	6 (2.46%)	£-	N/A
Fatigue	3 (1.2%)	5 (2.05%)	£-	N/A
Proteinuria	0 (0%)	19 (7.79%)	£-	N/A
Thrombocytopenia	14 (5.58%)	15 (6.15%)	£58	821 – Blood Transfusion
Thrombocytopenia (grade 4)	8 (3.19%)	15 (6.15%)		
Leukopenia	7 (2.79%)	8 (3.28%)	£253	XD25Z – Neutropenia drugs band 1
Neutropenia	30 (11.95%)	40 (16.39%)		
Neutropenia (grade 4)	9 (3.59%)	14 (5.74%)		
Hypertension	1 (0.4%)	33 (13.52%)	£441	EB04I – Hypertension without complications
Anaemia	13 (5.18%)	14 (5.74%)	£518	SA04F –Iron deficiency anaemia without CC
Neutrophil count decreased	8 (3.19%)	5 (2.05%)	£738	Course of G-CSF (14 days subcutaneous injection with 30M units of Neupogen)
Neutrophil count decreased (Grade 4)	3 (1.2%)	5 (2.05%)		
White blood cell count decreased	6 (2.39%)	1 (0.41%)		

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

In common with many clinical trials, in the OCEANS study patients were free to receive treatment as recommended by their physician following progression of disease and discontinuation of study drugs. The cost of some of these treatments was calculated in order to provide an accurate estimate of the total cost of treatment following disease progression. Since more than 200 different treatments (or treatment combinations), including surgery and radiotherapy, were received by patients after progression (September 2010 data cut-off) it was necessary to focus attention on the most relevant for this situation. These were applied as a one-off cost added to the total cost of post-progression treatment in the model.

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)
- Drugs received as part of a clinical trial (impossible to cost where price is unknown)
- 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 £2726 per patient for patients randomised to the chemotherapy arm, compared to £1326 for patients randomised to the bevacizumab arm (Table 45).

Table 45: Estimate of total cost of chemotherapy treatments received by patients after progression in the OCEANS study

	Number of Patients		Expected No of administrations		Expected dose per patient (mg)		Total cost (drug + admin)	
	B	**C**	**B**	**C**	**B**	**C**	**B**	**C**
Anastrozole	3	2	30	45	1	1	£9	£9
Bevacizumab	27	67	2	2	1135	1135	£154,365	£454,971
PLDH	14	15	1	1	71	71	£26,408	£24,941
Carboplatin	60	44	2	2	570	570	£15,278	£12,913
Cisplatin	16	12	2	2	121	121	£526	£368
Cyclophosphamide	6	15	2	2	713	713	£1,068	£2,270
Docetaxel	2	4	6	3	57	57	£1,357	£1,357
Doxorubicin	112	121	2	2	71	71	£20,313	£22,735
Etoposide	6	11	23	27	71	71	£2,174	£4,711
Gemcitabine	35	38	4	4	856	856	£12,868	£15,880
Irinotecan	2	5	4	2	499	499	£1,012	£1,215
Paclitaxel	53	71	2	2	250	250	£11,066	£15,641
Pemetraxed	4	2	1	1	713	713	£7,005	£3,502
Sorafenib	0	2	0	45	800	800	£0	£9,580
Tamoxifen	9	12	53	40	20	20	£13	£13
Trabectedin	2	1	1	1	2	2	£250	£125
Temozolomide	1	1	11	5	150	150	£211	£105
Thalidomide	0	2	0	30	200	200	£0	£2,558
Topotecan	58	68	7	7	2	2	£66,187	£82,494
Vinorelbine	1	6	6	6	36	36	£723	£4,341
						Total Cost	£320,834	£659,729
						Patients	242	242
						Average cost per patient	**£1,326**	**£2,726**

C: Chemotherapy alone, B: bevacizumab and chemotherapy

Radiotherapy treatment

Radiotherapy given to patients following disease progression was recorded in 22 different ways. In order to simplify the estimation of costs for these treatments, each entry was assigned to a type of radiotherapy regimen (e.g. palliative or targeted radiotherapy) which was associated with a specific number of radiotherapy fractions. The unit cost of delivering each fraction of radiotherapy was assumed to be £117.84 (SC23Z: Deliver a fraction of complex treatment on a megavoltage machine). The total cost of radiotherapy regimens received by patients after progression was calculated to be £63 per

patient for patients randomised to the chemotherapy arm, compared to £66 for patients randomised to the bevacizumab arm (Table 46).

Table 46: Estimate of total cost of radiotherapy received by patients after progression in the OCEANS study

	Number of Patients		No. of fractions	Expected cost	
	B	**C**		**B**	**C**
Palliative radiotherapy	3	2	1	£354	£236
Radiotherapy to brain	3	2	9	£3,182	£2,121
Radiotherapy to spine	5	0	10	£6,482	£0
Radiotherapy to pelvis	2	4	15	£3,535	£7,071
Undefined radiotherapy	2	5	10	£2,357	£5,892
Total cost				£15,909	£15,320
Average cost per patient				**£66**	**£63**

C: Chemotherapy alone, B: bevacizumab and chemotherapy

Surgical procedures

A total of 24 surgical procedures were carried out on 14 patients randomised to the chemotherapy arm and 11 patients randomised to the bevacizumab arm of the OCEANS study. For simplicity the reference cost for a gynaecological malignancy with length of stay of 1 day or more (£2792.83, MB05A) was applied to each procedure. Therefore, the expected cost of post-progression surgery in patients participating in OCEANS was £127 for the chemotherapy arm and £162 for the bevacizumab arm of the trial.

Total cost of post progression treatment

The total cost of treatments recorded for patients in the OCEANS study by treatment arm is summarised in Table 47. These costs are applied as a one-off cost added to the total cost of post-progression treatment in the model and are not subject to discounting.

Table 47: Total estimated costs of post-progression treatments for patients in the OCEANS study

Post-progression cost	Bevacizumab + chemotherapy	Chemotherapy
Subsequent lines of chemotherapy	£1326	£2726
Radiotherapy	£66	£63
Surgical procedures	£162	£127
TOTAL	£1553	£2916

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.

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. Drug costs based on the assumption that there was no wastage of bevacizumab from opened vials (Table 39) were used in a sensitivity analysis to explore the impact of this assumption on the cost-effectiveness model results.

7.6.1.2 Trial patient characteristics

The results of the OCEANS study are influenced by the characteristics of the patients enrolled and as such it is useful to explore the impact of using baseline demographic data for patients (i.e. age, body weight, height and body surface area) in their respective cost-effectiveness models where vial sharing is (Table 39), and is not (Table 38), permitted.

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.

Table 48: Deterministic sensitivity analysis

	Base case value	Alternative	Value High	Value Low	Rationale
PFS	Log Logistic	KM + Log Logistic tail	-	-	Maximal use of trial observations
		Weibull	-	-	Alternative plausible parameter curve
OS	Log Logistic	KM + Log Logistic tail	-	-	Maximal use of trial observations
		Weibull	-	-	Alternative plausible parameter curve
Time to off treatment (bevacizumab)	Trial Observation	PFS	-	-	Alternative treatment duration
Utility					
PFS	0.718	+/- 20%			
PD	0.649	+/- 20%			
Costs					
Administration costs	£265.47 (First visit) £85.07 (subsequent visits)	Different Admin costs	£298.10 £95.52	£172.20 £0	Upper and Lower Quartile reference costs
PFS supportive care costs	£44.08	+/-20%	£52.89	£35.26	
PD supportive care costs	£10.31	+/-20%	£12.37	£8.25	

	Base case value	Alternative	Value High	Value Low	Rationale
PD treatment costs	£ 2916 (Chemotherapy) £1553 (Bevacizumab)	no PD treatment costs	-	-	Assumption of no treatments after progression
Palliative care costs	£6727	no Palliative care costs	-	-	Assumption of no palliative care
AE costs	£146 (Chemotherapy) £224 (Bevacizumab)	no AE costs	-	-	Assumption of no adverse events
Time Horizon	10 years		15 years	5 years	Shorter and longer time horizons
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 (beta)
- Parameter estimates for the parametric PFS and OS functions (as appropriate)
- Costs and frequency of adverse events (gamma)
- Weekly supportive care costs in both the PFS and Progressed health states (gamma)

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 and palliative care costs for both models). A total of 5000 iterations of the stochastic model were performed.

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.

The economic model presented here provides a good approximation of the results observed in the OCEANS study, on which it is based (Table B6).

Table B6 Summary of model results compared with clinical data

Outcome	Clinical trial result (median months)*	Model result
Chemotherapy arm		
Progression-free survival	8.4	8.77
Post-progression survival	21.53	21.92
Overall survival	29.93	30.69
Bevacizumab arm		
Progression-free survival	12.4	12.46
Post-progression survival	23.12	23.54
Overall survival	35.52	36.00

* September 2010 data cut.

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 within the main body of the submission. Please see the Excel workbook (Sheet: Life years) 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 within the main body of the submission. Please see the Excel workbook (Sheet: QALYs) 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. For example:

Table B7 Model outputs by clinical outcomes

Comparator	Outcome	LY	QALY	Cost (£)
Bevacizumab + chemotherapy	PFS	1.224	0.879	£50,118
	PD	2.152	1.397	£9,222
	Overall survival	3.377	2.276	£59,340
Carboplatin + gemcitabine	PFS	0.858	0.616	£4,380
	PD	2.099	1.362	£10,533
	Overall survival	2.956	1.978	£14,912

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 B8 Summary of QALY gain by health state

Health state	QALY intervention (Bev + Carbo + Gem)	QALY comparator (Carbo + Gem)	Increment	Absolute increment	% absolute increment
PFS	0.879	0.616	0.263	0.263	88.3%
PD	1.397	1.362	0.035	0.035	11.7%
Total	2.276	1.978	0.298	0.298	100.0%

Table B9 Summary of costs by health state

Health state	Cost intervention (Bev + Carbo + Gem)	Cost comparator (Carbo + Gem)	Increment	Absolute increment	% absolute increment
PFS	£50,118	£4,380	£45,738	£45,738	102.9%
PD	£2,712	£3,952	-£1,241	£1,241	-2.8%
Total	£59,340	£14,912	£44,428	£44,428	100.0%

Table B10 Summary of predicted resource use by category of cost

Item	Cost intervention (Bev + Carbo + Gem)	Cost comparator (Carbo + Gem)	Increment	Absolute increment	% absolute increment
Mean total treatment cost (Bev + Carbo + Gem)	£44,879		£44,879	£44,879	101.0%
Administration cost (Bev + Carbo + Gem)	£2,208		£2,208	£2,208	5.0%
Mean total treatment cost (Carbo + Gem)		£1,096	-£1,096	£1,096	2.5%
Administration cost (Carbo + Gem)		£1,172	-£1,172	£1,172	2.6%
Mean Supportive Care Cost of PFS	£2,806	£1,966	£841	£841	1.9%
Mean Supportive Care Cost of PD	£2,712	£3,952	-£1,241	£1,241	2.8%
Cost of AE's	£224	£146	£78	£78	0.2%
Total	£59,340	£14,912	£44,428	£44,428	100.0%

Base-case analysis

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 B11 Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus (LYs)	ICER (£) versus (QALYs)
(Carbo + Gem)	£14,912	2.956	1.978					
(Bev + Carbo + Gem)	£59,340	3.377	2.276	£44,428	0.420	0.298	£105,707	£149,050
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Sensitivity analyses

7.7.6 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

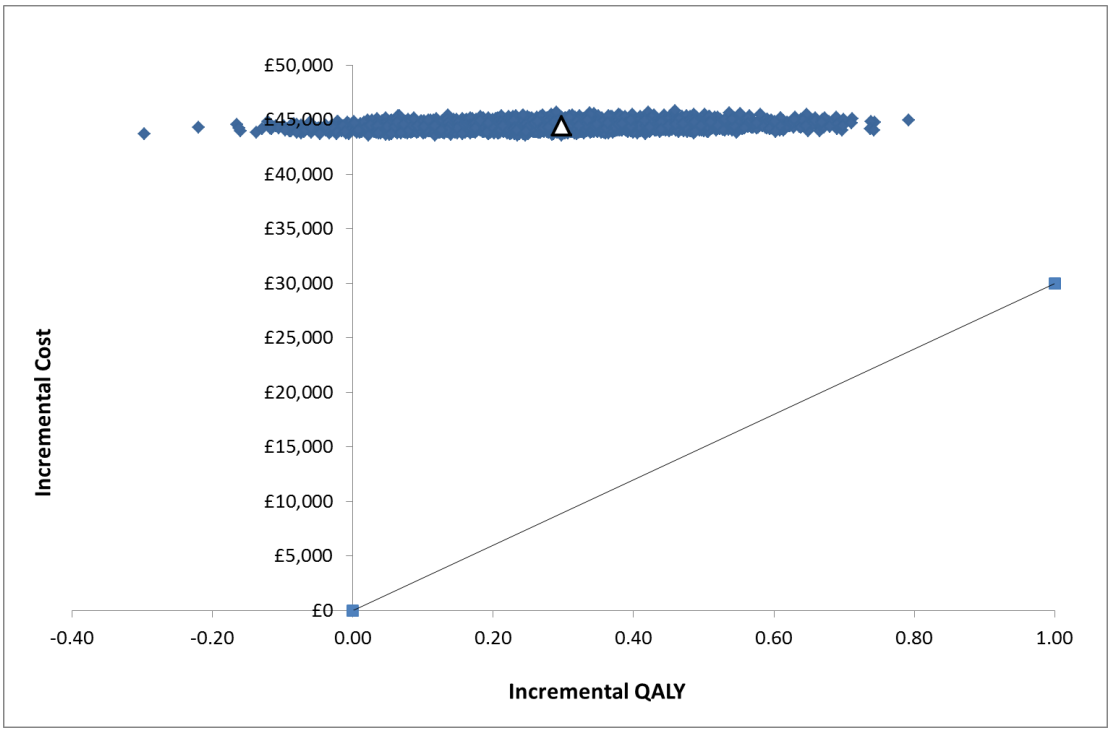
Table 49: Deterministic sensitivity analyses of OCEANS

	Base case value	Alternative	Incremental cost	Incremental QALY	Incremental ICER
Base case			£44,428	0.2981	£149,050
PFS	Log Logistic	KM + Log Logistic tail (24 months+)	£44,488	0.3004	£148,074
		Weibull	£44,403	0.2971	£149,461
OS	Log Logistic	KM + Log Logistic tail (35 months +)	£44,394	0.2314	£191,842
		Weibull	£44,470	0.2684	£165,683
Time to off treatment (bevacizumab)	Trial Observation	PFS	£56,596	0.2981	£189,873
Utility					
PFS	0.718	0.8616	£44,428	0.3507	£126,671
		0.5744		0.2454	£181,035

	Base case value	Alternative	Incremental cost	Incremental QALY	Incremental ICER
Base case			£44,428	0.2981	£149,050
PD	0.649	0.7788		0.3050	£145,653
		0.5192		0.2911	£152,610
Costs					
Administration costs	£265.47 (First visit) + £85.07 (subsequent visits)	£298.10 + £95.52	£44,546	0.2981	£149,445
		£172.20 + £0	£43,469		£145,832
PFS supportive care costs	£44.08	£52.89	£44,596		£149,614
		£35.26	£44,260		£148,486
PD supportive care costs	£10.31	£12.37	£44,434		£149,070
		£8.25	£44,422		£149,031
PD treatment costs	Bev + chemo = £1553 Chemo = £2916	no PD treatment costs	£45,697	0.2981	£153,308
Palliative care costs	£6726.53	no Palliative care costs	£44,498		£149,285
AE costs	Bev + chemo = £224 Chemo = £146	no AE costs	£44,349		£148,787
Time Horizon					
	10 years	15 years	£44,494	0.3171	£140,305
		5 years	£44,064	0.2181	£202,027
Discounting Costs and Benefits					
	0.035	0.06	£44,129	0.2754	£160,239
		0	£44,874	0.3357	£133,671

7.7.7 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

Figure 22: Cost-effectiveness plane for the addition of 15mg/kg bevacizumab to carboplatin/gemcitabine combination therapy (white triangle; deterministic estimate)



There is a 0.0% chance of the addition of 15mg/kg bevacizumab to carboplatin/gemcitabine combination therapy being considered cost-effective at a willingness to pay threshold of £30,000 per QALY. At a willingness to pay threshold of £100,000 per QALY, this rises to 14.7%.

Table 50: Average (and 95% CI) estimates of incremental costs and benefits for the economic evaluation of the OCEANS study

Technologies	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus incremental life years	ICER versus incremental QALYs
Carbo + Gem (95% confidence limits)	£14,937 (£14,302, £15,646)	2.960 (2.63, 3.31)	1.981 (1.75, 2.21)					
Bev + Carbo + Gem (95% confidence limits)	£59,368 (£58,305, £60,669)	3.382 (2.97, 3.78)	2.279 (2.01, 2.55)	£44,431 (£43,882, £45,105)	0.42 (-0.01, 0.84)	0.30 (0.02, 0.57)	£140,124 (-£163,277, £725,369)	£221,750 (£69,979, £857,367)

7.7.8 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

7.7.8.1 Vial sharing

The effect of relaxing the assumption that opened vials of bevacizumab are wasted if not delivered to the intended recipient (i.e. no vial sharing permitted), is relatively small. The expected cost of bevacizumab falls approximately 5% (from £2556 to £2428) and results in a similarly small reduction in the ICER from approximately £149,000 to £142,000 (Table 51).

Table 51: The impact of permitting vial sharing when using bevacizumab in the OCEANS study

Base case value	Alternative	Incremental costs	Incremental QALYs	ICER versus incremental QALYs
no vial sharing	**vial sharing permitted**			
£2556	£2428	£42,244	0.2981	£141,722

7.7.8.2 Study patient characteristics

Similar to the scenario analysis presented in section 7.7.9.1, the impact of assuming patients in the OCEANS study are representative of UK patients likely to be treated in this setting is small (approximately 8% increase in bevacizumab drug costs and a similar increase in costs per QALY, Table 52).

Table 52: The impact of basing the dose of drug received in the OCEANS study on actual baseline demographic data

Drug cost	Base case value	Alternative	Incremental costs	Incremental QALYs	ICER versus incremental QALYs
	Sacco	**OCEANS**			
No vial sharing of bevacizumab	£2556	£2762	£47,859	0.2981	£160,561
Carboplatin	£155.43	£166.36			
Gemcitabine	£21.53	£22.49			
Vial sharing of bevacizumab	£2428	£2640	£45,785	0.2981	£153,603
Carboplatin	£155.43	£166.36			
Gemcitabine	£21.53	£22.49			

7.7.9 What were the main findings of each of the sensitivity analyses?

The results of the deterministic sensitivity analysis demonstrated the insensitivity of the model 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 49). The model was most sensitive to assumptions around the modelling of OS, the duration of treatment and the utility of patients in PFS.

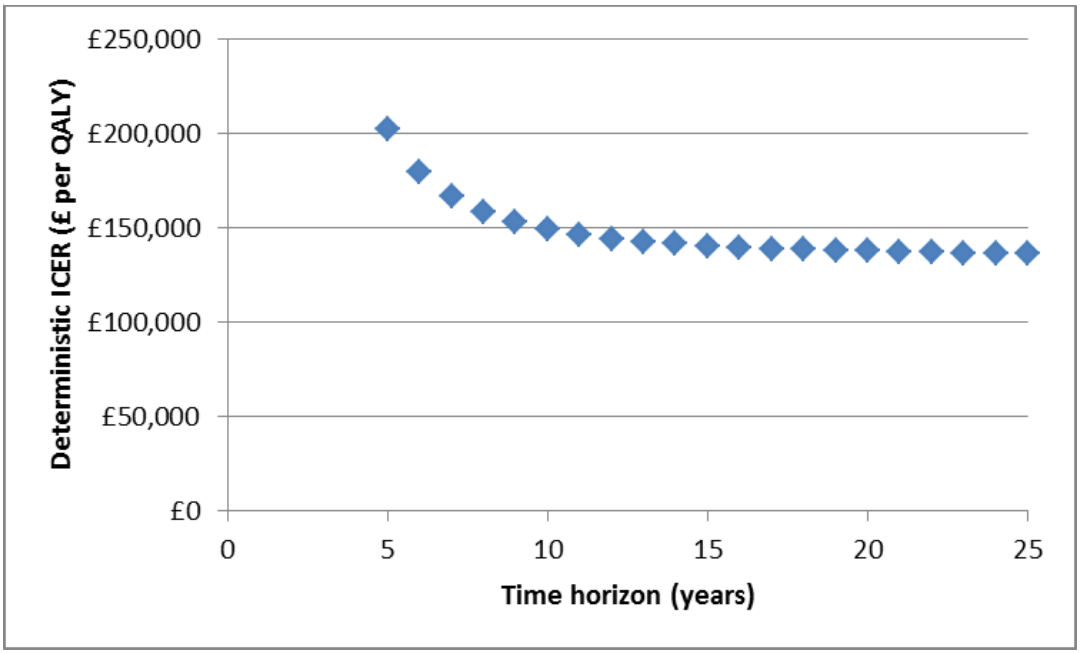
The results of the Probabilistic Sensitivity Analysis suggest that there is limited uncertainty in the degree of cost-effectiveness of the OCEANS study (Figure 22).

7.7.10 What are the key drivers of the cost-effectiveness results?

The key drivers of the cost-effectiveness results are the cost and duration of treatment with bevacizumab. The design of the OCEANS study allowed continuation of treatment with bevacizumab (or placebo) until disease progression (or safety concerns, whichever occurred first), but the time-to-off-treatment curves indicate patients came off bevacizumab treatment approximately 3.4 months before progression (Figure 19). The effect of extending duration of bevacizumab treatment until progression increases the ICER from £149k per QALY to almost £190k per QALY. However, the relevance of this sensitivity analysis is limited given the uncertainty of how PFS and OS are affected by this continuation of treatment.

The time horizon over which costs and benefits are calculated has an important influence on the ICER as observed in Figure 23. At time horizons of 5 years and less, the ICER is over £200k per QALY, but it decreases at longer time horizons to approach a plateau of approximately £130-140k per QALY by 20-25 years.

Figure 23: Sensitivity of the ICER to the time horizon of the model



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.

The internal validation and debugging of the model was performed by Outcomes International, an independent consultant company specialized in the development and validation of decision analytic models used for health economic analyses. The following validation procedures were performed:

- Check of completeness of reported results (health outcomes, economic outcomes) as compared to other published economic evaluations targeting the same indication
- Execution of selected extreme tests to check the plausibility of model outcomes. Extreme testing was applied to the following parameters: treatment efficacy, adverse event costs, cost of

study drugs and administration, discount rates, and health utilities

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.

Analysis of specific subgroups was not undertaken.

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.

Analysis of specific subgroups was not performed in this economic evaluation, but clinical effectiveness data has been presented elsewhere in this submission.

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?

N/A. There are no relevant economic evaluations of bevacizumab in the relapsed ovarian cancer setting with which to compare this submission.

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?

The economic evaluation presented in this submission is consistent with the population expected in the marketing authorisation (i.e. patients with platinum-sensitive or partially platinum-sensitive recurrent epithelial ovarian carcinoma).

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 makes it relevant for UK patients and clinicians.

Firstly, the clinical effects of bevacizumab in addition to carboplatin and gemcitabine compared with combination chemotherapy alone are based upon a large, randomised, placebo-controlled trial which demonstrated significant effect of bevacizumab in platinum-sensitive patients with recurrent ovarian cancer. The use of mature PFS data has minimised the need to extrapolate this outcome measure from the OCEANS study and therefore, the uncertainty of the treatment effect of bevacizumab in these patients is relatively low. Where possible, assumptions around the costs and utilities associated with treating ovarian cancer have been taken from a recent HTA economic evaluation (TA222). Furthermore, several types of uncertainties have been evaluated in both one-way and probabilistic sensitivity analysis. The resultant ICER has been demonstrated to be very stable to wide variations in model parameters.

The main weakness of the economic evaluation is the use of a relatively early data-cut (September 2010) from the OCEANS study to inform the model. This was necessary because of the incompleteness of later data-cuts which, although containing more mature overall survival data, lack completeness of other outcomes important for a robust economic evaluation. However, it is worth noting that subsequent analyses of the data have suggested that the OS benefit in this study is unstable, but that this may be confounded by the unrestricted use of subsequent therapies (Table 8 and Table 9).

Another weakness concerns the application of baseline characteristics pertaining to a representative UK cohort of ovarian cancer patients (in order to estimate drug costs), to outcomes from a study conducted in North America. The effect of this assumption is likely to be small, however, as demonstrated by the various sensitivity analyses described above.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The robustness of these results is likely to be improved by the use of more complete data regarding the overall survival and the use of post-progression therapies for patients in the OCEANS 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 1804 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 53.

Table 53: Eligible patient numbers and uptake for 5 years (2013 – 2017)

Year	2012	2013 (year 1)	2014 (year 2)	2105 (year 3)	2016 (year 4)	2017 (year 5)
Eligible Population	1795	1804	1813	1822	1831	1840
Uptake of bevacizumab		10%	20%	30%	40%	50%

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

Carboplatin and gemcitabine combination therapy has been a treatment option for recurrent platinum-sensitive ovarian cancer patients for several years.

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 53.

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 OCEANS study.

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 total incremental costs per patient of £44,428 (see Table B9 on page 166).

Table 54: 5-year budget impact

Year	2013	2014	2105	2016	2017
Eligible Population	1804	1813	1822	1831	1840
Uptake of bevacizumab	10%	20%	30%	40%	50%
Budget Impact (£,000's)	***£8,015***	***£16,110***	***£24,285***	***£32,542***	***£40,881***

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

Aghajanian, C., Blank, S. V., Goff, B. A., Judson, P. L., Teneriello, M. G., Husain, A., Sovak, M. A., Yi, J., & Nycum, L. R. 2012, "OCEANS: A randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer", *Journal of Clinical Oncology*, vol. 30, no. 17, pp. 2039-2045.

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.

Baum, M., Priestman, T., West, R. R., & Jones, E. M. 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, pp. 223-226.

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., Bergers, G., Benjamin, L. E., & Benjamin, L. E. 2003, "Tumorigenesis and the angiogenic switch", *Nat.Rev Cancer*, vol. 3, no. 6, pp. 401-410.

Boocock, C. A., Boocock, C. A., Charnock-Jones, D. S., Charnock-Jones, D. S., Sharkey, A. M., Sharkey, A. M., McLaren, J., McLaren, J., Barker, P. J., Barker, P. J., Wright, K. A., Wright, K. A., Twentyman, P. R., Twentyman, P. R., Smith, S. K., & 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.

BROOKMEYER, R. & CROWLEY, J. 1982, "A CONFIDENCE-INTERVAL FOR THE MEDIAN SURVIVAL-TIME", *BIOMETRICS*, vol. 38, no. 1, pp. 29-41.

Brundage, M., Gropp, M., Mefti, F., Mann, K., Lund, B., Gebski, V., Wolfram, G., Reed, N., Pignata, S., Ferrero, A., Brown, C., Eisenhauer, E., & Pujade-Lauraine, E. 2012, "Health-related quality of life in recurrent platinum-sensitive ovarian cancer--results from the CALYPSO trial", *Annals of oncology : official*

journal of the European Society for Medical Oncology / ESMO, vol. 23, no. 8, pp. 2020-2027.

Burger, R. A., Brady, M. F., Bookman, M. A., Fleming, G. F., Monk, B. J., Huang, H., Mannel, R. S., Homesley, H. D., Fowler, J., Greer, B. E., Boente, M., Birrer, M. J., & Liang, S. X. 2011, "Incorporation of bevacizumab in the primary treatment of ovarian cancer", *The New England journal of medicine*, vol. 365, no. 26, pp. 2473-2483.

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", *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 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. Statistics and outlook for ovaran cancer. http://cancerhelp.cancerresearchuk.org/type/ovarian-cancer/treatment/statistics-and-outlook-for-ovarian-cancer#gen . 21-3-2012. 9-8-2012.

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", *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, vol. 25, no. 33, pp. 5180-5186.

Chan, J., Monk, B., Fuh, K., Urban, R., Hu, L., Caughey, A., & Yu, X. 2011, "An economic analysis of bevacizumab in recurrent treatment of ovarian cancer", *Gynecologic Oncology*, vol. 120, p. S29-S30.

Cockcroft, D. W. & Gault, M. H. 1976, "Prediction of Creatinine Clearance from Serum Creatinine", *Nephron*, vol. 16, no. 1, pp. 31-41.

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 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.

Edbrooke, D. L., Hibbert, C. L., Kingsley, J. M., Smith, S., Bright, N. M., & Quinn, J. M. 1999, "The patient-related costs of care for sepsis patients in a United Kingdom adult general intensive care unit", *Crit Care Med.*, vol. 27, no. 9, pp. 1760-1767.

EMA. Questions and answers on final recommendations on Caelyx and Ceplene manufactured at Ben Venue Laboratories. European Medicines Agency 2012. 2012. 9-9-0012.

Ferrara, N. & Davis-Smyth, T. 1997, "The biology of vascular endothelial growth factor", *Endocr Rev*, vol. 18, p. 4.

Ferrara, N., Ferrara, N., Gerber, H. P., Gerber, H. P., LeCouter, J., & LeCouter, J. 2003, "The biology of VEGF and its receptors", *Nat.Med.*, vol. 9, no. 6, pp. 669-676.

Fuh, K., Chan, J., Monk, B., Urban, R., Hu, L., Kapp, D., Caughey, A., & Yu, X. 2011, "Is it more cost-effective to use bevacizumab in the primary

treatment setting or at recurrence? An economic analysis", *Gynecologic Oncology*, vol. 120, p. S98.

Gore, M., Vergote, I., Vasanthan, S., Chan, S., Arranz, J. M., Colombo, N., Fischer, M., Garcia San Andres, B., & Nieto, A. 2011, "Cost-effectiveness of trabectedin in combination with pegylated liposomal doxorubicin hydrochloride for the treatment of women with relapsed platinum-sensitive ovarian cancer in the UK - Analysis based on the final survival data", *European Journal of Cancer*, vol. 47, p. S542.

Gore, M. E., Gore, M. E., Fryatt, I., Fryatt, I., Wiltshaw, E., Wiltshaw, E., Dawson, T., & Dawson, T. 1990, "Treatment of relapsed carcinoma of the ovary with cisplatin or carboplatin following initial treatment with these compounds", *Gynecol.Oncol*, vol. 36, no. 2, pp. 207-211.

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.

Havrilesky, L. J., Pokrzywinski, R., Revicki, D., Higgins, R. V., Nycum, L. R., Kohler, M. F., Berchuck, A., Myers, E. R., & Secord, A. A. 2012, "Cost-effectiveness of combination versus sequential docetaxel and carboplatin for the treatment of platinum-sensitive, recurrent ovarian cancer", *Cancer*, vol. 118, no. 2, pp. 386-391.

Heintz, A. P. M., Odicino, F., Maisonneuve, P., Quinn, M. A., Benedet, J. L., Creasman, W. T., Ngan, H. Y., 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.

ICON Collaborators 1998, "ICON2: randomised trial of single-agent carboplatin against three-drug combination of CAP (cyclophosphamide,

doxorubicin, and cisplatin) in women with ovarian cancer. ICON Collaborators. International Collaborative Ovarian Neoplasm Study", *Lancet*, vol. 352, no. 9140, pp. 1571-1576.

Itakura, J., Itakura, J., Ishiwata, T., Ishiwata, T., Shen, B., Shen, B., Kornmann, M., Kornmann, M., Korc, 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.

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.

Krasner, C. N., Poveda, A., Herzog, T. J., Vermorken, J. B., Kaye, S. B., Nieto, A., Claret, P. L., Park, Y. C., Parekh, T., & Monk, B. J. 2012, "Patient-reported Outcomes in Relapsed Ovarian Cancer: Results from A Randomized Phase III Study of Trabectedin with Pegylated Liposomal Doxorubicin (PLD) versus PLD Alone", *Gynecologic Oncology*.

Ledermann, J. A. & Raja, F. 2006, "Management strategies for partially platinum-sensitive ovarian cancer", *American Journal of Cancer*, vol. 5, no. 5, pp. 341-354.

Liu, C. D., Liu, C. D., Tilch, L., Tilch, L., Kwan, D., Kwan, D., McFadden, D. W., & 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.

McGuire, W. P. & Markman, M. 2003, "Primary ovarian cancer chemotherapy: current standards of care", *Br.J.Cancer*, vol. 89 Suppl 3, p. S3-S8.

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.

Naumann, R. W. & Coleman, R. L. 2011, "Management Strategies for Recurrent Platinum-Resistant Ovarian Cancer", *Drugs*, vol. 71, no. 11, pp. 1397-1412.

NCCN Guidelines 2012, *Ovarian cancer - including fallopian tube cancer and primary peritoneal cancer.*

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 . 23-6-2008a. National Institute for Health and Clinical Excellence. 25-10-2011a.

NICE 2008b, *Paclitaxel, pegylated liposomal doxorubicin hydrochloride and topotecan for second-line or subsequent treatment of advanced ovarian cancer (review) (TA91)*.

NICE 2011, *The recognition and initial management of ovarian cancer: Clinical Guideline 122*, National Institute of Health and Clinical Excellence.

Nimeiri, H. S., Oza, A. M., Morgan, R. J., Friberg, G., Kasza, K., Faoro, L., Salgia, R., Stadler, W. M., Vokes, E. E., & Fleming, G. F. 2008, "Efficacy and safety of bevacizumab plus erlotinib for patients with recurrent ovarian, primary peritoneal, and fallopian tube cancer: a trial of the Chicago, PMH, and California Phase II Consortia", *Gynecologic Oncology*, vol. 110, no. 1, pp. 49-55.

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., Paley, P. J., Staskus, K. A., Staskus, K. A., Gebhard, K., Gebhard, K., Mohanraj, D., Mohanraj, D., Twiggs, L. B., Twiggs, L. B., Carson, L. F., Carson, L. F., Ramakrishnan, S., & 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.

Parmar, M. K. B., Ledermann, J. A., Colombo, N., du Bois, A., Delaloye, J. F., Kristensen, G. B., Wheeler, S., Swart, A. M., Qian, W., Torri, V., Floriani, I., Jayson, G., Lamont, A., & Trope, C. 2003, "Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial", *Lancet*, vol. 361, no. 9375, pp. 2099-2106.

Perren, T. J., Swart, A. M., Pfisterer, J., Ledermann, J. A., Pujade-Lauraine, E., Kristensen, G., Carey, M. S., Beale, P., Cervantes, A., Kurzeder, C., du, B. A., Sehouli, J., Kimmig, R., Stahle, A., Collinson, F., Essapen, S., Gourley, C., Lortholary, A., Selle, F., Mirza, M. R., Leminen, A., Plante, M., Stark, D., Qian, W., Parmar, M. K., & Oza, A. M. 2011, "A phase 3 trial of bevacizumab in ovarian cancer", *N.Engl.J Med.*, vol. 365, no. 26, pp. 2484-2496.

Pfisterer, J. & Ledermann, J. A. 2006, "Management of platinum-sensitive recurrent ovarian cancer", *Semin.Oncol*, vol. 33, no. 2 Suppl 6, p. S12-S16.

Pokrzywinski, R., Secord, A. A., Havrilesky, L. J., Puls, L. E., Holloway, R. W., Lewandowski, G. S., Higgins, R. V., Nycum, L. R., Kohler, M. F., & Revicki, D. A. 2011, "Health-related quality of life outcomes of docetaxel/carboplatin combination therapy vs. sequential therapy with docetaxel then carboplatin in patients with relapsed, platinum-sensitive ovarian cancer: results from a randomized clinical trial", *Gynecologic Oncology*, vol. 123, no. 3, pp. 505-510.

PSSRU 2011, *Unit Costs of Health and Social Care 2011*, Personal Social Services Research Unit, Canterbury, Kent.

Ramakrishnan, S., Ramakrishnan, S., Subramanian, I. V., Subramanian, I. V., Yokoyama, Y., Yokoyama, Y., Geller, M., & Geller, M. 2005, "Angiogenesis in normal and neoplastic ovaries", *Angiogenesis.*, vol. 8, no. 2, pp. 169-182.

Rustin, G. J., van der Burg, M. E., Griffin, C. L., Guthrie, D., Lamont, A., Jayson, G. C., Kristensen, G., Mediola, C., Coens, C., Qian, W., Parmar, M. K., & Swart, A. M. 2010, "Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial", *Lancet*, vol. 376, no. 9747, pp. 1155-1163.

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.

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.

Smith, D. H., Adams, J. R., Johnston, S. R. D., Gordon, A., Drummond, M. F., & Bennett, C. L. 2002, "A comparative economic analysis of pegylated liposomal doxorubicin versus topotecan in ovarian cancer in the USA and the UK", *Annals of Oncology*, vol. 13, no. 10, pp. 1590-1597.

Surveilance Epidemiology and End Results 2010, *SEER Cancer Statistics Review, 1975-2007*, National Cancer Institute., Bethesda, MD.

Vergote, I., Bidzinski, M., Kelley, J., Vasanthan, S., Runnebaum, I., Vermorken, J., Arranz, J. A., Almor+¡n, E., Park, Y., & Lisyanskaya, A. 2011, "Health-related quality of life (HRQOL)/patient reported outcomes (PRO) of patients (pts) with partially platinum sensitive (PPS) recurrent ovarian cancer (ROC) treated in a randomized phase III trial of trabectedin and pegylated liposomal doxorubicin (PLD) vs PLD alone (OVA-301) - An exploratory analysis", *European Journal of Cancer*, vol. 47, p. S536.