NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Bevacizumab in combination with gemcitabine and carboplatin for treating recurrent advanced ovarian cancer

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal. Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- The OCEANS trial was conducted in the US. The Evidence Review Group (ERG) agreed with the manufacturer that, with the exception of baseline weight, the characteristics of the patient population enrolled in OCEANS were representative of people with first recurrence of ovarian cancer in England and Wales. The ERG noted that UK practice is to administer a maximum of 6 cycles of chemotherapy. However, in the OCEANS trial approximately 50% of patients received 4–6 cycles of gemcitabine and carboplatin and approximately 40% of patients received 7–10 cycles of chemotherapy. What is the Committee's view on the generalisability of the OCEANS trial to UK clinical practice?
- The main comparator in the manufacturer's submission was gemcitabine plus carboplatin. The scope for the appraisal also lists other comparators (paclitaxel plus carboplatin, pegylated liposomal doxorubicin hydrochloride plus carboplatin, and carboplatin monotherapy). The ERG's clinical experts

highlighted that gemcitabine plus carboplatin may not be the preferred treatment in the NHS. What is the Committee's view on the comparator used in the manufacturer's submission?

- The manufacturer was unable to provide data on the number of patients lost to follow-up, number of patients censored and data on mean progression-free survival (PFS) at the time of the final PFS analysis. Does the Committee consider the presented PFS data to be appropriate?
- The manufacturer reported results from 3 interim analyses of overall survival (OS) data (September 2010, when 29% of the patients had died; August 2011, when 49% of the patients had died; and March 2012, when 59% of the patients had died). No statistically significant difference between bevacizumab and placebo treatment was found at any of these time-points. The direction of the effect in the first interim analysis favoured treatment with bevacizumab but there was no difference between bevacizumab and placebo in the duration of OS in the second and third interim analyses. The manufacturer stated that after disease progression, patients in both study arms could receive bevacizumab; at least 34% of patients in the placebo arm and 18% in the bevacizumab arm received bevacizumab, which introduced confounding in the results. What is the Committee's view on the OS data?
- A larger proportion of patients in the bevacizumab treatment group experienced an adverse event that led to discontinuation. However, the absolute number of patients discontinuing because of adverse events is unclear in the manufacturer's submission. What is the Committee's view on this disparity?
- The manufacturer did not consider it appropriate to perform a network meta-analysis based on the high level of heterogeneity between the studies identified. The ERG considered that the identified trials were sufficiently comparable and performed a network meta-analysis. The ERG stressed that these analyses were speculative and should be interpreted with caution, and added that additional relevant studies had possibly not been

identified. What is the Committee's view on the network meta-analysis carried out by the ERG?

Cost effectiveness

- The manufacturer used PFS, OS and incidence of adverse events data based on data cut-off date of September 2010 (29% died) of the OCEANS randomised controlled trial to guide the model. The manufacturer acknowledged that the OS data are immature and should be interpreted with caution. The ERG considered that the key driver of the cost-effectiveness results was the estimate of OS gain associated with bevacizumab and suggested that data from March 2012 (59% died) should be used instead. What is the Committee's view on the early OS data (September 2010) used by the manufacturer?
- The manufacturer applied a parametric log-logistic function to the Kaplan-Meier PFS data (cut-off date September 2010) from the OCEANS trial to estimate and extrapolate the proportion of patients in the progression-free health state. At a median follow-up of 24 months (final PFS analysis), 70% of the patients had experienced either disease progression or death. Patients in the bevacizumab arm reached 0% PFS at month 29.8, whereas 2 patients remained at risk at month 24.9 in the placebo arm. Does the Committee consider it appropriate to fit a parametric distribution for PFS given the Kaplan-Meier data available?
- The manufacturer used utility data from Trabectedin for the treatment of relapsed ovarian cancer (NICE technology appraisal 222) in the model because utility values were not reported in the OCEANS RCT. The manufacturer noted that these utility data should be used with caution in the analysis. The ERG noted that 1 of the main drivers of the cost effectiveness is utility data. Does the Committee consider the utility values used to be appropriate?
- Adverse events experienced by patients in the model were not subject to estimates of disutility in the model. The manufacturer mentioned that

serious adverse events were expected to result in either a short- or long-term detriment to health-related quality of life. Moreover, the costs of adverse events were assumed to occur within the first cycle of the model and therefore, they were not subject to discounting. What is the Committee's perspective about the assumptions regarding adverse events in the model?

- The ERG carried out exploratory analyses to assess the cost-effectiveness of bevacizumab in combination with carboplatin and gemcitabine versus the rest of comparators listed in the scope of this appraisal based on its network meta-analysis results. What is the Committee's view on these analyses?

1 Background: clinical need and practice

1.1 Ovarian cancer is a common gynaecological cancer which represents a group of different tumours that arise from diverse types of tissue contained in the ovary. Epithelial ovarian cancer is the most common form of ovarian cancer, accounting for over 90% of cases, and is when the tumour starts from the cells that cover the outer surface (epithelial cells) of the ovary. Ovarian cancer can often spread from the ovary to any surface in the abdominal cavity including the fallopian tubes and peritoneal cavity. Fallopian tube cancer and primary peritoneal cancer are histologically equivalent diseases to epithelial ovarian cancer. Symptoms of ovarian cancer tend to be non-specific and are widely experienced among the general population. Symptoms include persistent pelvic and abdominal pain, abdominal bloating, urinary frequency or urgency, loss of appetite, and abnormal or postmenopausal bleeding. Most women are diagnosed with advanced stage disease.

1.2 In 2009, around 7000 new cases of ovarian cancer were diagnosed in the UK, making it the second most common gynaecological

cancer and the fifth most common cancer in women. Ovarian cancer predominantly occurs in older women, with over 80% of cases being diagnosed in women over 50 years. In 2010, there were about 4300 deaths from ovarian cancer in the UK.

1.3 Ovarian cancer may be categorised according to the response to first-line platinum chemotherapy as follows:

- fully platinum-sensitive (disease responds to first-line platinum-based therapy but relapses after 12 months or more)
- partially platinum-sensitive (disease responds to first-line platinum-based therapy but relapses between 6 and 12 months)
- platinum-resistant (disease which relapses within 6 months of completion of initial platinum-based chemotherapy)
- platinum-refractory (disease does not respond to initial platinum-based chemotherapy).

Although the disease, in a significant percentage of women with ovarian cancer, responds to initial chemotherapy, between 55% and 75% of women whose tumours respond to first-line therapy relapse within 2 years of completing treatment. The overall 5-year survival rate for ovarian cancer is less than 43%.

1.4 Standard treatment for ovarian cancer consists of surgery to determine the type and stage of the disease and to remove as much of the cancer as possible. After surgery, chemotherapy is used to treat any residual disease. Increasingly chemotherapy is given before surgery. Guidance on the use of paclitaxel in the treatment of ovarian cancer (NICE technology appraisal guidance 55) recommends paclitaxel in combination with a platinum-based compound or platinum-based therapy alone (cisplatin or carboplatin) as options for first-line chemotherapy in the treatment of ovarian cancer.

1.5 In most of the patients whose disease responds to treatment, the disease eventually relapses. Patients in whom the relapse is more than 6 months after platinum therapy, are considered to be suitable to have retreatment with platinum combination therapy, but eventually the disease becomes platinum-resistant. NICE guidance on the use of Paclitaxel, pegylated liposomal doxorubicin hydrochloride and topotecan for second-line or subsequent treatment of advanced ovarian cancer (NICE technology appraisal guidance 91) recommends:

- paclitaxel in combination with a platinum compound in platinum-sensitive or partially platinum-sensitive disease
- pegylated liposomal doxorubicin hydrochloride in partially platinum-sensitive disease.

2 The technology

2.1 Bevacizumab (Avastin, Roche) is a humanised monoclonal antibody that inhibits vascular endothelial growth factor (VEGF). This reduces vascularisation of tumours, thereby inhibiting tumour growth. Bevacizumab is administered by intravenous infusion. Bevacizumab in combination with carboplatin and gemcitabine has a UK marketing authorisation 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 receptor-targeted agents'. The licensed dose of bevacizumab is 15 mg/kg of body weight given once every 3 weeks in combination with carboplatin and gemcitabine for 6 cycles and up to 10 cycles, followed by bevacizumab as single agent until disease progression.

2.2 The summary of product characteristics lists the following adverse reactions that may be associated with bevacizumab treatment:

gastrointestinal perforations, fistulae, wound healing complications, hypertension, proteinuria, arterial and venous thromboembolism, haemorrhage, pulmonary haemorrhage or haemoptysis, congestive heart failure, reversible posterior leukoencephalopathy syndrome, hypersensitivity or infusion reactions, osteonecrosis of the jaw, ovarian failure and neutropenia. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Bevacizumab is available in 100 mg and 400 mg vials at net prices of £242.66 and £924.40 respectively (excluding VAT; 'British national formulary' [BNF] edition 63). The manufacturer estimated the cost of a course of treatment with bevacizumab (excluding VAT and assuming wastage) to be £25,208 for a patient weighing 60.5 kg at a dosage of 15 mg/kg every 3 weeks for a mean treatment duration of 10.8 cycles (7.5 months). Costs may vary in different settings because of negotiated procurement discounts.

3 Remit and decision problem

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of bevacizumab within its licensed indication for the treatment of platinum-sensitive or partially platinum-sensitive recurrent advanced ovarian cancer (including fallopian tube and primary peritoneal cancer).

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	Women with recurrent platinum-sensitive or partially platinum-sensitive advanced epithelial ovarian, fallopian tube of primary peritoneal cancer	

3.2 The ERG noted that the population in the subsequent marketing authorisation restricts the population relevant to the decision problem stating that bevacizumab is indicated for the treatment of

patients with first-recurrence of platinum-sensitive ovarian cancer who have not received previous therapy with a VEGF inhibitor or VEGF receptor-targeted agent.

	Final scope issued by NICE	Decision problem addressed in the submission
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

3.3 The ERG noted that the intervention addressed by the manufacturer in the submission is in line with the marketing authorisation received for bevacizumab in this indication.

	Final scope issued by NICE	Decision problem addressed in the submission
Comparators	• 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	

3.4 The ERG highlighted that the manufacturer indicates in their submission that the gemcitabine and carboplatin combination is the most relevant comparator for the decision problem. The manufacturer noted that clinical data are available only for the addition of bevacizumab to gemcitabine and carboplatin compared with the addition of placebo to gemcitabine plus carboplatin. In response to clarification, the manufacturer stated that 'the most popular chemotherapy option for recurrent ovarian cancer, liposomal doxorubicin, is currently unavailable'. The ERG's clinical expert highlighted that the preferred treatment for first recurrence of platinum-sensitive ovarian cancer would be paclitaxel plus carboplatin. In addition, the use of pegylated liposomal doxorubicin hydrochloride is likely to increase when it becomes available again.

The manufacturer decided against a network meta-analysis after evaluating the trials from a systematic review, citing that clinical heterogeneity in population baseline prognostic factors across the identified trials was too high to generate results that would be informative. The ERG considered that an adjusted indirect comparison could be performed to show how the addition of bevacizumab to gemcitabine plus carboplatin can be compared to the comparators stated in the scope for this appraisal.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Outcomes	The outcome measures to be considered include: • overall survival • PFS • 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	

3.5 The ERG noted that the manufacturer has, with the exception of health-related quality-of-life data, provided direct evidence on the outcomes listed in the final scope. The ERG noted that that cost effectiveness was assessed as recommended in the NICE reference case.

	Final scope issued by NICE	Decision problem addressed in the submission
Subgroups to be considered	None	• Fully platinum-sensitive (relapse more than 12 months after last platinum therapy) • Partially platinum-sensitive (relapse 6–12 months after last platinum therapy) These subgroups arose from a stratification factor in the OCEANS trial.

3.6 The ERG highlighted that the manufacturer presented subgroup analyses based on the degree of platinum-sensitivity and whether cytoreductive surgery had occurred or not.

4 Clinical-effectiveness evidence

4.1 The manufacturer conducted a literature search and identified 1 RCT (OCEANS) that met the criteria for inclusion in the review. OCEANS was a phase III randomized, double-blinded, placebo-controlled trial that assessed the safety and efficacy of bevacizumab plus gemcitabine and carboplatin. The trial was a multinational study conducted in 96 centres in the US. The study population comprised 484 adults with platinum-sensitive recurrent epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC) or fallopian tube cancer (FTC) with a first recurrence of ovarian cancer and who had not previously received VEGF receptor-targeted agents. Full details of the inclusion and exclusion criteria are presented in the manufacturer's submission (table 3, section 6.3.3, page 37 in the manufacturer's submission). Patients were randomized to 1 of the following 2 treatment arms:

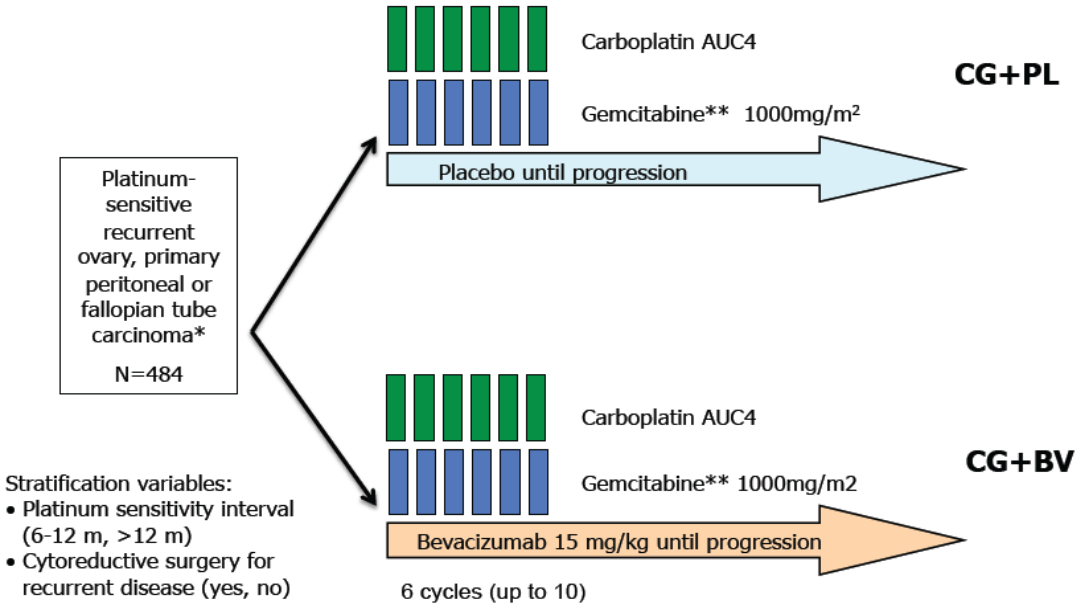
- Bevacizumab plus gemcitabine and carboplatin arm (n=242) (bevacizumab 15 mg/kg body weight on day 1 every 3 weeks, carboplatin on day 1 every 3 weeks, and gemcitabine

1000 mg/m^2 on days 1 and 8 every 3 weeks for 6–10 cycles, followed by bevacizumab 15 mg/kg body weight alone on day 1 every 3 weeks until disease progression or unacceptable toxicity).

- Placebo plus gemcitabine and carboplatin (n=242) (placebo 15 mg/kg body weight on day 1 every 3 weeks, carboplatin on day 1 every 3 weeks, and gemcitabine 1000 mg/m^2 on days 1 and 8 every 3 weeks for 6–10 cycles, followed by placebo 15 mg/kg body weight alone on day 1 every 3 weeks until disease progression or unacceptable toxicity).

Randomization was stratified by platinum-sensitive category (platinum-sensitive or partially platinum-sensitive) and incidence of cytoreductive surgery for recurrent disease (see figure 1).

Figure 1: OCEANS study design



*Only patients with measurable disease at baseline are enrolled

**Gemcitabine was given on Day 1 and Day 8

Source: Manufacturer's submission, section 6.3.2, page 37

4.2 The manufacturer stated that overall the baseline characteristics of the patients were comparable between treatment arms. The primary site of cancer was ovarian carcinoma in 84.1% of patients. The median age was 61, with just over a third of patients (36.8%) 65 years or older. Almost all patients were of good performance status at baseline (ECOG 0: 75.8%; ECOG 1: 24.0%) (complete baseline characteristics for patients in the OCEANS trial are presented in the manufacturer's submission, table 4, section 6.3.4, page 40).

4.3 The primary outcome was PFS, defined as the period from randomisation to disease progression or death (by any cause). Progression was assessed by the investigators using radiologic evaluation according to the Response Evaluation Criteria for Solid Tumours (RECIST) criteria. Progression could also be determined by symptomatic progression, but not by cancer antigen 125 (CA-125) elevation alone. Sensitivity analysis of PFS included an assessment by an Independent Review Committee (IRC) using RECIST criteria. For the IRC analysis, PFS definition was period from randomisation until disease progression or on-study death (that is, death occurring within 9 weeks of the last dose of chemotherapy or study drug). All patients needed to undergo computer tomography scans every 9 weeks from day 1 of cycle 1. Secondary outcomes were overall survival, objective response rate (ORR) and duration of objective response. Objective response and duration of objective response were also subject to an assessment by the IRC using RECIST criteria as exploratory analyses. Safety outcome measures were frequency and severity of adverse events.

4.4 Of the 484 randomised patients, 5 patients (4 in the placebo arm and 1 in the bevacizumab arm) did not receive any study treatment. In the study, 222 and 213 patients discontinued treatment in the

placebo and bevacizumab groups respectively. The most common reason was disease progression (n=160 [66.1%] in placebo; 104 [43.0%] in bevacizumab). Adverse event complications resulted in treatment discontinuation in 12 patients in the control group and 55 patients in the bevacizumab group. A CONSORT flow chart is presented by the manufacturer in their submission (see manufacturer's submission, figure 3, section 6.3.8, page 56).

4.5 Results presented by the manufacturer were obtained from an intention-to-treat (ITT) population (by investigator assessment) which included all patients randomised to a study treatment. Analysis of the primary outcome, PFS in the ITT population, was based on a cut-off date of 17 September 2010 once 338 (70%) patients had experienced disease progression or death (62.4% of patients in the bevacizumab arm and 77.3% in the placebo arm). The median follow-up was 24 months. PFS in the bevacizumab arm was compared with the placebo arm using a 2-sided stratified log-rank test. Stratification factors were time to recurrence since the last platinum therapy (platinum-sensitive or partially platinum-sensitive) and incidence of cytoreductive surgery. Results from an unstratified log-rank test were also presented. Kaplan-Meier curves were also provided by the manufacturer to represent the difference between the 2 treatment arms. Median PFS for each treatment arm were also estimated using Kaplan-Meier methodology. The Brookmeyer-Crowley methodology was used to construct 95% confidence intervals (CI) for median PFS. Data for patients who had not progressed or died at the time of the last tumour assessment were censored, that is, excluded from the analysis. Data for patients who received non-protocol therapy before disease progression were also censored at the time of the last tumour assessment before therapy initiation. Results of the investigator-

assessment analysis showed that there was a statistically significant improvement in the median PFS of 4 months in the bevacizumab arm compared with the placebo arm. In the stratified analysis, there was a 51.6% reduction in disease progression in patients in the bevacizumab arm compared with those in the placebo arm. Unstratified analysis showed a reduction in disease progression of 50.8% with bevacizumab compared with placebo. The manufacturer also presented an IRC analysis of PFS on the same data and a sensitivity analysis without censoring patients for receiving non-protocol therapies. At 29.8 months, all patients still at risk in the bevacizumab arm had progressed or died, and at month 29, 2 patients remained at risk in the placebo arm (see Kaplan-Meier plot in the manufacturer's submission, figure 7, section 6.4, page 66). IRC analysis results of PFS were consistent with the primary analysis showing a reduction in disease progression in patients in the bevacizumab arm compared with the placebo arm. Results from the sensitivity analysis not censoring for non-protocol specified therapy were also consistent with the primary analysis results. Results are shown in table 1.

Table 1: Primary PFS analysis

	Investigator-assessed[a]		IRC-determined		Sensitivity analysis (includes patients censored for receiving non-protocol therapies)	
Outcome	**Bevacizumab (n=242)**	**Placebo (n=242)**	**Bevacizumab (n=242)**	**Placebo (n=242)**	**Bevacizumab (n=242)**	**Placebo (n=242)**
Number (%) of patients with an event	151 (62.4)	187 (77.3)	119 (49.2)	148 (61.2)	174 (71.9)[b]	203 (83.9)[b]
Disease progression	146 (60.3)	185 (76.4)	NA	NA	146 (60.3)[b]	185 (76.4)[b]
Death	5 (2.1)	2 (0.8)	NA	NA	5 (2.1)[b]	2 (0.8)[b]
Number of patients not known to have an event	91 (37.6)	55 (22.7)	NA	NA	NA	NA
Progression-free survival, months						
Median (95% CI)	12.4 (11.40 to 12.71)	8.4 (8.31 to 9.66)	12.3 (10.7 to 14.6)	8.6 (8.3 to 10.2)	12.4	8.4
HR (relative to placebo) (95% CI)	Stratified analysis[c]: 0.48 (0.39 to 0.61) p<0.0001		Stratified analysis[c]: 0.45 (0.35 to 0.58) p<0.0001		0.52 (0.43 to 0.65) p<0.0001	
	Unstratified analysis: 0.49 (0.40 to 0.61) p<0.0001		NA		NA	

Note: HR<1 favours addition of bevacizumab to gemcitabine plus carboplatin.

[a] Analysis is based on investigator-assessment of randomly-assigned patients, censoring for non-protocol-specified cancer therapies.

[b] Data provided by the manufacturer in the clarification process.

[c] Strata are the time to recurrence since the last platinum therapy (6–12 months, and >12 months) and cytoreductive surgery for recurrent disease (yes/no).

Abbreviations: CI, confidence interval; HR, hazard ratio; IRC, Independent review committee; NA, not available

Source: Evidence Review Group report, table 10, page 55.

4.6 The manufacturer also reported subgroup analyses of PFS based on baseline prognostic factors. Across most subgroups, bevacizumab was associated with a reduced risk of progression compared with placebo that was consistent with the overall result for the primary analysis. Results based on the predefined stratification factors (platinum-sensitive classification and incidence of cytoreductive surgery for recurrent disease) showed that there was a statistically significant reduction in PFS observed for patients in the bevacizumab group irrespective of whether they had cytoreductive surgery or not. Partially platinum-sensitive patients

showed a median PFS of 11.9 months and 8.0 months with bevacizumab placebo respectively (HR 0.41, 95% CI 0.29 to 0.58). There was also an increase in PFS in fully platinum-sensitive patients observed in the bevacizumab arm (HR 0.55, 95% CI 0.41 to 0.73). Further subgroup analyses are shown at the manufacturer's submission (figure 5, page 64).

4.7 Three interim analyses of OS have been conducted, 2 of which were protocol-specified. The first interim analysis was carried out at the time of final PFS analysis (17 September 2010) when approximately 29% of patients had died. The second one was carried out 29 August 2011, when approximately 49% of the patients had died, and the third, using a data cut-off of 30 March 2012 (required by the European Medicine Agency), was conducted at which time approximately 59% of the patients had died. None of the interim analyses found a statistically significant difference between bevacizumab and placebo in the duration of OS. The results of the third analysis showed that the median OS was 33.4 months in the bevacizumab arm and 33.7 months in the placebo arm (HR of placebo relative to bevacizumab 0.96, 95% CI 0.76 to 1.21). The manufacturer stated that patients in both study arms in third and subsequent lines of therapy received post-progression bevacizumab; at least 18.1% of patients in the bevacizumab group and 34.7% in the placebo group received bevacizumab, and therefore confounding may have occurred (for further details of post-progression therapy, see table 9 in the manufacturer's submission). Results for OS are shown in table 2.

Table 2: Interim analysis of OS

OS	Bevacizumab (n=242)	Placebo (n=242)
First interim OS analysis[a]		
Number (%) of patients with an event	63 (26.0)	78 (32.2)
Median OS (months) (95% CI)	35.5 (30.0 to not estimable)	29.9 (26.4 to not estimable)
HR (relative to placebo) (95% CI)	**0.75 (0.53 to 1.05)**	
Second interim OS analysis[a]		
Number (%) of patients with an event	123 (50.8)	112 (46.3)
Median OS (months) (95% CI)	33.3 (29.8 to 35.5)	35.2 (29.9 to 40.3)
HR (relative to placebo) (95% CI)	**1.03 (0.79 to 1.33)**	
Third interim OS analysis[a]		
Number (%) of patients with an event	144 (59.5)	142 (58.7)
Median OS (months) (95% CI)	33.4 (30.3 to 35.8)	33.7 (29.3 to 38.7)
HR (relative to bevacizumab) (95% CI)	**0.96 (0.76 to 1.21)[b]**	

[a] First patient was enrolled on 17 April 2007. Cut-off dates for analyses were: first interim analysis of 17 September 2010 (final PFS analysis); second interim analysis of 29 August 2011; and third interim analysis (carried out at the request of the European Medicines Agency) = 30 March 2012.

[b] HR reported in the manufacturer's submission to be relative to placebo (HR<1 favours addition of bevacizumab to gemcitabine plus carboplatin). However, the quoted HR here is for placebo relative to bevacizumab (HR<1 favours placebo).

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Source: Evidence Review Group report, table 11, page 59

4.8 ORR was defined as the occurrence of a complete or partial response using RECIST criteria, and was confirmed by a repeat assessment performed 4 weeks or more after the criteria for response were first met. Differences in ORRs between the 2 treatment arms were compared by the Cochran-Mantel-Haenszel test. ORR, according to investigator assessment, was statistically significantly different between the 2 arms (78.5% in the

bevacizumab arm compared with 57.4% in the placebo arm, p<0.0001). Duration of response was estimated with the Kaplan-Meier method. Median duration of response was 10.4 and 7.4 months in patients in the bevacizumab arm and the placebo arm respectively. IRC assessment of ORR was consistent with the results of the investigator-assessed analysis (for further details see manufacturer's submission, section 6.4.6.5, page 66).

4.9 The evaluation of adverse effects of treatment was based on the safety evaluable population of the OCEANS trial, which comprised patients who received at least 1 dose of protocol treatment (bevacizumab, placebo, gemcitabine or carboplatin). All patients experienced an adverse effect from treatment. More patients in the bevacizumab arm experienced a serious adverse event compared with patients in the placebo arm (34.8% and 24.9% respectively). The percentage of patients experiencing adverse events of special interest (that is, events previously associated with bevacizumab across indications; grade 3–5) was also higher in the bevacizumab arm than in the placebo arm (29.1% and 20.2% respectively). The incidence of a grade 3–5 adverse effect was also higher in patients taking bevacizumab compared with placebo (94.3% and 85.0% respectively). Adverse events for which the incidence was greater than 10 per cent higher in the bevacizumab-containing arms than in the placebo arm were hypertension, nose bleeds, headache and proteinuria. Adverse events of special interest (grade 3-5) that occurred with an incidence of at least 2 per cent higher in the bevacizumab arm compared with the placebo arm were hypertension, proteinuria and non-central nervous system bleeding (full details of adverse events are shown in manufacturer's submission, section 6.8, page 84).

4.10 No generic measure of health-related quality of life was collected in the OCEANS trial.

4.11 The manufacturer carried out a literature review and identified 4 RCTs (CALYPSO, ICON4, AGO-OVAR-2.5 and OCEANS) that assess the comparative clinical effectives of bevacizumab in combination with gemcitabine and carboplatin compared with:

- paclitaxel plus platinum-based treatment
- platinum-based treatment (monotherapy)
- pegylated liposomal doxorubicin hydrochloride plus platinum-based treatment
- gemcitabine plus platinum-based treatment.

Table 3 shows a summary of the studies identified. The manufacturer noted that the ICON4 trial includes a smaller proportion of patients with partially platinum-sensitive disease (23–29%) compared with the other trials (35–42%), 42% of patients in the OCEANS trial had partially platinum-sensitive disease. The manufacturer also identified that the ICON4 and CALYPSO trials included patients who had received more than 1 line of therapy. It was additionally stated that AGO-OVAR-2.5 trial included fewer than 50% of patients with an ECOG score of 0, compared with 75% of patients in OCEANS. CALYPSO, ICON4 and AGO-OVAR-2.5 included patients with an ECOG score of 2. Only 1 patient in the OCEANS trial had an ECOG score of 2. The manufacturer identified that a small proportion of patients (2.2%) in the ICON4 trial was diagnosed to have recurrent disease based on raised CA-125 levels alone. The manufacturer stated that raised levels of CA-125 are not specific to ovarian tumours and it is not recommended that this measure alone would be used to diagnosed ovarian cancer or disease progression. Finally, the manufacturer

highlighted that the ICON4 trial evaluated the efficacy of adding paclitaxel to conventional therapy, which implied that 20% of patients in the paclitaxel plus platinum-based therapy and 29% of patients in the conventional chemotherapy group did not receive carboplatin. Therefore, the manufacturer argued that patients in ICON4 were not comparable with patients in other studies. After assessing the feasibility of conducting an indirect comparison of bevacizumab in combination with gemcitabine and carboplatin compared with the comparators listed in the final scope, the manufacturer decided against carrying out a network meta-analysis (for further details see manufacturer's submission, section 6.5, page 73).

Table 3: Summary of the trials relevant for the indirect comparison

References of trials	Platinum + pegylated liposomal doxorubicin hydrochloride	Platinum + paclitaxel	Platinum	Platinum + gemcitabine	Platinum + gemcitabine + bevacizumab
CALYPSO	✓	✓			
ICON4		✓	✓		
AGO-OVAR-2.5			✓	✓	
OCEANS				✓	✓
Source: Manufacturer's submission, table 12, section 6.6.3.1, page 77					

Evidence Review Group comments and exploratory analyses

4.12 The ERG considered that the manufacturer's search strategies in the systematic review of the clinical effectiveness were generally appropriate. It was satisfied that all relevant evidence was identified for the direct comparison of bevacizumab in combination with platinum-based therapy compared with other chemotherapy regimens in recurrent platinum-sensitive ovarian cancer. The ERG had concerns about the inclusion criteria that limited eligible studies to those involving a minimum number of 200 patients. The

manufacturer provided details of excluded studies on request during the clarification process.

4.13 The ERG considered the OCEANS trial to be a well-designed trial, and the results of the submitted evidence to be relevant to the decision problem. The ERG agreed that, with the exception of baseline weight, the characteristics of the patient population enrolled in OCEANS (carried out exclusively in US) were representative of people with first recurrence of ovarian cancer in England and Wales. The ERG heard from clinical experts that clinical practice in the UK is to administer a maximum of 6 cycles of chemotherapy; whereas the OCEANS trial allowed patients to receive a maximum of 10 cycles of chemotherapy. The summary of product characteristics states that bevacizumab in combination with carboplatin and gemcitabine should be taken for 6 cycles and up to 10 cycles followed by continued use of bevacizumab as a single agent until disease progression.

4.14 The ERG noted that the number of recorded events in terms of PFS was higher in the investigator-assessed analysis than in the IRC-determined analysis. Diagnosis of disease progression in both analyses was based on RECIST criteria and thus, the ERG was unclear as to why there was a variation in the number of recorded events. The ERG also had concerns about the number of patients censored in each group at the time of final PFS in both analyses being unknown. Moreover, the ERG highlighted that data on the mean PFS and the number of patients lost to follow-up at the time of the final analysis were also not available from the manufacturer at the clarification stage.

4.15 The ERG agreed with the manufacturer that the OS data from OCEANS were immature. Therefore, the ERG suggested that there

was uncertainty around the benefit of adding bevacizumab in combination with carboplatin and gemcitabine in terms of OS. The manufacturer stated that, for a trial with an observed p-value of 0.001 (like OCEANS) there is less than 20% probability for statistical significance in OS if the median time between progression and death is 24 months (Broglio and Berry, 2009). The manufacturer also stated that the large number of subsequent therapies, including bevacizumab, could be confounding the OS results. The ERG agreed with the manufacturer that confounding because of post-progression treatment is a well-recognised difficulty associated with interpretation of OS data, but considered that this issue is common to trials evaluating cancer treatments.

4.16 The ERG identified inconsistency in the proportion of patients achieving complete response reported for the investigator-assessed and IRC-determined analyses. The investigator-assessed complete response rate was 17.4% in the bevacizumab arm and 9.1% in the placebo arm. The IRC classified most patients as achieving partial response, and the proportion of patients achieving a complete response was larger in the placebo group (0.8% in the bevacizumab arm compared with 1.2% in the placebo arm). When complete and partial responses are combined, ORR is a direct measure of antitumor activity of a drug. Therefore, the ORR for the investigator-assessed and IRC-determined analyses were comparable and suggested that bevacizumab was associated with a statistically significant increase in ORR compared with placebo. However, the ERG had concerns about the differences in complete and partial response rates between the 2 analyses.

4.17 The ERG noted that the absolute number of patients discontinuing treatment because of an adverse effect varied in the manufacturer's submission, and the correct number remained

unclear after seeking clarification from the manufacturer. In a patient flow diagram (CONSORT flow diagram, figure 3, section 6.3.8, page 56 in the manufacturer's submission), the number of patients discontinuing treatment as a result of an adverse event was 55 in the bevacizumab group and 12 in the placebo group. In table 18 of the manufacturer's submission (section 6.8.2.1, page 90), the manufacturer reflected that the number of patients discontinuing treatment because of an adverse event were 49 in the bevacizumab group and 11 in the placebo group. During the clarification process, the manufacturer confirmed the flow diagram with 55 and 12 patients discontinuing as a result of an adverse event. However, the manufacturer also provided a breakdown of adverse events leading to discontinuation that resulted in a total of 49 and 11 patients in the bevacizumab and placebo groups respectively.

4.18 The ERG discussed the search and the points raised by the manufacturer for not performing an indirect comparison between bevacizumab in combination with carboplatin and gemcitabine, and the rest of comparators listed in the final scope. The ERG heard from their clinical experts that no relevant studies had been omitted from either the direct or indirect comparison. The ERG reviewed the studies excluded by the manufacturer because of population size, and decided to exclude all but 2 studies (Alberts et al. 2008 and González-Martín et al. 2005 [See ERG report, appendix 12, pages 183 and 184]). The ERG agreed with the manufacturer that there were differences across the key trials identified for an indirect comparison. However, the ERG considered that the differences were sufficiently minor such that their inclusion would have a minimal impact on clinical heterogeneity. Therefore, the ERG decided to perform a network meta-analysis for the primary

outcome measure, including the 4 key trials identified by the manufacturer and the 2 studies considered inclusive by the ERG.

4.19 Results from the network meta-analysis performed by the ERG suggest that bevacizumab in combination with carboplatin and gemcitabine is associated with a statistically significant improvement in duration of PFS compared with all comparators listed in the final scope (bevacizumab in combination with carboplatin and gemcitabine compared with: paclitaxel plus carboplatin, HR 0.47, 95% credible interval (CrI) 0.33 to 0.66; pegylated liposomal doxorubicin hydrochloride plus carboplatin, HR 0.58, 95% CrI 0.39 to 0.82; platinum monotherapy, HR 0.35, 95% CrI 0.25 to 0.47; gemcitabine plus carboplatin, HR 0.48, 95% CrI 0.38 to 0.60). Results from the network meta-analysis also suggest that there were no statistically significant differences between most of the remainder of the comparators. The ERG highlighted that this analysis was exploratory and results should be interpreted with caution. The ERG was uncertain about the direction of the overall bias in the analysis. Table 4 shows results from the network meta-analysis.

Table 4: Results from the network meta-analysis on PFS performed by the ERG

Comparison	HR	95% CrI	
		Lower limit	Upper limit
Versus paclitaxel plus carboplatin (HR<1 favours comparator, HR>1 favours paclitaxel plus carboplatin)			
PLDH plus carboplatin	0.82	0.72	0.93
Platinum as monotherapy	1.35	1.18	1.55
Gemcitabine plus carboplatin	0.98	0.75	1.26
Bevacizumab added to gemcitabine plus carboplatin	0.47	0.33	0.66
Versus PLDH plus carboplatin (HR<1 favours comparator, HR>1 favours PLDH plus carboplatin)			
Platinum as a monotherapy	1.66	1.37	1.98
Gemcitabine plus carboplatin	1.20	0.89	1.58
Bevacizumab added to gemcitabine plus carboplatin	0.58	0.39	0.82
Versus platinum monotherapy (HR<1 favours comparator, HR>1 favours platinum monotherapy)			
Gemcitabine plus carboplatin	0.72	0.58	0.89
Bevacizumab added to gemcitabine plus carboplatin	0.35	0.25	0.47
Versus gemcitabine plus carboplatin (HR<1 favours comparator, HR>1 favours gemcitabine plus carboplatin)			
Bevacizumab added to gemcitabine plus carboplatin	0.48	0.38	0.60

Abbreviations: CrI, Credible Interval; HR, hazard ratio; PLDH, pegylated liposomal doxorubicin hydrochloride

Source: ERG report, table 21, page 75

5 Comments from other consultees

5.1 The professional groups stated that the key treatments used in platinum-sensitive and partially platinum-sensitive patients are carboplatin and paclitaxel; carboplatin and gemcitabine; carboplatin and pegylated liposomal doxorubicin hydrochloride; carboplatin monotherapy alone; cisplatin (in patients allergic to carboplatin); pegylated liposomal doxorubicin hydrochloride alone. Pegylated liposomal doxorubicin hydrochloride, in combination with

trabectedin, is also considered a key treatment for partially platinum-sensitive patients, specifically for those who are allergic to platinum.

5.2 The professional groups acknowledged that bevacizumab would represent an additional treatment rather than an alternative treatment considering the available treatment options. Bevacizumab would be a concomitant treatment delivered jointly with chemotherapy and continued as maintenance treatment. The professional groups also acknowledged that there is no current standard treatment option for the maintenance stage. The professional groups highlighted that the main strengths of bevacizumab in platinum-sensitive patients are the extension of PFS and the increasing percentage of tumours that respond to the treatment. The professional groups noted that there is variation in access to bevacizumab as a first-line treatment for advanced ovarian cancer in England.

5.3 The professional groups noted that, apart from the classification depending on relapse stage, the key prognosis variable is tumour histology. The professional groups commented that tumours with clear cell or mucinous histology could benefit or respond less well to chemotherapy. The professional groups noted that this specific subgroup of patients was not excluded from entry into the OCEANS trial. Therefore, the professionals groups concluded that it is not possible to derive the clinical effectiveness of the treatment in relation to the tumour histology of the patient from the evidence provided in the OCEANS trial.

5.4 Patient groups highlighted that the main advantage of bevacizumab was in extending PFS. Giving bevacizumab to patients as part of their treatment would make patients feel that they were receiving

the best possible chance of prolonging the disease interval. Patient groups noted that once the cancer relapses, further recurrence is expected, which has a significant impact on women in terms of their emotional and mental health, and physical wellbeing. Therefore, improving PFS would allow woman to recover from the emotional impact of recurrence and enable a better physical recovery to successfully undergo subsequent treatments. Patient groups mentioned that increasing treatment choices makes women feel more involved in making decisions about the care and treatments they receive.

5.5 Patient groups also noted that the major disadvantages of using bevacizumab would be the potential side-effects associated with it and the likelihood of needing frequent visits to the hospital. Patient groups commented that there is a possibility of patients experiencing side-effects over a longer period because of maintenance with bevacizumab.

5.6 The professional groups highlighted that the use of bevacizumab would have implications in the NHS. Firstly, treatment time would increase by 1 hour on average every 3 weeks (bevacizumab is given over 90 minutes for the first infusion, reduced to 1 hour for subsequent infusions). Secondly, during maintenance treatment, bevacizumab would be continued every 3 weeks until disease progression or toxicity. The professional groups noted that the median number of infusions in the OCEANS trial was 10 at the time of publication. Thirdly, there would be extra interventions (such as blood pressure and urine tests conducted every 3 weeks) that would need additional medical or nursing input.

6 Cost-effectiveness evidence

6.1 The manufacturer carried out a systematic review to identify cost-effectiveness publications and economic evaluations on the use of bevacizumab in the treatment of relapsed or recurrent ovarian cancer from the perspective of the NHS. Of the 9 publications identified, 2 published cost-effectiveness evaluations were initially considered relevant by the manufacturer. However, both studies were excluded because the analysis in the first study was based entirely on data in the first-line setting, and the cost estimates in the second study were based on a US setting (for further details, see table 26, section 7.1.2, page 107 of the manufacturer's submission).

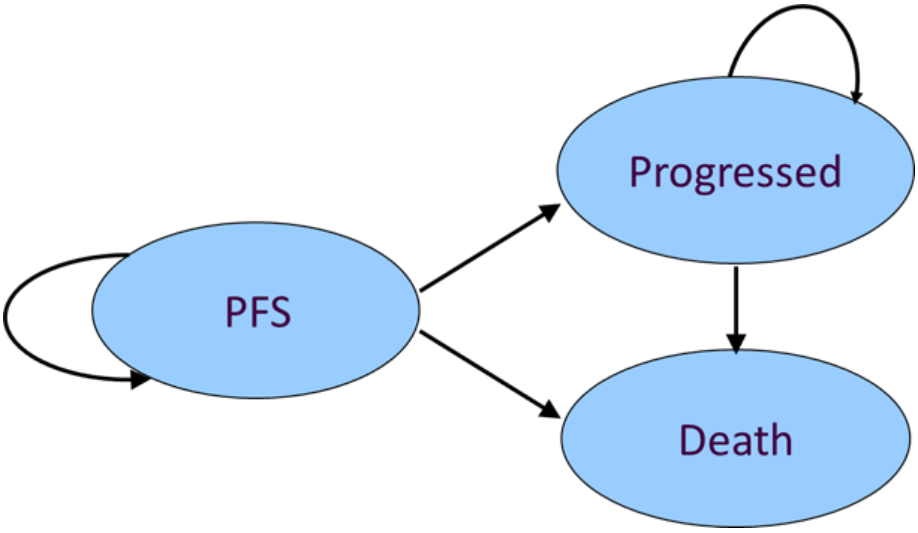
Manufacturer's economic model

6.2 The manufacturer submitted a de novo economic analysis that assessed the cost effectiveness of bevacizumab in combination with carboplatin and gemcitabine compared with placebo in combination with carboplatin and gemcitabine for the treatment of people with advanced, recurrent, platinum-sensitive ovarian cancer. Data from the OCEANS trial were used to guide model inputs. The manufacturer specified that, because the OCEANS study was undertaken in the US, it was likely that the patients had different baseline characteristics from the patients in the UK. Because the dose is dependent on characteristics (such us body weight, body surface area and creatinine clearance rates which are influenced by age), demographic data from the Sacco et al. (2010) study (which included 321 women treated for ovarian cancer in 3 UK centres in 2005) were used by the manufacturer in their base case to calculate the dose of bevacizumab, carboplatin and gemcitabine. The cost-effectiveness analysis was conducted from an NHS and Personal and Social Services perspective, costs and outcomes

were discounted at 3.5% per annum and a 10-year time horizon was used.

6.3 For the de novo economic analysis, the manufacturer developed a 3-state semi-Markov model with health states consisting of PFS, progressed disease (PD) and death (see figure 2). The cycle length was 1 week. The proportion of patients in each health state was derived from patient-level observations in the OCEANS trial (September 2010 clinical cut-off date for PFS and OS).The manufacturer fitted 2 separate parametric functions to the PFS and OS data. The proportion of patients in the PD health state was estimated by subtracting the proportion of patients with PFS from the proportion of patients with OS. The treatment duration was derived from observations in the OCEANS study (see table 42, section 7.5.5.6, page 152 of the manufacturer's submission). The manufacturer noted that this model structure and health states are typical of metastatic oncology economic models and have been used in previous NICE technology appraisals.

Figure 2: Model structure



6.4 PFS in the model used the Kaplan-Meier survival curves from the OCEANS trial based on the (ITT population) investigator-

assessment analysis (data cut-off date September 2010). The manufacturer examined the fit of various parametric functions to the progression-free data and considered a log-logistic model as the best fit to estimate and extrapolate the proportion of patients in the PFS health state. This proportion of patients was applied in the model at each corresponding week. The OS from OCEANS was used in the model to estimate the proportion of people in the PD health state and, implicitly, the death health state. The manufacturer also applied a log-logistic distribution to the Kaplan-Meier curves. Results from this extrapolation were weekly for the full-time horizon of the model. The manufacturer stated that because final OS data were not available, the first interim analysis (data cut-off September 2010) was chosen. The incidence of adverse events adopted in the model was derived from adverse events of at least grade 3 that occurred in more than 2% regardless of the study arm. Adverse events data were also taken from the OCEANS data (cut-off September 2010). The manufacturer used the number of patient events to assign a cost associated with each adverse event and assumed that all adverse events needing treatment occurred in the first week of the model; costs were therefore not discounted in the model.

Utility values

6.5 The manufacturer carried out a systematic review to identify health-state utility value studies relevant to the health states considered in the model. The manufacturer identified 9 of 35 studies as potentially relevant studies. However, these studies either did not collect utility data or did not report utilities associated with PFS and PD health states. Therefore, health-related quality of life and utilities applied in the model were obtained from the NICE technology appraisal Trabectedin for the treatment of relapsed

ovarian cancer (NICE technology appraisal guidance 222). The data used in technology appraisal 222 were taken from the OVA-301 trial using EQ-5D. The utility values used in the model for PFS and PD health states were 0.718 and 0.649 respectively. The manufacturer assumed in the model that health-related quality of life remained constant during PFS and reduced once disease progressed but also remained constant after that. The manufacturer did not apply disutilities in the model derived by the incidence of adverse events.

Costs

6.6 The manufacturer conducted a systematic review to identify published sources of UK resource data for patients with recurrent or relapsed advanced or metastatic ovarian cancer. Two studies were identified as potentially relevant. However, these studies did not provide enough information for use in the model. Demographic data from Sacco et al. (2010) were used to estimate the body weight of the patients in the model, to derive the drug dosages. For the price of bevacizumab and carboplatin, the manufacturer used public list prices from the BNF, and for the price of gemcitabine, drug price was obtained from the Commercial Medicines Unit (CMU) 2012 electronic Market Information Tool (eMit). Costs of drug administration were taken from the Unit Costs of Health and Social Care and NHS reference cost data. Carboplatin and gemcitabine preparation pharmacy time was assumed to be 12 minutes. The manufacturer stated that an additional 12 minutes of pharmacy time was needed for the preparation of bevacizumab infusion, however, an additional 6 minutes was the assumption used in the model. The manufacturer assumed vial sharing (that is, any unused drug from a vial is reallocated and not wasted) for

carboplatin and gemcitabine but not for bevacizumab. Table 5 shows the total intervention cost.

Table 5: Total intervention cost

	Drug cost per visit	Administration cost per visit	Pharmacy cost per visit	Total cost per visit
Bevacizumab				
Cost of bevacizumab, carboplatin and gemcitabine (cycle 1, first administration)	Bevacizumab: £2556.65 Carboplatin: £155.43 Gemcitabine: £21.53	£265.37	£4.60×3 =£13.80	£3012
Cost of gemcitabine (cycles 1 to 6, day 8)	Gemcitabine: £21.53	£85.07	£4.60	£111
Cost of bevacizumab, carboplatin and gemcitabine (cycle 2 to 6)	Bevacizumab: £2556.65 Carboplatin: £155.43 Gemcitabine: £21.53	£85.07	£4.60×3= £13.80	£2832
Cost of bevacizumab (cycle 7 onwards)	Bevacizumab: £2556.65	£85.07	£4.60	£2645
Placebo				
Cost of carboplatin + gemcitabine (cycle 1, first administration)	Carboplatin: £155.43 Gemcitabine: £21.53	£265.37	£4.60×3= £13.80	£456
Cost of gemcitabine (cycles 1 to 6, day 8)	Gemcitabine: £21.53	£85.07	£4.60	£111
Cost of carboplatin + gemcitabine (cycle 2 to 6)	Carboplatin: £155.43 Gemcitabine: £21.53	£85.07	£4.60×2= £9.20	£271

Source: Evidence Review Group report, table 48, page 121

6.7 The weekly costs of supporting patients in the PFS and progressed health states were included. Patients in the PD health state were assumed to have an outpatient review by a consultant oncologist approximately every 3 months. Resource use for supportive care was based on assumptions used in Trabectedin for the treatment of relapsed ovarian cancer (NICE technology appraisal guidance 222) and unit cost data were based on NHS reference costs. Total costs per weekly cycle were £44.08 and £10.31 for the PFS and PD health states respectively. Costs of palliative care were taken from Guest et al. (2006) and applied to patients as they transitioned to

the death health state. Costs of post-progression therapies were taken from the OCEANS trial (cut-off date of September 2010) and included other chemotherapy drugs, radiotherapy and/or surgery. These costs were added together and applied as a one-off cost in the model, and thus, were not subject to discounting. Total costs of post-progression treatments were £1553 and £2916 for patients in the bevacizumab and placebo treatment groups respectively (see the manufacturer's submission, section 7.5.8.1, page 156). These costs differ slightly from the costs of post-progression treatments included in the model (£1559 in the bevacizumab arm and £2828 in the placebo arm) because of small differences in the costs of chemotherapy. The ERG considered that the costs included in the model were likely to be correct. Costs associated with adverse events which occurred at grade 3 or 4 severity in more than 2% of patients from the OCEANS trial (cut-off date of September 2010) were incorporated into the analysis. NHS reference costs were utilised when possible and all adverse events were assumed to occur in cycle 1 of the model and so were not discounted. Table 44 in the manufacturer's submission (section 7.5.7, page 156) lists the adverse events and their costs. The total cost of treating adverse events in patients was £224 in the bevacizumab arm and £146 in the placebo arm.

6.8 The base-case results estimate that the addition of bevacizumab to carboplatin and gemcitabine provides an additional 0.298 quality-of-life years gained (QALYs) to patients with an expected survival of approximately 3 years. This benefit is achieved with an incremental cost of £44,428, resulting in an incremental cost-effectiveness ratio (ICER) of £149,050 per QALY gained for bevacizumab in addition to carboplatin and gemcitabine compared with carboplatin and gemcitabine alone. The base-case results, as

presented in the manufacturer's submission, are summarised in table 6.

Table 6: Manufacturer's base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Δcosts (£)	ΔLYG	Δ QALYs	ICER (£) versus (QALYs)
Placebo arm	£14,912	2.956	1.978				
Bevacizumab arm	£59,340	3.377	2.276	£44,428	0.420	0.298	£149,050

Source: Manufacturer's submission, table B11, section 7.7.5, page 168

6.9 The manufacturer undertook 1-way sensitivity analyses to explore the impact of changes in the base-case assumptions in the ICER. Results showed that the model was most sensitive to assumptions around the extrapolation of OS, the duration of treatment and the utility of patients in PFS (for further details see the manufacturer's submission, section 7.7.6, table 49, page 168). The manufacturer also presented scenario analyses examining the impact of vial sharing for bevacizumab and including demographic characteristics from OCEANS. The impact of these changes on the ICER was relatively small showing insensitivity of the model to different estimates. For the vial sharing scenario, the cost of bevacizumab is reduced to £2428 per dose leading to an ICER of £141,722 per QALY gained. Using the OCEANS demographic data, where mean body weight of women recruited was approximately 5 kg more than the mean weight of UK ovarian cancer patients (Sacco et al. [2010]), dose costs of bevacizumab, carboplatin and gemcitabine increased to £2762, £166.36 and £22.49 respectively. These changes resulted in an ICER of £160,561 per QALY gained (for further details see the manufacturer's submission, section 7.7.8, tables 51 and 52, pages 172 and 173).

6.10 The manufacturer also undertook probabilistic sensitivity analyses to explore uncertainty around the parameters of the model. The probability of bevacizumab in combination with carboplatin and gemcitabine being cost effective compared with carboplatin and gemcitabine alone at a threshold of £30,000 per QALY was 0.0%. (see manufacturer's submission, section 7.7.7, figure 22, page 170). The manufacturer concluded that the key drivers of the cost-effectiveness results were the cost and duration of treatment with bevacizumab and the time horizon of the analysis.

ERG comments and exploratory analysis

6.11 The ERG considered that the manufacturer's model structure was appropriate to describe the decision problem, was well constructed and transparent. However, the ERG identified a number of minor errors in the model and inconsistencies between the numbers reported in the manufacturer's submission and the model. The ERG conducted additional analyses to correct for these errors (see table 62, page 142 in the ERG report). The resulting ICER was estimated to be £147,368 per additional QALY.

6.12 The ERG highlighted and agreed with the manufacturer that the main criticism of the submitted economic evaluation was the use of September 2010 OCEANS clinical-effectiveness, cost, and adverse event incident data. The ERG believed that the use of data from September 2010, when 29% of the patients had died (rather than data from March 2012, where available, when 59% of patients had died) may introduce unnecessary uncertainty in the estimate of the ICER and may have overestimated the OS benefit associated with bevacizumab. The ERG noted that analysis of OS in September 2010 showed a non-statistically significant OS increase for patients in the bevacizumab group, which was not sustained in the 2 later interim analyses. The ERG found that OS was a key driver in the

model and estimated that approximately 90% of the QALYs gained in the model were a function of the OS. The ERG was unable to model OS using March 2012 data because the manufacturer did not provide the necessary data. Instead, the ERG conducted a scenario analysis assuming that OS was the same for patients in both treatment groups. The results of the analysis was an increase in the ICER to over £1.7 million per QALY gained.

6.13 The ERG noted that adverse events experienced by patients in the model were not subject to estimates of disutility. The manufacturer mentioned that serious adverse events were expected to result in either a short- or long-term detriment to health-related quality of life. The ERG suggested that not applying disutilities associated with adverse events was likely to favour the cost-effectiveness of bevacizumab, because a larger proportion of patients in the bevacizumab treatment group experienced an adverse event compared with the placebo group in the OCEANS trial. Therefore, the ERG investigated the impact of applying disutilities associated with adverse events in a scenario analysis (for source of disutilities used in the ERG scenario analysis, see table 42, page 115 in the ERG report). The ERG assessed a range of average duration of adverse events disutilities and concluded that, for example, for an average event duration of 1 week, the ICER increased to £149,391 per QALY gained, and for an average adverse event duration of 1 month, the ICER increased to £150,544 per additional QALY.

6.14 The ERG revised the base case of the manufacturer's cost-effectiveness results incorporating model corrections and the following scenarios:

- PFS estimated using Kaplan-Meier data rather than parametric extrapolation (for further details about why this scenario was selected, see pages 96–102 of the ERG report)
- including the cost of 1000 mg of gemcitabine from the BNF rather than from the CMU eMit
- assuming no vial sharing of gemcitabine and carboplatin
- including (as per clinical advice) 25 minutes pharmacy time per infusion.

The revised base-case ICER was estimated to be £148,360 per QALY gained in the deterministic analysis and £212,079 (2.5% and 97.5% percentiles –£314,539 to £982,628) per QALY gained in the probabilistic analysis. Table 7 shows the cost-effectiveness results for each scenario conducted by the ERG.

Table 7: Cost-effectiveness results based on ERG scenario analyses

Analysis	Intervention	Total costs	Total QALYs	Δ costs	Δ QALYs	ICER for individual scenario	ICER including model corrections
Manufacturer's base case (deterministic)	**Placebo**	**£14,912**	**1.98**	**£44,428**	**0.30**	**£149,050**	N/A
	Bevacizumab	**£59,340**	**2.28**				
Modelling PFS using only Kaplan–Meier data	Placebo	£14,834	1.98	£44,398	0.30	£149,539	£147,851
	Bevacizumab	£59,232	2.27				
Assuming OS was the same for placebo as bevacizumab	Placebo	£15,068	2.25	£44,272	0.03	Over £1.7 million	Over £1.7 million
	Bevacizumab	£59,340	2.28				
Cost of gemcitabine 1000 mg at £162 (BNF)	Placebo	£17,839	1.98	£44,450	0.30	£149,124	£147,411
	Bevacizumab	£62,289	2.28				

Assuming no vial sharing of gemcitabine and carboplatin	Placebo	£17,181	1.98	£44,445	0.30	£149,108	£147,402
	Bevacizumab	£61,626	2.28				
Including 25 minutes pharmacy preparation time per infusion	Placebo	£15,149	1.98	£44,672	0.30	£149,868	£147,841 (excluding analysis 5 in table 62 in the ERG report)
	Bevacizumab	£59,821	2.28				
Applying costs of adverse events from TA222[a]	Placebo	£15,010	1.98	£44,460	0.30	£149,160	£147,447
	Bevacizumab	£59,471	2.28				
Applying cost of hypertension using overall average activity cost from NHS reference costs (£1225)	Placebo	£14,916	1.98	£44,557	0.30	£149,482	£147,793
	Bevacizumab	£50,472	2.28				

[a] Trabectedin for the treatment of relapsed ovarian cancer (NICE technology appraisal guidance 222)

Abbreviations: BNF, British National Formulary; ICER, incremental cost-effectiveness ratio; N/A, not applicable; NHS, National Health Service; OS, overall survival; QALYs, quality-adjusted life years.

Source: ERG report, table 64, page 144

6.15 The ERG also noted that omission of comparison with the full list of comparators outlined in the scope was a key limitation of the analysis. The ERG explored the impact of the network meta-analysis results in terms of cost effectiveness of adding bevacizumab to carboplatin and gemcitabine compared with: paclitaxel in combination with a platinum-based therapy; pegylated liposomal doxorubicin hydrochloride in combination with platinum-based therapy; and platinum-based monotherapy. The ERG assumed, based on network meta-analysis results, that OS and PFS estimates for patients in every comparator group to be the same as for patients in the placebo group in the manufacturer's

model. This yielded to a bias in the cost effectiveness of bevacizumab in combination with carboplatin and gemcitabine compared with carboplatin monotherapy. Carboplatin and gemcitabine therapy was associated with a statistically significant increase in PFS compared with carboplatin alone, and therefore the number of additional QALYs associated with bevacizumab was likely to be underestimated leading to an overestimated ICER. Table 9 shows cost-effectiveness results from the ERG exploratory analysis based on the network meta-analysis.

Table 9: Cost-effectiveness results from the ERG exploratory analysis

Intervention	Total costs	Total LYG	Total QALYs	Δ costs	Δ LYG	Δ QALYs	ICER (Δ cost per Δ QALY)
Carboplatin	£13,329	3.14	1.98	–	–	–	–
Bevacizumab, gemcitabine and carboplatin	**£60,617**	**3.62**	**2.27**	**£47,288**	**0.48**	**0.30**	**£159,273**
Paclitaxel plus carboplatin	£16,672	3.14	1.98	–	–	–	–
Bevacizumab, gemcitabine and carboplatin	**£60,616**	**3.62**	**2.27**	**£43,945**	**0.48**	**0.30**	**£148,014**
Pegylated liposomal doxorubicin hydrochloride plus carboplatin	£17,382	3.14	1.98	–	–	–	–
Bevacizumab, gemcitabine and carboplatin	**£60,617**	**3.62**	**2.27**	**£43,234**	**0.48**	**0.30**	**£145,621**

Source: Evidence Review Group report, tables 67–69, pages 150 and 151

7 Equalities issues

7.1 No equality issues were identified during scoping consultation or in the evidence submitted.

8 End-of-life considerations

8.1 The manufacturer did not make any statement about the end-of-life considerations.

9 Innovation

9.1 The manufacturer stated that bevacizumab is the first licensed anti-VEGF targeted therapy in ovarian cancer. Bevacizumab directly targets VEGF-driven angiogenesis to reduce vascularisation of the tumour and thereby inhibit tumour growth.). The manufacturer also added that its adverse events profile allows it to be combined with cytotoxic chemotherapies without providing an intolerable additional burden of toxicity. Therefore, the manufacturer considered that bevacizumab provides an innovative step-change in the management of ovarian cancer.

10 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Ovarian cancer: the recognition and initial management of ovarian cancer. NICE clinical guideline 122 (2011).
- Trabectedin for the treatment of relapsed ovarian cancer. NICE technology appraisal guidance 222 (2011).
- Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for the treatment of advanced ovarian cancer (review of TA28, TA45 and TA55 [for relapsed disease only]). NICE technology appraisal guidance 91 (2005).
- Guidance on the use of paclitaxel in the treatment of ovarian cancer (review of TA03). NICE technology appraisal 55 (2003).

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Bevacizumab in combination with paclitaxel and carboplatin for the treatment of first-line advanced ovarian cancer. NICE technology appraisal guidance (publication expected April 2013).
- Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for the treatment of advanced recurrent ovarian cancer (including review of technology appraisal 91 and technology appraisal 222). NICE technology appraisal guidance (publication expected February 2014).
- Vintafolide in combination with pegylated liposomal doxorubicin hydrochloride for the treatment of folate receptor positive, platinum-resistant ovarian cancer. NICE technology appraisal guidance (publication expected July 2014).

Appendix B: Clinical efficacy section of the draft European public assessment report

The European public assessment report for bevacizumab was published on 24 January 2006 and is available from: www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000582/human_med_000663.jsp&mid=WC0b01ac058001d124&murl=menus/medicines/medicines.jsp&jsenabled=true