

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Bevacizumab in combination with paclitaxel and carboplatin for the first-line treatment of 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

- The summary of product characteristics for bevacizumab states that 'the recommended dose of bevacizumab is 15 mg/kg of body weight given once every 3 weeks'. The European Medicines Agency concluded that there was insufficient evidence of an acceptable balance of clinically relevant benefit to risk at the lower dose (7.5 mg/kg) used in the ICON7 study. Therefore, NICE is unable to produce guidance for the unlicensed dose of 7.5 mg/kg.

Clinical effectiveness

- The Gynaecology Oncology Group (GOG)-0218 trial included a patient population as defined by the scope and used the licensed dose of 15 mg/kg, but the trial was conducted in North America and Asia. The results suggest a significant benefit in each of the 3 patient groups by disease stage. What is the Committee's view on the generalisability of the GOG-0218 trial to UK practice?
- The ICON7 trial was conducted in Europe (including UK). However, it was an open-label trial, used an unlicensed dose of bevacizumab and it

included patients with high-risk early stage ovarian cancer in addition to patients with advanced ovarian cancer. What is the Committee's view on this trial? Is the trial outside the scope of this appraisal?

- The ICON7 trial pre-planned subgroup is made up of 31% of the trial population and includes resected stage IV patients and stage III patients with more than 1 cm residual disease. Does the Committee consider the patients in the subgroup analyses to match those defined in the scope?
- In the GOG-0218 trial, progression-free survival (PFS) was assessed by the investigator based on the Response Evaluation Criteria in Solid Tumours (RECIST) criteria or using rising serum anticancer antigen 125 (CA-125). The primary regulatory analysis used data where patients with disease progression based on CA-125 criteria alone were censored (see section 4.7). The ERG commented that CA-125 measurement is commonly used in the UK for disease progression. Which data for progression-free survival does the Committee view as the most appropriate and relevant to UK practice?

Cost effectiveness

- PFS results from the GOG-0218 trial have been presented both with and without censoring (see section 4.7). Which PFS data does the Committee consider most appropriate to be used in the model?
- Crossover was permitted in the GOG-0218 trial and the manufacturer stated that the latest data indicate that 40% of patients in the control arm had received bevacizumab in their subsequent therapy. Overall survival results from the trial have shown no significant difference between the arms. The model assumed a constant rate of death post progression for both treatments which resulted in a 2 month overall survival benefit in favour of bevacizumab. Does the Committee consider this approach to modelling overall survival to be appropriate?

- The manufacturer has used utility values from the ICON7 trial for the GOG-0218 base-case model. Does the Committee consider the utility values used to be appropriate?
- The treatment duration used in the model was 1 year, rather than 15 months as stated in the summary of product characteristics. The time horizon was 10 years and not a lifetime horizon. These parameters were re-run by the ERG. What does the Committee consider to be most appropriate for the base-case estimate?

1 Background: clinical need and practice

- 1.1 Ovarian cancer is a common gynaecological cancer. 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 of the ovary. Fallopian tube cancer and primary peritoneal cancer are histologically equivalent diseases to epithelial ovarian cancer; International Federation of Gynecology and Obstetrics (FIGO) recommend that treatment for these cancers follows the guidance for epithelial ovarian cancer. According to the FIGO classification system, ovarian cancer is classified into the following stages:
- stage I, when the cancer is confined to 1 or both ovaries
 - stage II, when ovarian cancer has spread beyond the ovaries to the uterus, fallopian tubes or other areas in the pelvis
 - stage III, when the cancer has spread beyond the pelvis into the abdominal cavity (IIIA), grown up to 2 cm in size (IIIB), grown more than 2 cm in size or affects the para-aortic lymph nodes (IIIC)
 - stage IV, when ovarian cancer is defined by distant metastases (that is, the cancer has spread into other body organs such as the liver or lungs).

- 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 is predominantly a disease of older women with over 80% of cases being diagnosed in women over 50 years.
- 1.3 Survival for ovarian cancer has improved over the last 35 years, but long-term rates are still low. For women diagnosed in England during 2005–09, the 1- and 5-year age-standardised relative survival rates are 72.3% and 42.9% respectively. There were about 4300 deaths from ovarian cancer in the UK in 2010.
- 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.

2 The technology

- 2.1 Bevacizumab (Avastin, Roche) is a humanised monoclonal antibody that inhibits both vascular endothelial growth factor (VEGF)-induced signalling and VEGF-driven angiogenesis. This reduces vascularisation of tumours, thereby inhibiting tumour growth. Bevacizumab is administered by intravenous infusion. Bevacizumab in combination with carboplatin and paclitaxel has a marketing authorisation for ‘the front-line treatment of advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or

primary peritoneal cancer'. The licensed dose is 15 mg/kg body weight given once every 3 weeks in addition to carboplatin and paclitaxel for up to 6 cycles of treatment, followed by continued use of bevacizumab as single agent until disease progression or for a maximum of 15 months or until unacceptable toxicity is reached, whichever occurs earlier.

- 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 bevacizumab (excluding VAT and assuming wastage) to be £36,078 for a patient weighing 65 kg at a dosage of 15 mg/kg every 3 weeks, amounting to an average monthly cost of £2577. 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 in combination with paclitaxel and carboplatin for the first-line treatment of ovarian cancer.

	Final scope issued by NICE
Population	Women with advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian cancer, fallopian tube or primary peritoneal cancer, who have not received prior chemotherapy for ovarian cancer, fallopian tube or primary peritoneal cancer.
Intervention	Bevacizumab in combination with paclitaxel and carboplatin
Outcomes	The outcome measures to be considered include: <ul style="list-style-type: none"> • overall survival • progression free 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.
Other considerations	If the evidence allows, consideration should be given to subgroups of people defined by the presence or absence of residual disease. Guidance will only be issued in accordance with the marketing authorisation.
FIGO, Federation of Gynecology and Obstetrics	

3.2 The manufacturer’s approach to the decision problem was in line with the NICE scope for the population, intervention, outcomes, economic analysis and subgroups considered.

	Final scope issued by NICE	Decision problem addressed in the submission
Comparators	Platinum-based chemotherapy (cisplatin or carboplatin with or without paclitaxel) without bevacizumab	The comparator in the submission is carboplatin with paclitaxel.

3.3 The manufacturer’s rationale for the focus on chemotherapy with carboplatin and paclitaxel as the comparator was because it is the internationally recognised standard therapy for first-line treatment

of advanced ovarian cancer and it was also used as the comparator regimen in both clinical trials for bevacizumab in this setting. The ERG confirmed that this is 1 of the recommended platinum-based treatment options for advanced ovarian cancer in the UK.

4 Clinical-effectiveness evidence

4.1 The manufacturer conducted a literature search and identified 2 randomised trials (GOG-0218 and ICON7) that investigated the effect of bevacizumab in combination with carboplatin and paclitaxel as a first-line treatment for people with advanced ovarian cancer.

GOG-0218 trial

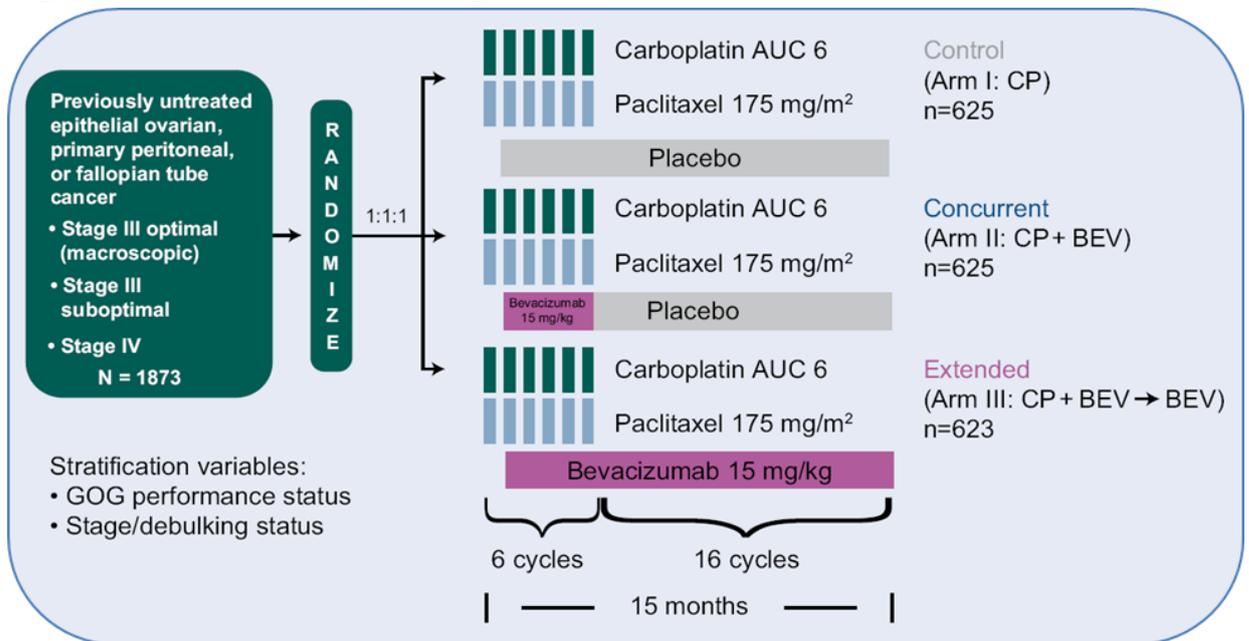
4.2 GOG-0218 was a randomised, double-blinded, placebo-controlled multicentre trial conducted in North America and Asia in 1873 patients with previously untreated stage III (incompletely resectable) or stage IV epithelial ovarian cancer who had undergone debulking surgery. Patients were randomised to 1 of 3 treatment arms (see figure 1):

- CPP group (n=625) received standard chemotherapy (carboplatin at an area under the curve of 6 and paclitaxel 175 mg/m² every 3 weeks for 6 cycles) plus placebo for cycles 2 to 22
- CPB15 group (n=625) received standard chemotherapy as the CPP group plus concurrent bevacizumab (15 mg/kg) for cycles 2 to 6 and placebo as monotherapy for cycles 7 to 22
- CPB15+ group (n=623) received standard chemotherapy as the CPP group every 3 weeks for 6 cycles plus bevacizumab (15 mg/kg) for cycles 2 to 22.

Cycles were of 3 weeks duration and treatment was discontinued at the onset of disease progression, unacceptable toxic effects, completion of all 22 cycles or withdrawal. Patients in the placebo arm were allowed to crossover after disease progression.

Randomisation was stratified for GOG performance status (0 versus 1 versus 2) and disease stage (optimally debulked stage III, suboptimally debulked stage III and stage IV). Exclusion criteria included central nervous system disease, significant cardiovascular disease or other invasive malignancies. Full details of the inclusion and exclusion criteria are presented in the manufacturer’s submission (see table 5, page 47).

Figure 1 GOG-0218 study design



Source: Manufacturer’s submission, page 43

4.3 The primary outcome was PFS, defined as the period from randomisation to disease progression or death. Progression was assessed by the investigator based on any of the following measures: global clinical deterioration, RECIST criteria and rising serum CA-125. CA-125 progression was defined as greater than or equal to twice the nadir or upper limit of normal. Secondary

outcomes were overall survival and objective response rate. Sensitivity analyses of progression-free survival included an Independent Review Committee (IRC) review and PFS which was not censored by CA-125 progression. Safety outcome measures were the frequency and severity of adverse events. Quality of life was measured using the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) questionnaire, the Ovarian Cancer Subscale measure and abdominal discomfort score.

4.4 Results presented in the manufacturer's submission were obtained from an intention-to-treat analysis which included all patients randomized to a study treatment. Progression-free survival in each bevacizumab arm (CPB15 and CPB15+) was compared to the control arm (CPP) using a 1-tailed test and applying Dunnett's procedure to account for multiple comparisons. Progression-free survival was analysed using a stratified log-rank test with initial GOG status and disease stage (optimally debulked stage III, suboptimally debulked stage III and stage IV) as stratification factors and an unstratified log-rank test. Kaplan-Meier methodology was used to estimate median PFS in each arm. For most of the subgroup analyses of PFS the results for the bevacizumab arms were pooled. Further details of the approach to the statistical analysis of the other outcomes can be found in the manufacturer's submission, pages 65–68.

4.5 In the GOG-0218 trial, approximately one-third of patients (n=639; 34.1%) had stage III macroscopic optimally debulked disease, 751* patients (40.1%) had stage III suboptimally debulked disease, and 483* patients (25.8%) had stage IV disease. The majority of

* There are some very small differences between the numbers in the submission and the published paper by Burger et al. (2011).

patients (1591* patients; 84.9%) had serous adenocarcinoma. Approximately two-thirds of patients (1192 patients; 63.6%) had measurable disease at baseline. At study entry, most patients (1768 patients; 94.4%) had CA-125 values higher than the upper limit of normal. Baseline characteristics* for patients in the GOG-0218 trial are presented in the manufacturer's submission (see section 6.3.3 and table 6, page 49-51).

- 4.6 Of the 1873 randomised patients, 9 patients (4 in the CPP arm, 1 in the CPB15 arm, 4 in the CPB15+) did not receive any study treatment. In the study, 68% of patients discontinued the treatment prematurely (n=456: 73% in CPP, n=457: 73% in CPB15 and n=365: 59% in CPB15+) and the most common reason was disease progression (n=310: 50% in CPP, n=270: 43% in CPB15 and n=173: 28% in CPB15+). Adverse event complications resulted in treatment discontinuation in 11% of patients in the control group, 14% in the CPB15 group and 16% in the CPB15+ group. A CONSORT flow chart is presented by the manufacturer in their submission (see manufacturer's submission, figure 4, page 75).
- 4.7 Analysis of the primary outcome (PFS in the intention-to-treat (ITT) population [by investigator assessment]) was based on a cut-off date of 29 September 2010. For the regulatory efficacy analysis patients with disease progression based on CA-125 criteria alone and patients who received non-protocol therapies were censored, that is, excluded from the analysis. Using the CA-125 and non-protocol therapy censored data, there was a statistically significant improvement in the median PFS of 6 months in the CPB15+ arm compared to the CPP arm (CPP: 12 months, CPB15+: 18 months,

* There are some very small differences between the numbers in the submission and the published paper by Burger et al. (2011).

hazard ratio [HR]: 0.645, 95% confidence interval [CI] 0.551 to 0.756, $p < 0.001$). There was a 0.7 month increase in the median PFS in the CPB15 arm compared to the control arm (CPP: 12 months, CPB15: 12.7 months, HR: 0.84 (95% CI 0.71 to 0.99, $p = 0.0204$). The manufacturer's submission also presents an IRC analysis of PFS on the same data and two further analyses of PFS without censoring from data taken at February 2010 and August 2011. All these results are shown in table 1. The Kaplan-Meier plot (figure 6 of the manufacturer's submission, page 81) showed a separation of the curves in favour of the CPB15+ which was maximal after the end of bevacizumab therapy.

Table 1: Median PFS for the different analyses from Study GOG-0218 (ITT population)

		CPP (n=625)	CPB15 (n=625)	CPB15+ (n=623)
Investigator assessed ¹ (censored)	Median PFS months	12.0	12.7	18.0
	Stratified hazard ratio (95% CI)		0.84 (0.71 to 0.99)	0.645 (0.551 to 0.756)
	P value		0.0204	<0.001
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IRC ¹ (censored)	Median PFS months	13.1	13.2	19.1
	Stratified hazard ratio (95% CI)		0.93 (0.76 to 1.13)	0.62 (0.50 to 0.77)
	P value		0.222	<0.0001
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Investigator assessed ² (not censored)	Median PFS months	10.3	11.2	14.1
	Stratified hazard ratio (95% CI)		0.908 (0.795 to 1.040)	0.717 (0.625 to 0.824)
	P value		0.16	<0.0001
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Investigator assessed ³ (not censored) Updated	Median PFS months	n/a	n/a	n/a
	Stratified hazard ratio (95% CI)		n/a	0.77 (0.681 to 0.870)
	P value			n/a
¹ Independent Review Committee; Final analysis, September 2010 ² Primary analysis, February 2010 ³ Updated analysis, August 2011 n/a not available CI, confidence interval; CPB, carboplatin, paclitaxel and bevacizumab (bevacizumab up to cycle 6); CPP, carboplatin, paclitaxel and placebo; CPB15+, carboplatin, paclitaxel and bevacizumab (bevacizumab up to cycle 22); PFS, progression-free survival. Source: ERG report, page 23				

4.8 Exploratory subgroup analyses of PFS using baseline risk factors were also reported by the manufacturer. Results from these analyses are presented for the CPP group compared with a combined CPB15 and CPB15+ group and are consistent with the

primary analysis. Hazard ratios of less than 1 and the median PFS close to the 6 month benefit are reported in the primary analysis. Subgroup analysis by disease stage (optimally debulked stage III, suboptimally debulked stage III and stage IV) and debulking status are presented (manufacturer’s submission, table 14, page 84) which show a statistically significant increase in PFS for all stages of disease when CPB15+ is compared with CPP alone. No significant increase was shown for the CPB15 arm.

4.9 The overall survival analysis was calculated when 46.9% of patients had died. The median overall survival was 3.2 months longer in the CPB15+ arm compared to the CPP arm (CPP: 40.6 months; CPB15+ months: 43.8 months, hazard ratio 0.88 (95% CI 0.75 1.04), p=0.0641) however this was not statistically significant at the p-value boundary of 0.0116. The objective response rate according to the investigator assessment was not statistically different between the arms (63.4% in the CPP arm, 66% in the CPB15+ arm, p=0.204). A significant increase in the objective response rate was observed in the IRC analysis (68.8% in the CPP arm, 77.4% in the CPB15+ arm, p<0.0012) (for further details see table 16, page 85 of the manufacturer’s submission).

Table 2: Overall survival for Study GOG-0218 (ITT population)

	CPP (n=625)	CPB15 (n=625)	CPB15+ (n=623)
Median months	40.6	38.8	43.8
Hazard ratio		1.07	0.88
(95% CI)		(0.91, 1.25)	(0.75, 1.04)
P value		0.2197	0.0641
CI, confidence interval; CPB, carboplatin, paclitaxel and bevacizumab (bevacizumab up to cycle 6); CPB15+, carboplatin, paclitaxel and bevacizumab (bevacizumab up to cycle 22); CPP, carboplatin, paclitaxel and placebo			

Source: ERG report, page 24

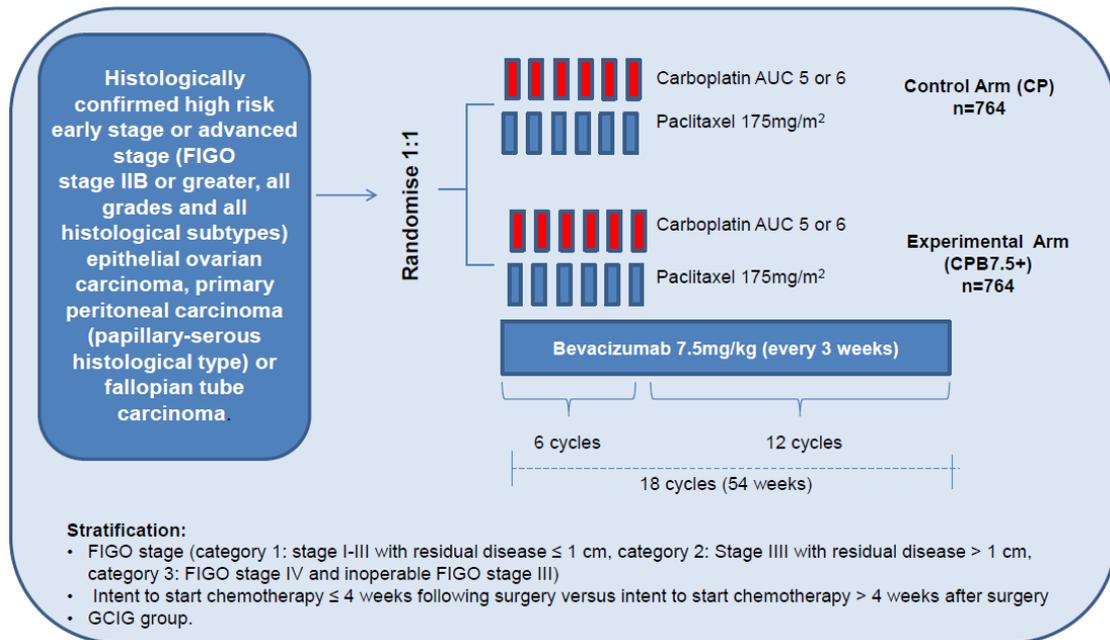
ICON7 trial

4.10 ICON7 was a randomised open-label multicentre study conducted in Europe in 1528 patients with high-risk early stage or advanced stage IV epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer. Patients were randomised to 1 of 2 treatment arms (see figure 2):

- the CP control group (n=764) received standard chemotherapy (carboplatin at an area under the curve of 5 or 6 and paclitaxel 175 mg/m² every 3 weeks for 6 cycles)
- the CPB7.5 arm (n=764) received standard chemotherapy plus concurrent bevacizumab (7.5 mg/kg) every 3 weeks for 6 cycles and continued for an additional 12 cycles or until disease progression.

Randomisation was stratified for disease stage (category 1: FIGO stage I–III with residual disease less than 1 cm, category 2: FIGO stage I–III with residual disease more than 1 cm, category 3: FIGO stage IV and inoperable FIGO stage III) and the time of initiation of chemotherapy (intent-to-start chemotherapy less than or equal to 4 weeks after surgery, compared with intent-to-start chemotherapy more than 4 weeks after surgery). Patients received treatment until disease progression, unacceptable toxicity, or completion of 6 or 18 cycles of therapy as appropriate. No crossover was permitted. Full details of the inclusion and exclusion criteria are presented in the manufacturer's submission (see table 5, page 46–47).

Figure 2: ICON7 study design



4.11 The primary PFS outcome was based on RECIST criteria on the basis of radiological, clinical and symptomatic indicators of progression. Secondary outcomes were overall survival, objective response rate, duration of response and biological progression-free interval. Safety outcomes and quality of life assessments were also recorded.

4.12 There were 1528 patients enrolled in the ICON7 trial of whom only 81% had stage III or IV disease; 98% of patients had debulking surgery. A pre-planned 'high risk of progression' subgroup included resected stage IV patients and stage III patients with more than 1 cm residual disease and contained approximately 30% of the ICON7 trial population. In the GOG-0218 trial approximately 54% of patients had greater than 1 cm residual disease (see manufacturer's submission, table 6, page 50). The manufacturer stated that these patients in GOG-0218 had either resected stage IV or stage III disease (page 54 of the manufacturer's submission). Baseline characteristics for patients in the ICON7 trial are

presented in the manufacturer's submission (see section 6.3.3 and table 7, page 52).

- 4.13 Of the 1528 randomised patients, 19 patients (11 in the CP arm, 8 in the CPB7.5) did not receive any study treatment. In the study, 18% of patients discontinued the treatment prematurely (n=75 and 9.8% in CP; n=200 and 26.2% in CPB7.5). All of the patients in the CP arm were withdrawn during first 6 cycles of the trial when chemotherapy was administered; whereas in the CPB7.5 arm, 134 patients were withdrawn during the first 6 cycles and 66 withdrawn during the period when bevacizumab was administered alone. A CONSORT flow chart is presented by the manufacturer in the submission (see figure 5, page 76).
- 4.14 The intention-to-treat population analysis of the primary outcome demonstrated a statistically significant improvement in the median PFS of 2.4 months in the CPB7.5 arm compared to the CP arm (CP: 17.4 months, CPB7.5: 19.8 months, HR: 0.87, 95% CI 0.77 to 0.99, p=0.04). In the 'high risk of progression' subgroup, there was also a significant improvement in median PFS of 5.6 months in the CPB7.5 arm compared to the control arm (CPP: 10.5 months, CPB7.5: 16 months, HR: 0.73 (95% CI 0.60 to 0.93, p=0.002).

Table 3: Median progression-free survival from ICON7 trial

		CP (n=764)	CPB7.5+ (n=764)
ITT population	Median PFS months	17.4	19.8
	Hazard ratio		0.87
	(95% CI)		(0.77 to 0.99)
	P value		0.04
		CP (n=234)	CPB7.5+ (n=231)
Stage III suboptimal and stage IV debulking (‘high risk of progression’)	Median PFS months	10.5	16
	Hazard ratio		0.73
	(95% CI)		(0.60 to 0.93)
	P value		0.002
CI, confidence interval; CP, carboplatin and paclitaxel; CPB7.5+, carboplatin, paclitaxel and bevacizumab (bevacizumab up to cycle 18); PFS, progression-free survival.			

Source: ERG report, page 54

4.15 An interim analysis of overall survival after a median follow-up of 28 months was conducted when 47% of patients in the CP arm had died and 34% of patients in the CPB7.5 arm. In the ‘high risk of progression’ subgroup, there was a median overall survival improvement of 7.8 months in the CPB7.5 arm compared to the CP control arm (CP 28.8 months, CPB7.5 36.6 months; HR 0.64, 95% CI 0.47 to 0.85 p=0.002). The hazard ratio indicates a 36% reduction in risk of death in this group of patients treated with CPB7.5+ compared with CP patients. No results for the objective response rate are presented for this subgroup.

Table 4: Overall survival from ICON7 trial

		CP (n=764)	CPB7.5+ (n=764)
Early ITT population	Median months	Not reached	
	Hazard ratio (95% CI)		0.85 (0.69 to 1.04)
	P value		0.1167
		CP (n=234)	CPB7.5+ (n=231)
ICON7 stage III suboptimal debulking and stage IV	Median months	28.8	36.6
	Hazard ratio (95% CI)		0.64 (0.48 to 0.85)
	P value		n/a*
*Clarification requested from the manufacturer stated that the missing p value was not available (n/a) CI, confidence interval; CP, carboplatin and paclitaxel; CPB7.5+, carboplatin, paclitaxel and bevacizumab (bevacizumab up to cycle 18)			

Source ERG report, page 55

- 4.16 The manufacturer did not consider that a meta-analysis was appropriate because the GOG-0218 and ICON7 trials used different doses and durations of bevacizumab and different study populations.
- 4.17 Almost all patients in the GOG-0218 trial experienced at least 1 adverse event. Adverse events for which the incidence was greater than 10 per cent higher in the bevacizumab-containing arms than in the placebo arm were stomatitis, dysarthria, headache, epistaxis and hypertension. Adverse events of special interest (grade 3–5) that occurred with an incidence of at least 1 per cent greater in the CPB15+ arm compared to the CPP arm were hypertension, gastrointestinal perforation and non-central nervous system bleeding.
- 4.18 In the ICON7 trial, proportionally, more patients in the CPB7.5+ arm than in the CP arm experienced a grade 3–5 adverse effect (64.6% and 54.3% respectively), serious adverse effects (37.7% and 23.5% respectively) and adverse effects leading to treatment discontinuation (22.0% and 8.9% respectively). A greater

proportion of patients in the CPB7.5+ arm than in the CP arm (74% and 47.4% respectively) also experienced adverse effects of special interest to bevacizumab. Grade 3–5 adverse effects of special interest to bevacizumab in the overall safety population and in the ‘high risk of progression’ subgroup of patients were similar between groups. However, proportionally, more patients in the overall population and the high-risk subgroup experienced hypertension in the CPB7.5+ arm than in the CP arm. (Overall population: 6.0% in CPB7.5+ arm and 0.3% in the CP arm. High-risk subgroup: 7.8% in CPB7.5+ arm and 0.4% in CP arm.) Additionally in the high-risk subgroup, proportionally, more patients in the CPB7.5+ arm experienced wound healing complications than in the CP arm (6.7% and 0.4% respectively).

- 4.19 Health-related quality of life was collected in the GOG-0218 trial using the Trial Outcome Index of the FACT-O survey, which is a patient self-report measure at 5 time-points during the study and 6 months after completing study therapy. The manufacturer concluded that the bevacizumab-containing therapy produced some statistically significant disruptions during chemotherapy; however, these differences were small and were not clinically significant. No results for the health-related quality of life data are presented for the ‘high risk of progression’ subgroup in the ICON7 trial.

Evidence Review Group comments

- 4.20 The ERG considered the systematic review in the manufacturer’s submission to be of reasonable quality and the risk of systematic error in the review to be low. The ERG highlighted the review was wider than the NICE scope and included an additional study (ICON7) which does not meet the scope criteria. This study used a bevacizumab dose of 7.5 mg/kg body weight which is unlicensed

and the patient population does not match the scope. The ERG acknowledged that the 7.5 mg/kg body weight dose is in current clinical practice in the UK. The ERG restricted their review of the evidence to the GOG-0218 trial but added a commentary for information on the ICON7 trial as an appendix to their report.

- 4.21 The ERG considered the manufacturer's interpretation of the evidence from the GOG-0218 trial was appropriate and justified. The ERG was concerned that the different assessments of PFS (investigator assessed, IRC, CA-125 censored, CA-125 not censored) are not consistently reported for all time points. The ERG commented that there may have been selective reporting of data and it is not clear what impact this may have on conclusions. In response to clarification, the manufacturer stated that updated PFS data censored for CA-125 are not available; also, exploratory analyses were not updated as they were intended only to confirm the validity of investigator assessed PFS. Although the direction of evidence is consistent, the size of effect varies with the different analyses and over time; for example, the median PFS gain varied between 4 and 6 months; the hazard ratio varied from 0.62 (IRC assessed, data censored) to 0.77 (updated investigator assessed, without data censoring).
- 4.22 Clinical advice to the ERG suggested that CA-125 is used routinely in UK clinical practice and therefore, the ERG considered results not censoring for increased CA-125 to be of most relevance to the UK. The ERG stated that it appears from the results that not censoring for CA-125 gives a more conservative estimate of effectiveness because when there is no censoring for progression based on rises in CA-125 alone, more patients potentially at high risk of progression remain in the analysis and a higher proportion of

patients progress sooner compared to an analysis based on the censored data.

- 4.23 There was no difference in overall survival between the CPB15+ arm and the CPP arm, and the ERG noted that the manufacturer stated these overall survival results may be confounded as the GOG-0218 protocol did not exclude the control arm patients from crossing over to receive treatment with bevacizumab (the latest data shows 40% of CPP patients in the GOG-0218 study have now received bevacizumab in their subsequent therapy).
- 4.24 The ERG noted that data from the ICON7 study support the results from the GOG-0218 study for PFS both for the ITT population and for the 'high risk of progression' subgroup of patients. However, the 'high risk of progression' subgroup does not match the patient group in the GOG-0218 study (it only covers 2 of the patient groups: stage III suboptimal debulking and stage IV) and the definition of optimal debulking differs between the 2 studies. Clinical advice to the ERG was that current UK clinical practice is to give bevacizumab to patients with stage III residual disease with the aim of maintaining PFS for as long as possible.
- 4.25 Clinical advice to the ERG indicated that the adverse events associated with bevacizumab, including hypertension, are manageable in clinical practice. However the ERG suggested that the manufacturer's textual summary of the differences in adverse events between the arms of the GOG-0218 trial should be interpreted with caution. The manufacturer was only able to provide limited statistical data for the reported adverse events because of the way the data has been analysed. In their response to clarification, the manufacturer stated that the criteria used were

chosen as an 'arbitrary threshold' to highlight the main differences between the arms.

5 Comments from other consultees

- 5.1 The professional groups stated that in the UK, the first-line treatment of epithelial ovarian cancer is surgery followed by carboplatin or carboplatin with paclitaxel, where the cytotoxic chemotherapy is administered on a 3-weekly basis for 6 cycles. The professional groups commented that survival of advanced disease has remained poor for many years and new treatments are needed. The professional groups stated recent data have shown that delayed primary surgery in FIGO stage IIIC disease yields progression-free and overall survival statistics that equate with those obtained through the conventional approach where surgery occurs first. Professional groups agreed that approximately 3185 patients would be eligible for treatment with carboplatin, paclitaxel and bevacizumab in the first-line setting each year. Professional groups stated that patients with good performance status (ECOG 0–2) and FIGO stage IIIc or IV ovarian cancer with any residual disease after primary debulking surgery should be offered bevacizumab in addition to carboplatin and paclitaxel, provided there are no contraindications to bevacizumab therapy.
- 5.2 The professional groups commented that, although licensed at 15 mg/kg every 3 weeks for 15 months in this setting, the efficacy of the 2 doses of bevacizumab is identical in the matched subgroups of the 2 pivotal trials, ICON7 and GOG-0218, suggesting that the higher dose of 15 mg/kg every 3 weeks is unnecessary. Professional groups agreed that maintenance therapy is an important component of the effect of bevacizumab and treatment should continue until progression in patients with

residual disease; or for up to 15 months in patients who achieve a radiological and biochemical complete response.

5.3 Patient groups highlighted that there are very limited options for patients with advanced ovarian cancer and if, for whatever reason, the existing treatment is not deemed suitable for patients, then this leaves patients with no alternative choices, causing distress in patients. Including bevacizumab with paclitaxel and carboplatin as a treatment option provides an alternative which may also be more effective. The patient groups agreed that the approximate 3 month increase in progression-free survival and an approximate 8 month improvement in overall survival which has been reported in the ICON7 trial in patients treated with bevacizumab with paclitaxel and carboplatin compared with the standard treatment (paclitaxel and carboplatin) for ovarian cancer, may seem modest but to patients with advanced disease, this increase in survival is considered to be significant and may have a positive impact on the mental state of patients and their families.

5.4 Patient groups stated that the period after the end of first-line treatment is vital; this is the time when women really come to terms with their diagnosis and start to regain a sense of normality. Any extension of the period before relapse is welcome as it allows the woman to deal with ongoing emotional challenges, and resume elements of their life before diagnosis such as returning to work, and feel more in control. It was highlighted by the patient groups that maintenance therapy is new to ovarian cancer and patient groups agreed that the end of first-line treatment is a typically challenging time because, after months of close contact with their medical team, women often feel abandoned and cut off. Regular hospital appointments during the bevacizumab maintenance phase provided patients comfort and a greater sense of confidence as

they felt that any medical problems would be picked up and acted upon quickly. It was also stated that choice was very important for these patients and that women welcome the opportunity to be involved in making decisions about their care and treatments, as they are able to take some control at what is typically a very uncertain time for many of them.

- 5.5 Patient groups agreed that the disadvantages of time or financial costs incurred as a result of ongoing hospital visits were far outweighed by the potential and perceived benefits of receiving the treatment. Patient groups highlighted concerns that the relatively small improvement in survival may come at a cost to the patient's quality of life. All patient groups agreed that any increase in overall survival that this treatment enables, despite the side effects, may be worth it from a patient's point of view. Patient groups noted that patients with high blood pressure may benefit less from this technology as they may be at a greater risk of developing heart complications as a side effect.
- 5.6 The professional groups stated that the impact on the NHS would be that chemotherapy administration time would increase from 5 to 5.5–6.5 hours (bevacizumab is given over 1.5 hours for the first infusion and if tolerated, subsequent infusions can be administered over 30 minutes from the third infusion). Patients would receive approximately up to 15 months maintenance therapy. Given a 3-weekly cycle, this would mean an extra 11 to 15 hospital visits and infusions of bevacizumab over 30–90 minutes. The professional groups highlighted that data from the GOG-0218 study suggest that the prevalence of hypertension during maintenance of bevacizumab exceeds that in the combined cytotoxic chemotherapy and bevacizumab arm and therefore community medical input would be required to support the monitoring and

management of hypertension during the entire period that the patient receives bevacizumab.

6 Cost-effectiveness evidence

6.1 The manufacturer conducted a systematic review of the literature and identified 3 cost-effectiveness studies relating to bevacizumab for treating advanced or metastatic ovarian cancer. The manufacturer presented results from these studies (see pages 127-128 of manufacturer's submission) but no conclusions were given.

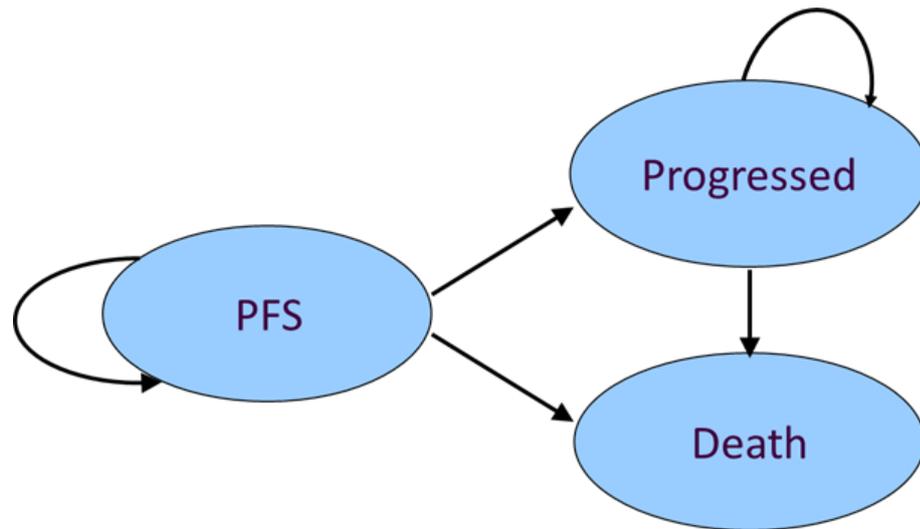
Manufacturer's economic model

6.2 The manufacturer submitted a de novo economic analysis that assessed the cost effectiveness of bevacizumab in combination with carboplatin and paclitaxel (CPB) compared with carboplatin and paclitaxel (CP) for first-line treatment in women with stage III or IV ovarian cancer. Data from the GOG-0218 trial were used to inform model inputs for dosing, survival and safety. Both the intervention and comparator in the model are implemented according to their marketing authorisations. The analysis was conducted from an NHS and Personal and Social Services perspective, the 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 and death (see figure 3). The manufacturer chose this structure because of the confounding of overall survival data in the trial as a consequence of the large proportion of patients randomised to the control arm who received bevacizumab after disease progression. With this model structure the analysis was based on a similar rate of death post progression in both arms. This means that the probability of death following progression was

constant between the two arms of the model irrespective of how long the patient spent in the progressed state. The manufacturer noted that this model structure and health states are typical of metastatic oncology economic models and has been used in previous NICE appraisals.

Figure 3: Model structure



- 6.4 Progression-free survival in the model uses the Kaplan-Meier survival curves from the GOG-0218 trial data up to the convergence of the intervention and comparator arms at month 28. The data used are the updated PFS analysis (February 2010) which includes censoring of patients who were presumed to experience progression based on rising CA-125 levels or who switched to non-protocol therapies. The manufacturer examined the fit of various parametric survival models to the progression-free data and considered a log-logistic model the best fit to extrapolate survival times beyond month 28. Separate weekly probability of death estimates were calculated for the PFS state and progression states. Within a health state the same weekly probability of death was applied to both treatment and comparator arms. The weekly probability of death whilst in PFS was derived from the GOG-0218

trial data, and estimates of all-cause mortality published by the UK government actuary department. In the progressed state, the weekly probability of death was constant (equal to 0.0599) and was based on patients' time from disease progression to death or censoring in the GOG-0218 trial, based on an assumption of constant probability of death (independent of time since progression).

Utility values

6.5 The model incorporates patients' health-related quality of life outcomes through the use of health-state utility values for the PFS and progressed states. The manufacturer conducted a systematic literature review for studies on health-related quality of life in advanced or metastatic ovarian cancer. The search identified 1 study which the manufacturer reviewed; however, the reported utility values were not appropriate because they had not been mapped to EQ-5D. Health-related quality of life was collected in both the GOG-0218 and ICON7 trials. The EQ-5D values from the ICON7 trial have been used in this model because of the overlap in the trial patient populations and the recommendation by NICE for the EQ-5D for assessment of health state utilities. In the PFS state a log-rank test showed that there was no difference in the utility values across the intervention and comparator arms, therefore the same utility values were used in the model in both arms. A trend test demonstrated that the utility values changed over time so this effect has been included in the model where the utilities vary between 0.6571 and 0.7760 over the first 53 weeks of the trial and then remain at 0.8129 from week 54 onwards. EQ-5D data was not routinely collected for patients whose disease had progressed in ICON7 and so, the health-related quality of life utility value for the progressed state was a constant (0.7248) estimated as the mean

utility in the limited data available for patients with progressed disease in the ICON7 trial. It is comparable to utility data available from a trial looking at trabectedin which studied a patient population with relapsed advanced ovarian cancer (mean utility of relapsed patients with stable disease of 0.718 [95% CI 0.699 to 0.737]) (Papaioannou et al. 2010). The disutilities associated with adverse effects were assumed to have been captured within the assessment of the health-related quality of life in the ICON7 trial.

Table 5: Utility values used in GOG-0218 model

State	Utility value	Standard error
PFS (weeks)		
0–2	0.6571	0.0133
3–5	0.7153	0.0118
6–8	0.7443	0.0110
9–11	0.7683	0.0100
12–14	0.7643	0.0112
15–20	0.7444	0.0121
21–26	0.7638	0.0131
27–32	0.7718	0.0129
33–38	0.7638	0.0136
29–44	0.7785	0.0155
45–50	0.7533	0.0165
51–53	0.7760	0.0170
54+	0.8129	0.0113
Progressed	0.7248	-
PFS, progression-free survival		

Source: Manufacturer’s submission, table B3, page 152.

Costs

6.6 Costs associated with bevacizumab were estimated using the dosage and frequency of administration in the summary of product characteristics. The mean weight of a cohort of UK ovarian cancer patients in a study by Sacco et al. (2010) was used to calculate the dose. Dosing and frequency of the paclitaxel and carboplatin treatments were based on their respective summary of product characteristics. Data for the mean body surface area, age and

weight measurements required to calculate an expected dose of paclitaxel and carboplatin per individual were taken from Sacco et al. (2010). Treatment duration for drugs in both arms was estimated using observations from the GOG-0218 trial. The base case assumed that any unused carboplatin or paclitaxel drug from a vial is reallocated and not wasted, whereas for bevacizumab it is assumed that any unused drug in a vial is wasted. The cost of bevacizumab was £2229 per patient per cycle, the cost of paclitaxel was £21.80 per patient per cycle and the cost of carboplatin was £18.51. The costs, based on the NHS reference costs 2010/2011, associated with the pharmacy preparation of the infusion and its administration based on outpatient hospital treatment, were included in the model. These costs for carboplatin and paclitaxel are £274.57 for the first cycle and £94.27 for subsequent cycles. For the first 6 cycles when bevacizumab is given with carboplatin and paclitaxel, the additional pharmacy and administration cost is based on 12 minutes of pharmacy preparation time (£9.20). For cycles 7–22 when bevacizumab is given alone, the pharmacy and administration costs are the same as that for carboplatin and paclitaxel (£94.27).

- 6.7 The weekly costs of supporting patients in the PFS and progressed health states were included. Clinical expert advice was used to inform PFS supportive care and the values used in the progressed state were based on NICE's technology appraisal '[Trabectedin for the treatment of relapsed ovarian cancer](#)' (NICE technology appraisal guidance 222; see manufacturer's submission, table 56, page 165–166). Post-progression drug acquisition costs were not included in the model as this information was not available in sufficient detail from the GOG-0218 trial. Costs associated with adverse events which occurred at grade 3 or 4 severity in more

than 2% of patients 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 57 in the manufacturer’s submission (page 167) lists the adverse events and their costs which range from £5373 for febrile neutropenia to negligible costs associated with events such as constipation and hypertension.

6.8 The base-case results demonstrate that the addition of bevacizumab to standard chemotherapy provides an additional 0.228 years (0.188 quality-of-life years gained [QALYs]) to patients with an expected survival of approximately 4 years. This benefit is achieved with an incremental cost of £27,089, resulting in an incremental cost-effectiveness ratio (ICER) of £144,066 per QALY gained for bevacizumab at the licensed dose in addition to carboplatin and paclitaxel chemotherapy compared with carboplatin and paclitaxel alone.

Table 6: Base-case cost-effectiveness results with GOG-0218 model

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)
CP	£17,166	2.973			
CPB	£44,254	3.161	£27,089	0.188	£144,066

CP, carboplatin and paclitaxel; CPB, carboplatin, paclitaxel and bevacizumab; ICER, incremental cost-effectiveness ratio; QALY, quality-of-life years.

Source: ERG report, page 32

6.9 The manufacturer examined the robustness of the model using deterministic sensitivity analyses. Table 63 in the manufacturer’s submission (page 186) summarizes the results of these analyses. The results suggest that the cost-effectiveness results are influenced by the parametric functions used for the PFS extrapolation and the time horizon used in the model. The manufacturer also presents scenario analyses examining the

impact of vial sharing for bevacizumab and including the trial patient characteristics. For the vial sharing scenario, the cost of bevacizumab is reduced to £2109 per dose compared with £2229 in the base-case analysis. The result of this reduction in the cost of bevacizumab leads to an ICER of £136,513 per QALY gained. The trial patient characteristics scenario analysis uses the drug usage based upon the demographics from the trial rather than values reported by Sacco et al. (2010). The mean body weight of women recruited to GOG-0218 is more than 10 kg more than the mean weight of UK ovarian cancer patients. The drug cost using the trial characteristics was £2583 per dose compared with £2229 in the base-case analysis. The result of this increase in the cost of bevacizumab is an ICER of £166,287 per QALY gained. The manufacturer identified the key drivers of the cost-effectiveness results as the dose and cost of bevacizumab and the duration of treatment.

- 6.10 The manufacturer undertook probabilistic sensitivity analyses to explore uncertainty in the model, which showed that, at £30,000 for an additional QALY, bevacizumab with carboplatin and paclitaxel was not cost effective.
- 6.11 The manufacturer also submitted an economic model based on the ICON7 trial data despite the fact that the dose of bevacizumab used is unlicensed. The manufacturer's submission (page 130) provides the rationale for submitting this model. The model is a 3-state area-under-the-curve model based on progression-free and overall survival data in a patient subgroup chosen to match the licensed indication. Progression-free survival was modelled using the Kaplan-Meier curves from the trial data until month 24, when the treatment and comparator arms converge, followed by extrapolation with a log-logistic parametric function. A log-logistic

function was also used to model overall survival based on the fit to the ICON7 data, other published data and clinical advice that suggested that a small but significant percentage of patients with advanced ovarian cancer experience long term survival in excess of 10 years. Resources and costs were similar to the GOG-0218 model; however, the manufacturer has considered post-progression drug costs in the ICON7 model. The base-case results indicated incremental costs of £17,729 and incremental QALYs of 0.561 for bevacizumab at the unlicensed 7.5mg/kg plus chemotherapy compared with carboplatin and paclitaxel alone. The cost per QALY gained was £31,592 for bevacizumab at the unlicensed 7.5 mg/kg dose plus chemotherapy compared with carboplatin and paclitaxel alone. A sensitivity analysis which used a gamma function, (this was the best fit to the ICON7 data), to model overall survival resulted in an ICER of £37,749 per QALY gained.

ERG comments

- 6.12 The ERG considered that the structure adopted for the economic model based on the GOG-0218 was reasonable, and consistent with previous economic evaluations developed for advanced cancer. The methods of analysis were generally appropriate and conform to NICE methodological guidelines. The ERG noted that a time horizon of 10 years was used in the model. However, the ERG considered a longer time horizon would have been more appropriate because, approximately 10% of patients are still alive after 10 years. The ERG agreed that the parameters used for the model are generally appropriate. The population used in the model is from the relevant trial (GOG-0218) and is generally representative of those treated in secondary care in the UK, although the population may not fully represent patients who have had comorbidities.

- 6.13 The ERG highlighted that the clinical-effectiveness data used in the model included censoring for patients with rising CA-125 levels and for those who switched to non-protocol therapies. It considered that the hazard ratio from this data was relatively favourable compared to other PFS hazard ratios presented from the trial data and this may have produced a more favourable cost-effectiveness estimate. The ERG also noted that the treatment duration was 1 year rather than the 15 months as specified in the summary of product characteristics.
- 6.14 The ERG highlighted that the overall survival in the trial data between the arms was similar with median values of 39.75 months for bevacizumab and 39.39 months for the chemotherapy only arm. However, in the model, there is a 2-month difference in the median overall survival between the arms: bevacizumab 47 months, and chemotherapy only 45 months.
- 6.15 The ERG also considers that the uncertainty around the model results has not been fully examined. Not all model parameters were considered in either the deterministic or probabilistic sensitivity analyses. Key parameters missing from the probabilistic sensitivity analysis include the variability in the clinical-effectiveness estimates based on the Kaplan-Meier survival data taken from the trial and variability in the cost of bevacizumab. In the deterministic sensitivity analysis input parameters such as the cost of bevacizumab, treatment duration and variation in effectiveness which might be expected to be highly influential on the cost-effectiveness results, have been omitted. The ERG also noted that from the deterministic sensitivity analyses presented in the submission (see table 63, page 186), the model is also sensitive to the time horizon, and the parametric functions used for the PFS extrapolation.

6.16 The ERG undertook several exploratory deterministic sensitivity analyses, which examined the impact of changes to duration, treatment cost and time horizon. The ERG noted that the treatment duration used within the model was 1 year, rather than the 15 months specified in the summary of product characteristics for bevacizumab. Using the trial discontinuation rates in the GOG-0218 trial and with treatment for a maximum of 15 months, the ICER of bevacizumab increased from the base case of £144,066 per QALY gained to £160,788 per QALY gained. The ERG investigated the effect of changing the 10-year time horizon to the maximum permitted in the model of 25 years. For this analysis, the ICER reduced from the base case of £144,066 per QALY gained to £127,701 per QALY gained. Finally, the ERG combined the analyses for treatment duration of 15 months and a time horizon of 25 years which produced an ICER similar to the base case of £142,477 per QALY gained. The ERG also explored the effect of changing the treatment cost of bevacizumab in the model to the treatment cost for the lower dosage of 7.5 mg/kg, assuming the same clinical effectiveness data from the GOG-0218 trial. For the lower bevacizumab dosage, a treatment duration of 1 year and the 10-year time horizon, the ICER of bevacizumab reduced to £77,884 per QALY gained.

Table 8: ERG exploratory analyses

Scenario	Treatment	Mean total costs (£)	Mean QALYs	ICER (£/QALY gained)
Base case	CPB	44,254	3.16	-
	CP	17,166	2.97	-
	Incremental	27,089	0.19	144,066
Total treatment duration 15 months using trial discontinuation rates	CPB	47,399	3.16	-
	CP	17,166	2.97	-
	Incremental	30,233	0.19	160,788
Reduced treatment cost using cost of 7.5 mg/kg (£1177)	CPB	31,810	3.16	-
	CP	17,166	2.97	-
	Incremental	14,645	0.19	77,884
Time horizon of 25 years	CPB	45,174	3.342	-
	CP	18,001	3.129	-
	Incremental	27,173	0.21	127,701
Treatment duration 15 months, and time horizon of 25 years	CPB	48,318	3.342	-
	CP	18,001	3.129	-
	Incremental	30,317	0.21	142,477
CP, carboplatin and paclitaxel; CPB, carboplatin, paclitaxel and bevacizumab; ICER, incremental cost-effectiveness ratio; QALY, quality-of-life years.				

Source: ERG report, page 47

6.17 The ERG considered the ICON7 model presented by the manufacturer. It noted that this model used the unlicensed dose of 7.5 mg/kg body weight and also had a treatment duration and study population different to the licensed indication. The ICON7 data used in the model were based on a subgroup and so, estimates may not be very precise because of the relatively small sample size. Overall, the ERG considered that the ICON7 model was built using appropriate data, with appropriate outcomes and was generally well described and justified in the manufacturer’s submission. The ICER appeared particularly sensitive to assumptions of parametric form for overall survival.

7 Equalities issues

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

8 Innovation

- 8.1 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. Its adverse effects profile allows it to be combined with cytotoxic chemotherapies without providing an intolerable additional burden of toxicity. The manufacturer considered that bevacizumab is a directly targeted therapy with a different toxicity profile for the treatment of advanced or metastatic ovarian cancer and so represents an innovative step-change in the management of this disease. A professional group also stated that bevacizumab targets the vascular supply of the tumour and is therefore novel.

9 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](#). NICE technology appraisal guidance 91 (2005).
- [Review of the clinical effectiveness and cost effectiveness of paclitaxel for ovarian cancer](#). NICE technology appraisal 55 (2003).

Under development

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

- [Bevacizumab for the treatment of recurrent advanced ovarian cancer](#). NICE technology appraisal guidance (publication expected June 2013).

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