NICE National Institute for Health and Care Excellence

Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer

Technology appraisal guidance

Published: 22 May 2013

www.nice.org.uk/guidance/ta284

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

Please note that NICE can only issue guidance on any drug within the terms of its marketing authorisation. Consequently, bevacizumab for first-line treatment of advanced ovarian cancer has only been appraised at its licensed dose of 15 mg/kg body weight.

1.1   Bevacizumab in combination with paclitaxel and carboplatin is not recommended for first-line treatment of advanced ovarian cancer (International Federation of Gynaecology and Obstetrics [FIGO] stages 3B, 3C and 4 epithelial ovarian, fallopian tube or primary peritoneal cancer).

1.2   People currently receiving bevacizumab for first-line treatment of advanced ovarian cancer should be able to continue treatment until they and their clinicians consider it appropriate to stop.

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 UK marketing authorisation for 'the front-line treatment of advanced (International Federation of Gynaecology and Obstetrics [FIGO] stages 3B, 3C and 4) 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, posterior reversible encephalopathy 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 prices of £242.66 and £924.40 respectively (excluding VAT; BNF edition 64). 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 £2,577. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee considered evidence submitted by the manufacturer of bevacizumab and a review of this submission by the Evidence Review Group (ERG).

3.1   The key evidence for the clinical effectiveness of bevacizumab plus paclitaxel and carboplatin came from 1 randomised controlled trial (GOG-0218). The trial assessed the efficacy and safety of bevacizumab (at its licensed dose of 15 mg/kg body weight) plus paclitaxel and carboplatin in people with previously untreated stage 3 (incompletely resected) or stage 4 epithelial ovarian, fallopian tube or primary peritoneal cancer who had undergone debulking surgery. This evidence was supported by results from a randomised open-label trial (ICON7) that assessed the efficacy and safety of bevacizumab at an unlicensed dose (7.5 mg/kg body weight) plus paclitaxel and carboplatin in people with high-risk early stage or advanced epithelial ovarian, fallopian tube or primary peritoneal cancer.

3.2   GOG-0218 was a double-blind randomised placebo-controlled multicentre trial conducted in North America and Asia, and included 1,873 patients with previously untreated stage 3 or stage 4 epithelial ovarian, fallopian tube or primary peritoneal cancer who had undergone debulking surgery. The trial was for up to 15 months and patients were randomised to 1 of 3 treatment arms:

- The CPP (carboplatin, paclitaxel and placebo) control group (n=625) received standard chemotherapy (carboplatin at a target area under the curve of 6 mg/ml•min and paclitaxel 175 mg/m^2 every 3 weeks for 6 cycles), plus placebo for cycles 2 to 22.

- The CPB15 (carboplatin, paclitaxel and bevacizumab [15 mg/kg]) group (n=625) received the same standard chemotherapy as the CPP group, plus bevacizumab (15 mg/kg) for cycles 2 to 6 and placebo as monotherapy for cycles 7 to 22.

- The CPB15+ group (n=623) received the same standard chemotherapy as the CPP group, plus bevacizumab (15 mg/kg) for cycles 2 to 22.

3.3   Cycles lasted 3 weeks and treatment was discontinued at the onset of disease

progression, unacceptable toxic effects, completion of all 22 cycles or withdrawal. Patients in the control arm were allowed to cross over to receive bevacizumab after disease progression. Randomisation was stratified for Gynaecologic Oncology Group (GOG) performance status (0, 1 or 2), and cancer stage and debulking status (optimally debulked stage 3 [with maximum residual lesion diameter of 1 cm or less], suboptimally debulked stage 3 [with maximum residual diameter of more than 1 cm] or stage 4). The primary outcome was progression-free survival (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, Response Evaluation Criteria in Solid Tumours (RECIST) or rising serum cancer antigen-125 (CA-125). CA-125 progression was defined as at least twice the nadir or upper limit of normal. Secondary outcomes included overall survival, objective response rate and health-related quality of life measured using the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) questionnaire, the Ovarian Cancer Subscale measure and abdominal discomfort score.

3.4   The primary efficacy analysis of PFS used censored data from September 2009 in which patients with disease progression based on rising serum CA-125 alone and patients who received non-protocol therapies before progression were censored at the time of their previous scan and excluded from the analysis. Based on an investigator assessment, the censored data showed a statistically significant improvement of 6 months in the difference between the median PFS of the CPB15+ arm and the CPP arm (CPP 12 months, CPB15+ 18 months; hazard ratio [HR] 0.645, 95% confidence interval [CI] 0.551 to 0.756, $p<0.001$). There was a 0.7-month difference in median PFS in favour of the CPB15 arm compared with the CPP arm (CPP 12 months, CPB15 12.7 months; HR 0.84, 95% CI 0.71 to 0.99, $p=0.0204$). An Independent Review Committee assessment of these data showed similar results: a 6-month difference in median PFS in favour of the CPB15+ arm compared with the CPP arm (CPP 13.1 months, CPB15+ 19.1 months; HR 0.62, 95% CI 0.50 to 0.77, $p<0.0001$) but only a non-statistically significant 0.1-month difference in median PFS in the CPB15 arm compared with the CPP arm (CPP 13.1 months, CPB15 13.2 months; HR 0.93, 95% CI 0.76 to 1.13, $p=0.222$). A GOG protocol-specified analysis of PFS was undertaken in February 2010 and the results were presented without censoring for CA-125 progression or use of non-protocol therapy before disease progression. The difference in the median PFS was 3.8 months in favour of the CPB15+ arm

compared with the CPP arm (CPP 10.3 months, CPB15+ 14.1 months; HR 0.717, 95% CI 0.625 to 0.824, p<0.0001) and 0.9 months in favour of the CPB15 arm compared with the CPP arm, although this difference was not statistically significant (CPP 10.3 months, CPB15 11.2 months; HR 0.908, 95% CI 0.795 to 1.040, p=0.16).

3.5   A subgroup analysis by cancer stage and debulking status using the uncensored data from February 2010 suggested that the improvement in PFS between CPB15+ and CPP was maintained across all subgroups: patients with stage 3 optimally debulked cancer showed a 5.1-month improvement in PFS in the CPB15+ compared with the CPP arm (CPP 12.4 months, CPB15+ 17.5 months; HR 0.66, 95% CI 0.5 to 0.86); patients with stage 3 suboptimally debulked cancer showed a 3.8-month improvement in PFS in the CPB15+ compared with the CPP arm (CPP 10.1 months, CPB15+ 13.9 months; HR 0.78, 95% CI 0.63 to 0.96); patients with stage 4 cancer showed a 3.3-month improvement in PFS in the CPB15+ compared with the CPP arm (CPP 9.5 months, CPB15+ 12.8 months; HR 0.64, 95% CI 0.49 to 0.82).

3.6   The overall survival analysis was calculated in August 2011 when 46.9% of patients had died. The median overall survival was 3.2 months longer in the CPB15+ arm than in the CPP arm (CPP 40.6 months, CPB15+ 43.8 months; HR 0.88, 95% CI 0.75 to 1.04, p=0.0641). However, this was not statistically significant at the p value boundary of 0.0116. The manufacturer stated that significant patient crossover from the control arm after progression would have confounded the data. The manufacturer's submission contained 2 estimates of the proportion of patients in the control arm receiving bevacizumab after progression: 27.7% and up to 40%.

3.7   ICON7 was a randomised open-label multicentre study conducted in Europe, and included 1,528 patients with high-risk early stage or advanced stage 4 epithelial ovarian, fallopian tube or primary peritoneal cancer. The trial was for up to 12 months and patients were randomised to 1 of 2 treatment arms:

- The CP (carboplatin and paclitaxel) control group (n=764) received standard chemotherapy (carboplatin at a target area under the curve of 5 or 6 mg/ml•min and paclitaxel 175 mg/m^2 every 3 weeks for 6 cycles).

- The CPB7.5+ arm (n=764) received the same standard chemotherapy as the

CP group plus bevacizumab (7.5 mg/kg) every 3 weeks for 6 cycles, and continued for an additional 12 cycles or until disease progression.

3.8   Randomisation was stratified for cancer stage and residual disease post surgery (category 1 – FIGO stage 1 to 3 with residual disease less than 1 cm; category 2 – FIGO stage 1 to 3 with residual disease more than 1 cm; category 3 – FIGO stage 4 and inoperable FIGO stage 3) and the time of initiation of chemotherapy (intention-to-start chemotherapy 4 weeks after surgery or sooner, or intention-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. A pre-specified, but not stratified, subgroup included 31% (n=462) of patients with high-risk disease (defined as stage 3 suboptimally debulked or stage 4 debulked ovarian cancer). The primary outcome of the trial was PFS based on RECIST on the basis of radiological, clinical and symptomatic indicators of progression. Secondary outcome measures included overall survival and quality of life. Health-related quality of life was measured using the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-OV28 questionnaires.

3.9   The manufacturer's submission presented analysis of PFS from ICON7 based on a data cut-off of November 2010. For the intention-to-treat population, the difference in median PFS was 2.4 months in favour of bevacizumab (CP 17.4 months, CPB7.5+ 19.8 months; HR 0.87, 95% CI 0.77 to 0.99, p<0.04). For the high-risk subgroup there was a statistically significant difference in median PFS of 5.5 months in favour of bevacizumab (CP 10.5 months, CPB7.5+ 16.0 months; HR 0.73, 95% CI 0.60 to 0.93, p=0.002). A pre-planned exploratory analysis of PFS using subgroups defined by cancer stage and debulking status was also reported. These analyses showed a statistically significant improvement in favour of bevacizumab for patients with stage 3 suboptimally debulked cancer (difference in median PFS of 6.8 months based on CP 10.1 months [n=154] and CPB7.5+ 16.9 months [n=140]; HR 0.67, 95% CI 0.52 to 0.87). However, no statistically significant differences between treatment arms were observed for stage 3 patients with optimally debulked cancer (difference in median PFS of 1.6 months based on CP 17.7 months [n=368] and CPB7.5+ 19.3 months [n=383]; HR 0.89, 95% CI 0.74 to 1.07) or patients with stage 4 cancer (difference in median PFS of 3.4 months based on CP 10.1 months [n=97] and CPB7.5+ 13.5 months [n=104]; HR 0.74, 95% CI 0.55 to 1.01).

3.10   The protocol-specified final overall survival analysis for ICON7 has not yet been reported. An exploratory overall survival analysis of the intention-to-treat population, conducted when approximately 25% of patients had died, could not calculate the median duration of overall survival because of low numbers, but gave a hazard ratio of 0.85 (95% CI 0.69 to 1.04). An interim overall survival analysis was conducted in the high-risk subgroup when approximately 47% of patients had died in the CP arm and 34% had died in the CPB7.5+ arm. There was a statistically significant difference in the median overall survival of 7.8 months in favour of bevacizumab (CP 28.8 months, CPB7.5+ 36.6 months; HR 0.64, 95% CI 0.48 to 0.85, p=0.002).

3.11   The manufacturer did not consider that a meta-analysis was appropriate because GOG-0218 and ICON7 used different doses and durations of bevacizumab, and different study populations.

3.12   Almost all patients in GOG-0218 experienced at least 1 adverse event. Incidences of stomatitis, dysarthria, headache, epistaxis and hypertension were more than 10% higher in the bevacizumab arms than in the placebo arm. Incidences of hypertension, gastrointestinal perforation and non-central nervous system bleeding (adverse events of special interest, grade 3 to 5) were at least 1% higher in the CPB15+ arm than in the CPP arm.

3.13   The manufacturer submitted a de novo economic analysis that assessed the cost effectiveness of bevacizumab plus carboplatin and paclitaxel compared with carboplatin and paclitaxel only for first-line treatment in women with stage 3 or 4 ovarian cancer. The model was a 3-state semi-Markov model with health states consisting of PFS, progressed disease and death. Data from GOG-0218 were used to inform model inputs for dosing, survival and safety. Both the intervention and comparator in the model were used in accordance with their marketing authorisations. The manufacturer also presented an economic analysis of bevacizumab at its unlicensed dose of 7.5 mg/kg based on ICON7, the results of which are not presented here. The analysis was conducted from an NHS and personal social services perspective, the costs and outcomes were discounted at 3.5% per year and a 10-year time horizon was used.

3.14   PFS 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 are from 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. In the progressed disease state, the weekly probability of death was assumed to be constant and the same for both arms of the model.

3.15   The model incorporates patients' health-related quality-of-life outcomes using health-state utility values for the PFS and progressed disease states. The manufacturer applied EQ-5D utility values from an expanded high-risk subgroup in the ICON7 study, which included all patients with stage 3 disease with suboptimal debulking or stage 4 disease or patients with unresectable disease (n=495). 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 both arms of the model. In the PFS state, the values varied with time and in the progressed state, a constant value was used because of the limited data available. The disutilities associated with adverse effects were assumed to have been captured in the assessment of health-related quality of life in ICON7.

3.16   Drug costs were estimated using the dose and frequency of administration in the summary of product characteristics. Data from a UK cohort study were used in the dose calculations. The base case assumed that any unused carboplatin or paclitaxel from a vial is reallocated and not wasted, whereas for bevacizumab it assumed that any unused drug in a vial is wasted. The costs per patient per cycle were £2,229 for bevacizumab, £21.80 for paclitaxel and £18.51 for carboplatin. The costs associated with pharmacy preparation of the infusion and its outpatient administration in hospital (based on NHS reference costs 2010 to 2011) were included in the model. The weekly costs of supporting patients in the PFS and progressed health states were included in the model. Post-progression drug acquisition costs were not included in the model because this information was not available in sufficient detail from GOG-0218. Costs associated with adverse events that occurred at grade 3 or 4 severity in more than 2% of patients were incorporated into the analysis.

3.17   The base-case results estimated that adding bevacizumab to standard chemotherapy provides an additional 0.228 life years (0.188 quality-adjusted life years [QALYs], resulting from a 0.243 QALY gain in the PFS state and a 0.055 QALY loss in the progressed disease state) 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 the licensed dose of bevacizumab plus carboplatin and paclitaxel, compared with carboplatin and paclitaxel alone. The manufacturer's deterministic sensitivity analysis suggested 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's scenario analyses identified the key drivers of the cost-effectiveness results as the dose and duration of bevacizumab treatment.

3.18   The ERG considered that GOG-0218 provided evidence of the clinical effectiveness of bevacizumab plus carboplatin and paclitaxel for the first-line treatment of people in the NHS with advanced ovarian cancer, as defined in the scope. It noted that the population from the trial is generally representative of patients treated in secondary care in the UK, although it may not fully represent patients with comorbidities.

3.19   The ERG was concerned that the different assessments of PFS (by investigator and Independent Review Committee, CA-125 censored, CA-125 not censored) were not consistently reported for all time points. It 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 a request for clarification, the manufacturer stated that updated PFS data censored for CA-125 are not available; also, exploratory analyses were not updated because they were intended only to confirm the validity of investigator-assessed PFS. The ERG considered that, although the direction of the evidence is consistent, the size of effect varies with the different analyses and over time. For example, the difference in median PFS varied from 4 to 6 months; the hazard ratio varied from 0.62 (assessed by Independent Review Committee, data censored) to 0.77 (updated investigator assessed, without data censoring). Clinical advice to the ERG suggested that CA-125 is used routinely in UK clinical practice; therefore, the ERG considered that results not censored for CA-125 rises were most relevant to the UK.

3.20   The ERG considered that the structure adopted for the economic model based on GOG-0218 was reasonable, and consistent with previous economic evaluations developed for advanced cancer. The methods of analysis were generally appropriate and conformed to the NICE reference case. 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 were still alive after 10 years. The ERG agreed that the parameters used for the model were generally appropriate.

3.21   The ERG highlighted that the clinical-effectiveness data used in the model included censoring for patients with rising CA-125 levels and for patients who switched to non-protocol therapies. It considered that the hazard ratio from these data was relatively favourable compared with other PFS hazard ratios from the trial and this may have produced a more favourable cost-effectiveness estimate. The ERG also noted that the treatment duration was 12 months rather than the 15 months specified in the summary of product characteristics.

3.22   The ERG highlighted that, in the trial, overall survival between the arms was similar, with median values of 39.8 months for the bevacizumab arm and 39.4 months for the chemotherapy-only arm. However, in the model, there is a 2-month difference in mean overall survival between the arms (bevacizumab: 47 months, chemotherapy-only: 45 months).

3.23   The ERG also considered that the uncertainty around the model results had 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 included 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 that might be expected to be highly influential on the cost-effectiveness results were omitted, such as the cost of bevacizumab, treatment duration and variation in effectiveness.

3.24   The ERG undertook several exploratory deterministic sensitivity analyses that examined the impact of changes to treatment duration, treatment cost and time horizon. Using the trial discontinuation rates in GOG-0218 and with treatment for a maximum of 15 months instead of the 12 months in the base case, the ICER for

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; this reduced the ICER to £127,701 per QALY gained. Finally, the ERG combined the analyses for a 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.

3.25   Full details of all the evidence are in the manufacturer's submission and the ERG report.

4 Consideration of the evidence

4.1   The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of bevacizumab plus paclitaxel and carboplatin, having considered evidence on the nature of advanced ovarian cancer and the value placed on the benefits of bevacizumab plus paclitaxel and carboplatin by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.2   The Committee discussed the current management of advanced ovarian cancer. The clinical specialists confirmed that chemotherapy with paclitaxel and carboplatin was current standard clinical practice in the NHS in England and Wales for first-line treatment of advanced ovarian cancer after debulking surgery. The Committee heard from the clinical specialists that 3 cycles of chemotherapy may be given before surgery for some patients expected to have residual disease left after surgery. After first-line treatment, decisions about progression are usually made using symptomatic and radiological evidence, and rises in CA-125 alone are not considered sufficient reason to consider changes in treatment. The clinical specialists also highlighted that the 10-year survival rate in ovarian cancer is only 35% and that, in clinical practice, only 1% of people with advanced ovarian cancer were likely to be alive at 10 years. This has improved in recent years but is below the rates for many other cancers. The Committee heard from the clinical specialists that they considered bevacizumab to be an innovative technology because there have been few new beneficial developments in ovarian cancer for several years. The Committee also heard from the clinical specialists that bevacizumab, at its unlicensed dose of 7.5 mg/kg, is currently being used in the NHS in England in combination with standard chemotherapy for patients with stage 4 cancer or those who have undergone surgery with more than 1 cm residual disease, followed by bevacizumab continued as maintenance therapy until progression. This is the dose that was used in ICON7, which was conducted across Europe and involved some centres in the UK. The commissioning representatives and patient experts also confirmed that the unlicensed dose of bevacizumab is the dose most commonly used in the NHS for advanced ovarian cancer. NICE informed the Committee that it would be unable to issue guidance on a technology used outside the terms of its marketing authorisation.

4.3   The Committee heard from the patient experts that treatment options are limited for people with advanced ovarian cancer and that bevacizumab provided an additional treatment option. The patient experts highlighted that the end of first-line treatment is a critical time for patients and it is important not to underestimate the impact of any extension to progression-free survival (PFS) for these patients and their families. They also highlighted the importance of patients' beliefs that they are receiving the best possible treatment to their wellbeing, and suggested that patients often choose to tolerate serious side effects in the hope of gaining additional PFS.

Clinical effectiveness

4.4   The Committee considered that the main source of evidence for the clinical effectiveness of bevacizumab plus paclitaxel and carboplatin was GOG-0218. The Committee agreed this was a well-designed double-blind randomised trial. It noted the Evidence Review Group's (ERG's) assessment of the quality of this trial, and accepted that the results of the trial are relevant to the first-line treatment of patients with advanced ovarian cancer in the NHS. The Committee noted that there were 3 arms in the trial but only the CPB15+ arm (bevacizumab given with chemotherapy and then for up to 15 months as maintenance therapy) showed a statistically significant improvement in PFS compared with chemotherapy alone. The CPB15 arm of the trial (bevacizumab given only with chemotherapy) showed no statistically significant PFS benefit compared with the control arm. The Committee concluded that GOG-0218 provided relevant evidence for this appraisal and that bevacizumab was shown to be clinically effective only when it is given within its marketing authorisation, that is, at the same time as paclitaxel and carboplatin and then as a maintenance treatment for up to 15 months.

4.5   The Committee noted that PFS results from GOG-0218 were reported in the manufacturer's submission using both censored data (in which patients with a CA-125 rise were censored at the time of their previous scan and their results removed from further PFS analysis), and uncensored data (in which a CA-125 rise indicated progression). The Committee heard from the clinical specialists that a rise in CA-125 alone was not used as an indication to change treatment because this approach had not been shown to alter prognosis and also approximately a third of patients did not express CA-125. The clinical specialists also commented

that a CA-125 rise often suggested the disease was progressing but that it could take up to 6 months or so for progression to become apparent. The Committee concluded that a significant rise in CA-125 is an indicator of progression and might be an early marker, but is not usually used in clinical practice in the UK as the sole indicator of progression.

4.6　　The Committee discussed the most relevant PFS results for the clinical effectiveness of bevacizumab plus paclitaxel and carboplatin in the UK. The Committee noted that the results from the uncensored data of a 3.8-month difference in median PFS in favour of bevacizumab was less than the 6-month difference in median PFS obtained from the censored data. The Committee noted the ERG's concerns about the lack of consistent reporting of the various PFS assessments at all time points. The Committee noted that clinical advice to the ERG was that the uncensored data are the most relevant to the NHS. However, the Committee heard from the clinical specialists that, in their opinion, the censored data are more relevant because patients in the NHS would not be treated as progressed based on a CA-125 rise alone (see section 4.5). The Committee was aware that the censored data had excluded patients with raised CA-125 from the analysis and, because these patients could be regarded as being at high risk of progression, this could have led to bias in the results. The Committee noted that all the analyses of PFS data presented in the manufacturer's submission taken at different time points, both censored and uncensored, showed a difference in median PFS in favour of bevacizumab of between 3.8 and 6 months. The Committee concluded that bevacizumab plus paclitaxel and carboplatin improved PFS compared with paclitaxel and carboplatin alone and that, of the available data, the censored PFS data are more relevant to UK clinical practice, although the Committee was aware of the potential bias introduced by censoring the data from patients with raised CA-125.

4.7　　The Committee considered the overall survival results from GOG-0218 and noted concerns from the ERG that switching patients in the control arm to bevacizumab after progression had confounded the overall survival analysis. The Committee noted the various estimates given in the manufacturer's submission of the percentage of patients switching and concluded that the precise extent of switching was unclear. It heard from the manufacturer that approximately 40% of patients in the chemotherapy arm compared with 20% of patients in the bevacizumab arm subsequently received bevacizumab after disease progression.

The Committee considered that patient crossover from the control arm would have an impact on the overall survival results only if second-line treatment with bevacizumab was more effective than other therapies given after progression, and the Committee did not have this information. Nevertheless, the Committee accepted that the interpretation of overall survival figures from GOG-0218 was problematic, and that the non-statistically significant difference in median overall survival of 3.2 months attributed to bevacizumab should be interpreted cautiously. The Committee concluded that the overall survival benefit of bevacizumab plus carboplatin and paclitaxel is uncertain from the results of GOG-0218 because of the uncertainty related to the extent to which patients received bevacizumab after progression and the impact of this.

4.8   The Committee noted the adverse events reported in GOG-0218. It understood that these events were as predicted from other studies with bevacizumab and did not raise new safety concerns. The Committee heard from the clinical specialists that most adverse events could be satisfactorily managed. The Committee concluded that adding bevacizumab to a paclitaxel and carboplatin regimen did not lead to unacceptable toxicity compared with paclitaxel and carboplatin alone and that adverse events were manageable.

4.9   The Committee discussed the evidence from the supporting ICON7 trial. It heard from the clinical specialists that the strengths of this trial were that it included some UK patients, and used the most appropriate definitions of progression, disease staging and surgical debulking. The clinical specialists stated that patients in the optimal debulking subgroups differed between the GOG-0218 and ICON7 trials. The clinical specialists considered that this is shown by fewer patients in the group with optimally debulked cancer in GOG-0218 having complete resection (that is, no visible disease) than in ICON7. The Committee also heard from the clinical specialists that this might be because another trial, conducted at the same time as GOG-0218, may have enrolled the patients who had complete resection. The Committee noted that the information on the proportion of patients with stage 3 and 4 disease in ICON7 who had completely resected disease was not available, and that the marketing authorisation for bevacizumab did not specify complete or incomplete resection. The Committee also noted that, in ICON7, no patient crossover was allowed after disease progression. The Committee was aware of the disadvantages of ICON7 relative to the NICE decision problem, including its open-label design and inclusion of some

patients with stage 1 and 2 cancer, which is not covered by the marketing authorisation for bevacizumab. In addition, the trial used a lower dose and shorter duration of bevacizumab treatment than is now licensed. Nevertheless, 81% of the patients were covered by the marketing authorisation and the Committee considered that the results from the trial contributed to the body of knowledge about the efficacy of bevacizumab plus paclitaxel and carboplatin for advanced ovarian cancer.

4.10   The Committee considered the PFS results from ICON7. It noted that the overall difference between the PFS medians in the intention-to-treat population was 2.4 months, which was less than the 6 months in the intention-to-treat population in GOG-0218 using the censored data. The clinical specialists emphasised that professional opinion was that this difference was related to patient selection and patient characteristics, not to the lower dose and duration of treatment in ICON7. The Committee also noted that, PFS in the chemotherapy comparator arm was worse in the high-risk subgroup from ICON7 than in the intention-to-treat population in GOG-0218 using the censored data, which could affect interpretation of the results. However, the Committee noted that the high-risk subgroup from ICON7 excluded patients with optimally debulked cancer, whereas the intention-to-treat population in GOG-0218 included approximately one-third of patients with optimally debulked cancer who might be expected to have a better prognosis, and who experienced the longest PFS of the subgroups in the GOG-0218 chemotherapy arm. The Committee concluded that the trials were difficult to compare because of different inclusion criteria, bevacizumab dose and duration of treatment, definitions of progression and optimal debulking, and differing baseline factors between the trials.

4.11   The Committee considered the results presented for the ICON7 high-risk subgroup. This subgroup was broadly comparable with 2 of the 3 stratified groups in GOG-0218 but did not represent the whole population covered by the marketing authorisation, which does not specify debulking status. Separate analysis of the high-risk subgroup showed a difference in median PFS of 5.5 months in favour of bevacizumab. This was higher than the 2.4-month difference in the ICON7 intention-to-treat population, and was comparable to the gain in the intention-to-treat GOG-0218 population using the censored data (6 months; see section 3.4). Hazard ratios were not provided for the non-high-risk subgroup (that is, the intention-to-treat population minus the high-risk

subgroup) but the Committee assumed that they would have shown little or no benefit. The Committee also considered the PFS results by cancer stage and debulking status in the population of ICON7 covered by the marketing authorisation. It noted that there was an apparent differential response, with little benefit shown in the stage 3 population with optimally debulked cancer (difference in median PFS 1.6 months in favour of bevacizumab) compared with the population with stage 3 suboptimally debulked cancer (difference in median PFS 6.8 months) or stage 4 cancer (difference in median PFS 3.4 months). The Committee heard from the clinical specialists that these PFS analyses from ICON7 showed benefit in only a proportion of the population covered by the marketing authorisation. The Committee noted that the subgroup data from GOG-0218 showed a benefit, which was not dependent on debulking status in stage 3 and 4 cancer, with the greatest PFS benefit shown in the optimally debulked subgroup (based on uncensored data from GOG-0218; corresponding censored subgroup data were not supplied by the manufacturer, see section 3.5). The Committee also noted that, although the results from ICON7 suggested a greater PFS benefit in patients with stage 3 suboptimally debulked or stage 4 cancer, the uncensored subgroup data from GOG-0218 did not appear to support the manufacturer's suggestion that bevacizumab provides greater benefit for ovarian cancer patients with a poor prognosis. The Committee agreed that the results of the open-label ICON7 trial indicated a smaller PFS benefit in the intention-to-treat population than was seen in GOG-0218, and also suggested a different benefit based on cancer stage and debulking status that had not been shown in GOG-0218. The Committee was aware that several hypotheses could explain these differences. The Committee concluded that the ICON7 data contributed to confidence that treatment with bevacizumab could delay progression, but that the reasons for the apparent differential response and differences in PFS suggested by the ICON7 subgroup analysis compared with the analysis of GOG-0218 uncensored data remained uncertain.

4.12   The Committee examined the overall survival data from ICON7 and noted that mature data on the intention-to-treat population were not yet available but an interim analysis of the high-risk subgroup showed a difference in median overall survival of 7.8 months in favour of bevacizumab. The Committee noted that, taking into account the shape of the Kaplan–Meier curve from the interim analysis of the high-risk patients, it is likely that the mean overall survival benefit would be much less than the median. The Committee concluded that the interim data for a

subgroup in the trial suggested a difference in overall survival in favour of bevacizumab, but that this should be interpreted with caution.

Cost effectiveness

4.13   The Committee discussed the cost-effectiveness estimates and the assumptions on which these were based from the manufacturer's economic model based on GOG-0218. The Committee concluded that the model adhered to the NICE reference case for economic analysis and was acceptable for assessing the cost effectiveness of bevacizumab plus paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer.

4.14   The Committee considered the model inputs including clinical effectiveness, patient outcomes, resource use and costs. It noted that PFS was based on the Kaplan–Meier curve from the censored data of GOG-0218 until month 28, after which PFS is represented by a log-logistic parametric function. The Committee also noted that the model used an equal post-progression death rate between the arms. It understood the ERG's concerns about the treatment duration of 12 months instead of the15 months specified in the marketing authorisation and the time horizon of 10 years. The ERG did not consider this time horizon to be long enough, although the Committee heard from the clinical specialists that 10 years was probably appropriate because only a very small number of patients are likely to survive beyond 10 years. The Committee noted that the EQ-5D utilities from the expanded high-risk subgroup of ICON7 (see section 3.15) were used in the model and that the same utilities were assumed in both arms of the model. It also noted that no disutilities associated with adverse events had been incorporated into the model. The Committee concluded that the model inputs used by the manufacturer were reasonable.

4.15   The Committee considered the most plausible incremental cost-effectiveness ratios (ICERs) from the model based on the GOG-0218 trial presented by the manufacturer and by the ERG in their exploratory analyses. It noted that the manufacturer's base-case ICER was approximately £144,000 per quality-adjusted life year (QALY) gained. The Committee considered the ERG's exploratory analyses, which examined the changes in the ICER with a treatment duration of 15 months or a time horizon of 25 years or both, and gave a range of ICERs from

£128,000 to £161,000 per QALY gained. The Committee agreed that the range of ICERs obtained from the cost-effectiveness model of bevacizumab plus paclitaxel and carboplatin were outside the range normally considered as a cost-effective use of NHS resources. It therefore concluded that bevacizumab within its marketing authorisation (that is, at a dose of 15 mg/kg), plus paclitaxel and carboplatin, would not be a cost-effective use of NHS resources for first-line treatment of advanced ovarian cancer compared with paclitaxel and carboplatin alone.

4.16 After receiving comments from the manufacturer in response to the appraisal consultation document, the Committee further considered the impact of patient crossover on overall survival in the GOG-0218 study as previously discussed (see section 4.7) and how this had been accounted for in the economic model. The Committee was aware that, because a proportion of patients in the chemotherapy arm from the GOG-0218 study subsequently received bevacizumab after disease progression, the manufacturer had assumed a similar probability of death in both treatment arms in its base-case analysis. The Committee also noted from the ERG that, by using this approach, the model resulted in a greater survival difference in favour of bevacizumab than was observed in the GOG-0218 study (see section 3.22). The Committee noted that this would result in a lower ICER than if the overall survival observed in the GOG-0218 study had been used. The Committee heard from the manufacturer that it did not consider it appropriate to use other alternative approaches to adjust for crossover, such as the rank-preserving structural failure time method. The Committee noted the manufacturer's response to the appraisal consultation document, which attempted to adjust for crossover in the trial by applying the overall survival curves estimated for the control and treatment arms in the expanded high-risk subgroup from the ICON7 study, rather than using post-progression survival data from the GOG-0218 study. The manufacturer justified this approach on the basis that the expanded high-risk subgroup from the ICON7 study, which did not permit crossover at progression, was broadly comparable to the intention-to-treat population in the GOG-0218 study. However, the Committee agreed that this was an unconventional approach that lacked credibility because of the significant differences identified between the expanded high-risk subgroup in the ICON7 study and the intention-to-treat population in the GOG-0218 study (see section 4.10). The Committee concluded that the manufacturer's novel approach to adjust for patient crossover in the GOG-0218

study was not a robust basis on which to estimate the cost effectiveness of bevacizumab, and agreed that the base-case ICER remained the most plausible one on which to base its decision.

4.17   The Committee considered the comments received by the consultees and commentators on the cost-effectiveness estimate for bevacizumab at its unlicensed dose of 7.5 mg/kg, noting that the manufacturer had submitted an economic analysis of bevacizumab at the unlicensed dose based on ICON7. The Committee also noted from 1 consultee comment that an estimate of the cost effectiveness of bevacizumab at its unlicensed dose had been submitted to and presented by the Scottish Medicines Consortium. The Committee noted that the cost-effectiveness estimate presented to the Scottish Medicines Consortium by the manufacturer differed from the one that was submitted to NICE. The Committee was aware that the ERG had not provided a detailed critique of the ICON7 economic model because it was based on the unlicensed dose of bevacizumab and therefore outside the scope of this appraisal. Therefore, the Committee concluded that it was unable to comment on the validity of the cost-effectiveness analysis of bevacizumab for the first-line treatment of advanced ovarian cancer at its unlicensed dose of 7.5 mg/kg.

4.18   The Committee also discussed whether it could comment on the use of bevacizumab for the first-line treatment of advanced ovarian cancer at its unlicensed dose of 7.5 mg/kg, noting the request for this from the comments received from consultees and commentators in response to the appraisal consultation document. The Committee noted from the European Medicines Agency's statement 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. In response to the Committee's question as to whether it was able to recommend a drug outside its licensed dose, NICE reiterated its position that the Committee was only permitted to make a recommendation on the licensed dose of bevacizumab (15 mg/kg). The Committee therefore concluded that it was reasonable not to consider further the cost effectiveness of bevacizumab at its unlicensed dose.

4.19   The Committee discussed whether bevacizumab should be considered an innovative treatment. The Committee acknowledged that advanced ovarian cancer is a disease with limited treatment options, and that bevacizumab

represented a novel biological approach to therapy. It also noted the clinical specialists' comments (see section 4.2). However, the Committee concluded that all benefits of a substantial nature relating to treatment with bevacizumab plus paclitaxel and carboplatin had been captured in the QALY calculation.

5 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam (Chair)
Department of Diagnostic Radiology, St George's Hospital

Professor Iain Squire (Vice Chair)
Consultant Physician, University Hospitals of Leicester

Professor A E Ades
Professor of Public Health Science, Department of Community Based Medicine, University of Bristol

Professor Thanos Athanasiou
Professor of Cardiovascular Sciences and Cardiac Surgery and Consultant Cardiothoracic Surgeon, Imperial College London and Imperial College Healthcare NHS Trust

Dr Jeremy Braybrooke

Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Dr Gerardine Bryant

GP, Swadlincote, Derbyshire

Dr Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Mr Andrew England

Lecturer in Medical Imaging, NIHR Fellow, University of Liverpool

Mr Adrian Griffin

Vice President, HTA and International Policy, Johnson and Johnson

Professor Jonathan Grigg

Professor of Paediatric Respiratory and Environmental Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University London

Dr Brian Hawkins

Chief Pharmacist, Cwm Taf Health Board, South Wales

Dr Peter Heywood

Consultant Neurologist, Frenchay Hospital, Bristol

Dr Sharon Saint Lamont

Head of Quality and Innovation, North East Strategic Health Authority

Dr Ian Lewin

Consultant Endocrinologist, North Devon District Hospital

Dr Louise Longworth

Reader in Health Economics, HERG, Brunel University, London

Dr Anne McCune

Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Professor John McMurray

Professor of Medical Cardiology, University of Glasgow

Dr Alec Miners

Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Dr Mohit Misra

GP, Queen Elizabeth Hospital, London

Ms Sarah Parry

Central Nervous System Paediatric Pain Management, Bristol Royal Hospital for Children

Ms Pamela Rees

Lay Member

Dr Ann Richardson

Lay Member

Dr Paul Robinson

Medical Director, Merck Sharp and Dohme

Ms Ellen Rule

Programme Director, NHS Bristol

Mr Stephen Sharp

Senior Statistician, MRC Epidemiology Unit

Dr Peter Sims

GP, Devon

Dr Eldon Spackman

Research Fellow, Centre for Health Economics, University of York

Mr David Thomson

Lay Member

Dr John Watkins

Clinical Senior Lecturer, Cardiff University; Consultant in Public Health Medicine, National Public Health Service Wales

Dr Olivia Wu

Reader in Health Economics, University of Glasgow

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Bernice Dillon (until December 2012) and **Matthew Dyer** (from January 2013)
Technical Leads

Joanna Richardson
Technical Adviser

Bijal Joshi
Project Manager

6 Sources of evidence considered by the Committee

The Evidence Review Group (ERG) report for this appraisal was prepared by Southampton Health Technology Assessments Centre:

- Cooper K, Pickett K, Frampton GK et al. Bevacizumab in combination with carboplatin and paclitaxel for the first-line treatment of ovarian cancer. A single technology appraisal. October 2012

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Manufacturers or sponsors were also invited to make written submissions. Professional or specialist and patient or carer groups, and other consultees, had the opportunity to give their expert views. Manufacturers or sponsors, professional or specialist and patient or carer groups, and other consultees, also have the opportunity to appeal against the final appraisal determination.

Manufacturers or sponsors:

- Roche Products (bevacizumab)

Professional or specialist and patient or carer groups:

- Macmillan Cancer Support

- Ovacome

- Ovarian Cancer Action

- Rarer Cancers Foundation

- Royal College of General Practitioners

- Royal College of Nursing

- Royal College of Obstetricians and Gynaecologists

- Royal College of Pathologists

- Royal College of Physicians (NCRI, RCP, RCR, ACP, JCCO)

- Target Ovarian Cancer

- United Kingdom Clinical Pharmacy Association

Other consultees:

- Department of Health

- Outer North East London PCT Cluster

- Welsh Government

Commentator organisations (did not provide written evidence and without the right of appeal):

- British National Formulary

- Commissioning Support Appraisals Service

- Department of Health, Social Services and Public Safety for Northern Ireland

- Health Care Improvement Scotland

- MRC Clinical Trials Unit

- National Collaborating Centre for Cancer

- National Institute for Health Research Health Technology Assessment Programme

- Southampton Health Technology Assessments Centre

The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They gave their expert personal view on bevacizumab by attending the Committee discussions and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Marcia Hall, Consultant in Medical Oncology, nominated by organisation representing NCRI, RCP, RCR, ACP, JCCO – clinical specialist

- Dr Sarah Blagden, Clinical Senior Lecturer and Honorary Consultant in Medical

Oncology, nominated by organisation representing Ovarian Cancer Action – clinical specialist

- Ms Louise Bayne, CEO, nominated by organisation representing Ovacome – patient expert

- Dr Sharon Tate, Public Affairs Manager, nominated by organisation representing Target Ovarian Cancer – patient expert

The following individuals were nominated as NHS Commissioning experts by the selected PCT Cluster located to this appraisal. They gave their expert or NHS commissioning personal view on bevacizumab by attending the Committee discussions and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Mrs Oge Chesa, Commissioning and Interface Pharmacist Advisor, NHS Waltham Forest, selected by Outer North East London PCT Cluster – NHS commissioning expert

- Ms Rajinder Nijjar, Lead Cancer Pharmacist, North East London Cancer Network, selected by Outer North East London PCT Cluster – NHS commissioning expert

Representatives from the following manufacturer or sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Roche Products

ISBN: 978-1-4731-0136-4