Bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer

Technology appraisal guidance
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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

1.1 Bevacizumab in combination with gemcitabine and carboplatin is not recommended within its marketing authorisation, that is, for treating people with the first recurrence of platinum-sensitive advanced ovarian cancer (including fallopian tube and primary peritoneal cancer) who have not received prior therapy with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor-targeted agents.

1.2 People currently receiving bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer should be able to continue treatment until they and their clinician 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 gemcitabine has a marketing authorisation for 'treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents'. The licensed dose of bevacizumab is 15 mg/kg of body weight given once every 3 weeks in combination with carboplatin and gemcitabine for 6 cycles and up to 10 cycles, followed by continued use of bevacizumab as single agent until disease progression.

2.2   The summary of product characteristics lists the following adverse reactions that may be associated with bevacizumab treatment: gastrointestinal perforations, fistulae, wound healing complications, hypertension, proteinuria, arterial and venous thromboembolism, haemorrhage, pulmonary haemorrhage or haemoptysis, congestive heart failure, 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 net prices of £242.66 and £924.40 respectively (excluding VAT; BNF edition 65). The manufacturer estimated the cost of a course of treatment with bevacizumab (excluding VAT and assuming vials are not shared between patients) to be £25,208 for a patient weighing 60.5 kg at a dosage of 15 mg/kg every 3 weeks for a mean treatment duration of 10.8 cycles (7.5 months). Costs may vary in different settings because of negotiated procurement discounts.

3 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 gemcitabine and carboplatin came from 1 randomised controlled trial (OCEANS). This double-blind, randomised, placebo-controlled trial assessed the safety and efficacy of bevacizumab plus gemcitabine and carboplatin in 484 adults with platinum-sensitive recurrent epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer, with a first recurrence of ovarian cancer and who had not previously received vascular endothelial growth factor (VEGF) receptor-targeted agents. The trial was a multicentre study conducted in 96 centres in the USA. Patients were randomised to 1 of the following 2 treatment arms:

- Bevacizumab plus gemcitabine and carboplatin (n=242; bevacizumab 15 mg/kg body weight on day 1 every 3 weeks, carboplatin at a dose corresponding to an area under the curve of concentration versus time of 4 mg/ml•min on day 1 every 3 weeks, and gemcitabine 1,000 mg/m^2 on days 1 and 8 every 3 weeks for 6 to 10 cycles; followed by bevacizumab 15 mg/kg body weight alone on day 1 every 3 weeks until disease progression or unacceptable toxicity).

- Placebo plus gemcitabine and carboplatin (n=242; placebo on day 1 every 3 weeks, carboplatin area under the curve 4 mg/ml•min on day 1 every 3 weeks, and gemcitabine 1,000 mg/m^2 on days 1 and 8 every 3 weeks for 6 to 10 cycles; followed by placebo alone on day 1 every 3 weeks until disease progression or unacceptable toxicity).

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

3.2 The primary outcome was progression-free survival (PFS), defined as the period from randomisation to disease progression or death (from any cause). Progression was assessed by investigators using radiological evaluation

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

3.3   Analysis of the primary outcome, PFS in the intention-to-treat population, was based on a cut-off date of 17 September 2010, once 338 (70%) patients had experienced disease progression or died (62.4% of patients in the bevacizumab arm and 77.3% in the placebo arm). The median follow-up was 24 months. Data for patients whose disease had not progressed or who had not died at the time of the last tumour assessment were censored (that is, excluded from the analysis from that point onwards). Data for patients who received non-protocol therapy before disease progression were also censored at the time of the last tumour assessment before therapy was initiated. At 29.8 months, all patients still at risk in the bevacizumab arm had experienced disease progression or had died, and at 24.9 months, 2 patients remained at risk in the placebo arm. Results of the investigator-assessed analysis showed that there was a statistically significant difference of 4 months between the median PFS in the bevacizumab arm compared with the placebo arm (bevacizumab 12.4 months, placebo 8.4 months). In the stratified analysis, there was a 51.6% reduction in disease progression in patients in the bevacizumab arm compared with those in the placebo arm (hazard ratio [HR] 0.48, 95% confidence interval [CI] 0.39 to 0.61, p<0.0001). An unstratified analysis showed a reduction in disease progression of 50.8% with bevacizumab compared with placebo (HR 0.49, 95% CI 0.40 to 0.61, p<0.0001). An IRC analysis of PFS on the same data and a sensitivity analysis without censoring patients for receiving non-protocol therapies were also conducted. The IRC analysis results of PFS were consistent with the primary analysis showing a reduction in disease progression in patients in the bevacizumab arm compared with the placebo arm (bevacizumab 12.3 months, placebo 8.6 months; HR 0.45,

95% CI 0.35 to 0.58, p<0.0001). Results from the sensitivity analysis that did not censor for non-protocol specified therapy were also consistent with the primary analysis results (bevacizumab 12.4 months, placebo 8.4 months; HR 0.52, 95% CI 0.43 to 0.65).

3.4   PFS results for subgroups based on the predefined stratification factors (platinum-sensitive classification and incidence of cytoreductive surgery for recurrent disease) showed that there was a statistically significant reduction in PFS observed for patients in the bevacizumab arm, irrespective of whether they had undergone cytoreductive surgery for recurrent disease or not. Patients whose disease was partially platinum sensitive showed a median PFS of 11.9 months and 8.0 months with bevacizumab and placebo respectively (HR 0.41, 95% CI 0.29 to 0.58). There was also an increase in PFS in patients whose disease was fully platinum sensitive seen in the bevacizumab arm (HR 0.55, 95% CI 0.41 to 0.73).

3.5   Three interim analyses of overall survival were conducted, 2 of which were protocol specified. None of the interim analyses found a statistically significant difference between bevacizumab and placebo in the duration of overall survival. The first interim analysis was carried out at the time of final PFS analysis (17 September 2010), when approximately 29% of patients had died (median overall survival: 35.5 and 29.9 months in the bevacizumab and placebo arms respectively; HR 0.75, 95% CI 0.54 to 1.05). The second analysis was carried out on 29 August 2011, when approximately 49% of the patients had died (median overall survival: 33.3 and 35.2 months in the bevacizumab and placebo arms respectively; HR 1.03, 95% CI 0.79 to 1.33). The third analysis, using a data cut-off date of 30 March 2012 (required by the European Medicine Agency), was conducted when approximately 59% of the patients had died (median overall survival: 33.4 and 33.7 months in the bevacizumab and placebo arms respectively; HR 0.96, 95% CI 0.76 to 1.21). The manufacturer stated that patients in both study arms in third and subsequent lines of therapy received post-progression bevacizumab (at least 18.1% of patients in the bevacizumab arm and 34.7% in the placebo arm received bevacizumab), and therefore confounding may have occurred.

3.6   Objective response rate, according to investigator assessment, was statistically significantly different between the 2 arms (78.5% in the bevacizumab arm

compared with 57.4% in the placebo arm, p<0.0001). Median duration of response was 10.4 and 7.4 months in patients in the bevacizumab and placebo arms respectively. IRC assessment of objective response rate was consistent with the results of the investigator-assessed analysis (bevacizumab 74.8%, placebo 53.7%, p<0.0001).

3.7   All patients in the OCEANS trial experienced an adverse event. More patients in the bevacizumab arm experienced a serious adverse event compared with patients in the placebo arm (34.8% and 24.9% respectively). Adverse events for which the incidence was more than 10% higher in the bevacizumab arm than in the placebo arm were hypertension, nose bleeds, headache and proteinuria. Adverse events of special interest (grades 3 to 5) that occurred with an incidence of at least 2% higher in the bevacizumab arm compared with the placebo arm were hypertension, proteinuria and non-central nervous system bleeding. The proportion of patients who experienced an adverse event that led to discontinuation was larger in the bevacizumab arm (19.8%) compared with the placebo arm (4.7%). However, the absolute number of patients stopping treatment because of adverse events was unclear.

3.8   The manufacturer carried out a literature review and identified 4 randomised controlled trials (CALYPSO, ICON4, AGO-OVAR-2.5 and OCEANS) that had assessed the comparative clinical effectiveness of the following comparators:

- paclitaxel plus platinum-based treatment compared with pegylated liposomal doxorubicin hydrochloride plus platinum-based treatment

- platinum-based treatment (monotherapy) compared with paclitaxel plus platinum-based treatment

- gemcitabine plus platinum-based treatment compared with platinum-based treatment (monotherapy)

- bevacizumab plus gemcitabine and carboplatin compared with gemcitabine plus carboplatin treatment.

  After assessing the feasibility of conducting an indirect comparison of bevacizumab plus gemcitabine and carboplatin with the comparators listed in the final scope, the manufacturer decided against carrying out a network meta-analysis.

3.9   The manufacturer submitted a de novo economic analysis that assessed the cost effectiveness of bevacizumab plus carboplatin and gemcitabine compared with placebo plus carboplatin and gemcitabine for treating people with advanced, recurrent, platinum-sensitive ovarian cancer. The model was a 3-state semi-Markov model with health states consisting of PFS, progressed disease and death. Data from the OCEANS trial were used to guide model inputs. Because the drug dose is dependent on characteristics (such as body weight, body surface area and creatinine clearance rates) that are influenced by age, demographic data from a UK study were used by the manufacturer in their base case to calculate the dose of bevacizumab, carboplatin and gemcitabine. The cost-effectiveness analysis was conducted from an NHS and personal social services perspective, costs and outcomes were discounted at 3.5% per annum and a 10-year time horizon was used. The cycle length was 1 week.

3.10   PFS in the model used the Kaplan–Meier survival curves from the OCEANS trial based on the (intention-to-treat population) investigator-assessed analysis (data cut-off date September 2010). The manufacturer examined the fit of various parametric functions to the PFS data and considered a log-logistic model as the best fit to estimate and extrapolate the proportion of patients in the PFS health state. The overall survival from the OCEANS trial (data cut-off date September 2010) was used in the model to estimate the proportion of people in the progressed-disease health state and, implicitly, the death state. The manufacturer also applied a log-logistic distribution to the Kaplan–Meier curves. The incidence of adverse events adopted in the model was derived from adverse events (cut-off September 2010) of at least grade 3 that occurred in more than 2% regardless of the study arm. The manufacturer used the number of patient events to assign a cost associated with each adverse event.

3.11   Health-related quality of life and utilities applied in the model were obtained from NICE's technology appraisal guidance on trabectedin for the treatment of relapsed ovarian cancer (now replaced by NICE's technology appraisal guidance on topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer). The data used in this guidance were taken from the OVA-301 trial using EQ-5D. The utility values used in the model for PFS and progressed-disease health states were 0.718 and 0.649 respectively. The manufacturer assumed in the model that health-related quality of life remained constant during PFS and reduced once

disease progressed but remained constant after that. The manufacturer did not apply disutilities caused by adverse events in the model.

3.12 Drug costs were estimated using the dose and frequency of administration in the summary of product characteristics. Data from a UK cohort study (Sacco et al. 2010) were used in the dose calculations. The base case assumed that any unused carboplatin and paclitaxel from a vial was reallocated and not wasted, whereas for bevacizumab, it was assumed that any unused drug in a vial was wasted. For bevacizumab and carboplatin, the manufacturer used public list prices from the BNF, and the price of gemcitabine (£12.57 for a 1,000 mg vial) was obtained from the Commercial Medicines Unit (CMU) 2012 electronic Market Information Tool (eMit). Costs of drug administration were taken from the Unit Costs of Health and Social Care and NHS reference cost data, and included in the model. The weekly costs of supporting patients in the PFS and progressed health states were also included. Costs of palliative care were applied to patients as they moved to the death state. Costs of post-progression therapies were taken from the OCEANS trial (cut-off date September 2010) and included other chemotherapy drugs, radiotherapy or surgery. These costs were added together and applied as a one-off cost in the model, and so were not subject to discounting. Costs associated with adverse events that occurred at grade 3 or 4 severity in more than 2% of patients from the OCEANS trial (cut-off date September 2010) were incorporated into the analysis. NHS reference costs were utilised when possible; all adverse events were assumed to occur in cycle 1 of the model, so costs were not discounted.

3.13 The base-case results estimated that adding bevacizumab to carboplatin and gemcitabine provides an additional 0.42 life years and 0.298 quality-adjusted life years (QALYs). These benefits are achieved with an incremental cost of £44,428, resulting in an incremental cost-effectiveness ratio (ICER) of £149,050 per QALY gained for bevacizumab plus carboplatin and gemcitabine compared with carboplatin and gemcitabine alone. The manufacturer's deterministic sensitivity analysis suggested that the cost-effectiveness results were most sensitive to assumptions around the extrapolation of overall survival, the duration of treatment and the utility of patients in PFS. The manufacturer's probabilistic sensitivity analyses concluded that the probability of bevacizumab plus carboplatin and gemcitabine being cost effective compared with carboplatin and gemcitabine alone at a threshold of £30,000 per QALY gained was 0%. The

manufacturer identified the key drivers of the cost-effectiveness results to be the cost and duration of treatment with bevacizumab and the time horizon of the analysis.

3.14 The ERG considered the OCEANS trial to be well designed and agreed that, except for baseline weight, the characteristics of the patient population enrolled in the trial were representative of people with first recurrence of ovarian cancer in England and Wales. The ERG noted that the course of treatment assumed in the OCEANS trial (allowing up to a maximum of 10 cycles of bevacizumab plus carboplatin and gemcitabine) may not fully represent clinical practice in the UK (where a maximum of 6 cycles of chemotherapy would be administered). The ERG also noted that the main comparator in the manufacturer's submission was gemcitabine plus carboplatin, whereas this may not be the treatment routinely used in the NHS.

3.15 The ERG highlighted the differences between the number of recorded events in terms of PFS in the investigator-assessed analysis and the IRC-determined analysis. The ERG also highlighted that the number of patients censored in each group at the time of final PFS analysis (September 2010), and the mean PFS and the number of patients lost to follow-up at the time of the final analysis were unknown. The ERG also noted that the absolute number of patients stopping treatment because of an adverse event varied in the manufacturer's submission, and the correct number remained unclear after seeking clarification from the manufacturer.

3.16 The ERG considered the literature search and the reasons given by the manufacturer for not performing an indirect comparison between bevacizumab plus carboplatin and gemcitabine, and the other comparators listed in the scope. The ERG considered that the differences between trials were sufficiently minor such that their inclusion would have a minimal impact on clinical heterogeneity, and decided to perform a network meta-analysis for the primary outcome measure (PFS). Results from the network meta-analysis performed by the ERG suggested that bevacizumab plus carboplatin and gemcitabine is associated with a statistically significant improvement in duration of PFS compared with all comparators listed in the scope (bevacizumab plus carboplatin and gemcitabine compared with: paclitaxel plus carboplatin, HR 0.47, 95% credible interval [CrI] 0.33 to 0.66; pegylated liposomal doxorubicin hydrochloride plus

carboplatin, HR 0.58, 95% CrI 0.39 to 0.82; platinum monotherapy, HR 0.35, 95% CrI 0.25 to 0.47; gemcitabine plus carboplatin, HR 0.48, 95% CrI 0.38 to 0.60). Results from the network meta-analysis also suggested that there were no statistically significant differences between most of the other comparators.

3.17   The ERG considered the manufacturer's model structure was appropriate to describe the decision problem and was well constructed and transparent. The ERG highlighted and agreed with the manufacturer that the main criticism of the submitted economic evaluation was the use of the September 2010 OCEANS clinical-effectiveness, cost and adverse-event incidence data. The ERG suggested that the use of data from September 2010, when 29% of the patients had died (rather than data from March 2012, when available, when 59% of the patients had died), may have introduced unnecessary uncertainty into the estimate of the ICER and may have overestimated the overall survival benefit associated with bevacizumab because the analysis of overall survival in September 2010 showed a non-statistically significant overall survival increase for patients in the bevacizumab group, which was not sustained in the 2 later interim analyses. The ERG noted that overall survival was a key driver in the model and estimated that approximately 90% of the QALYs gained in the model were a function of the overall survival. The ERG conducted a scenario analysis assuming that overall survival was the same for patients in both treatment groups. The result of the analysis was an increase in the ICER to over £1.7 million per QALY gained.

3.18   The ERG noted that the manufacturer applied a parametric log-logistic function to the Kaplan–Meier PFS data (cut-off date September 2010) from the OCEANS trial to estimate and extrapolate the proportion of patients in the progression-free health state. At a median follow-up of 24 months (final PFS analysis), 70% of the patients had either experienced disease progression or died. Patients in the bevacizumab arm reached 0% PFS at month 29.8, whereas 2 patients remained at risk at month 24.9 in the placebo arm. The ERG assumed in their exploratory analysis that, by 29 months, all patients would have had disease progression or died according to the last Kaplan–Meier data available, and suggested that mean values for PFS might be available, rather than only medians. The ERG also had concerns about fitting a parametric distribution for PFS given the Kaplan–Meier data available and undertook a scenario analysis using only the Kaplan–Meier data, although this did not have a significant impact on the ICER.

3.19   The ERG noted that adverse events experienced by patients in the model were not subject to estimates of disutility and suggested that this was likely to favour the cost effectiveness of bevacizumab because a larger proportion of patients in the bevacizumab treatment group experienced a serious adverse event compared with the placebo group in the OCEANS trial. The ERG conducted a scenario analysis and assessed a range of average duration of adverse event disutilities. It concluded that, for example, for an average event duration of 1 week, the ICER increased to £149,391 per QALY gained and, for an average adverse event duration of 1 month, the ICER increased to £150,544 per additional QALY gained.

3.20   The ERG explored the impact of the network meta-analysis results in terms of cost effectiveness. The ERG assumed, based on the these results, that overall survival and PFS estimates for patients in every comparator group were the same as for patients in the placebo group in the manufacturer's model. Cost-effectiveness results from the ERG exploratory analysis were:

- ICER for bevacizumab plus gemcitabine and carboplatin compared with carboplatin £159,273 per QALY gained

- ICER for bevacizumab plus gemcitabine and carboplatin compared with paclitaxel plus carboplatin £148,014 per QALY gained

- ICER for bevacizumab plus gemcitabine and carboplatin compared with pegylated liposomal doxorubicin hydrochloride plus carboplatin £145,621 per QALY gained.

3.21   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 gemcitabine and carboplatin, having considered evidence on the nature of recurrent advanced ovarian cancer and the value placed on the benefits of bevacizumab plus gemcitabine 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 recurrent advanced ovarian cancer. It noted comments received from the professional groups that paclitaxel plus carboplatin; carboplatin as monotherapy; cisplatin monotherapy (in patients who are allergic to carboplatin); gemcitabine plus carboplatin; pegylated liposomal doxorubicin hydrochloride monotherapy; pegylated liposomal doxorubicin hydrochloride plus carboplatin; and pegylated liposomal doxorubicin hydrochloride plus trabectedin (which in some cases is considered a key treatment for patients whose disease is partially platinum sensitive, specifically those who are allergic to platinum) are the most relevant therapies for treating recurrent advanced ovarian cancer in patients whose disease is platinum sensitive or partially platinum sensitive. The Committee also heard from clinical specialists that pegylated liposomal doxorubicin hydrochloride is not currently available and for patients whose disease is platinum sensitive, the most commonly used treatment would be paclitaxel plus carboplatin. The clinical specialists highlighted that gemcitabine plus carboplatin is not the most commonly used treatment in UK clinical practice but stated that its use may increase in the future, particularly in light of the combination therapy being appraised (bevacizumab plus gemcitabine and carboplatin). The Committee heard from the clinical specialists that this new combination therapy had been used in the UK in this patient group only on a compassionate basis before it received its marketing authorisation.

4.3   The Committee heard from patient experts the importance of increasing progression-free survival (PFS). The patient experts highlighted that, once the cancer relapses, further recurrence is expected. Therefore, increasing PFS gives additional time to deal with the physical, emotional and psychological effects of ovarian cancer and its treatment, and allows patients and their families to come

to terms with the implications of relapse. The patient experts also noted that gains in PFS may seem small to people not affected by the disease; however, to patients and their families, this additional period of time is extremely important in helping them to recover from the shock of relapse, and enables them to use the period of wellbeing to make the most of their lives. The clinical specialists reiterated the patient experts' comments about the importance of PFS. The Committee also noted comments received from a consultee in response to the appraisal consultation document restating the importance of PFS to patients. The Committee also heard from the patient experts that they considered bevacizumab to be an innovative technology because, outside clinical trials, there are very few options for treating recurrent ovarian cancer other than standard chemotherapy, and therefore this was seen as a new beneficial development.

4.4　　The Committee considered the importance of platinum sensitivity and the platinum-free interval for the prognosis of the disease. It heard from the clinical specialists that the most effective treatment for ovarian cancer is platinum-based chemotherapy. Some people's tumours respond better to this than others and the term platinum sensitivity refers to the length of initial remission after first-line platinum chemotherapy. For people whose disease shows a response to platinum, there is an arbitrary classification into platinum-resistant disease (less than a 6-month disease-free interval) and platinum-sensitive disease (more than a 6-month disease-free interval). The Committee heard that the development of drugs that increase the length of the platinum-induced remission will allow some people to achieve a platinum-free interval of 6 months or more. It also heard that there is an underlying assumption that, if the platinum-free interval is longer, the disease will respond better to platinum (that is, be more platinum sensitive) when the drug is re-administered. Some of the assumptions related to platinum sensitivity and the platinum-free interval are currently being tested in trials.

Clinical effectiveness

4.5　　The Committee considered that the main source of evidence for the clinical effectiveness of bevacizumab plus gemcitabine and carboplatin was the OCEANS trial that had been conducted in the USA. The Committee agreed with the Evidence Review Group's (ERG's) comments that overall, this was a well-designed double-blind, randomised, placebo-controlled trial. The Committee

understood from the clinical specialists that there were no clinical differences
between the patients in the trial and patients in the UK with recurrent ovarian
cancer, apart from body weight and body surface area. The Committee heard
from the clinical specialists that the comparator used in the trial, gemcitabine and
carboplatin, is not the most widely used treatment option for recurrent advanced
ovarian cancer in the NHS. However, it also heard that gemcitabine and
carboplatin could be considered to have a similar efficacy to other treatment
options currently used in the NHS, particularly in terms of PFS. The Committee
concluded that the results from the OCEANS trial were generalisable to UK
clinical practice.

4.6   The Committee discussed PFS results reported in the manufacturer's submission
based on the OCEANS trial. It noted that the results for the intention-to-treat
population at the September 2010 cut-off date gave a difference in median PFS
of 4 months in favour of bevacizumab and this was statistically significant. The
Committee noted that in the OCEANS trial, there was a statistically significant
difference of approximately 20% in response rate with bevacizumab plus
gemcitabine and carboplatin compared with gemcitabine and carboplatin,
indicating that bevacizumab is an active drug. Nevertheless, it also
acknowledged the ERG's concerns about the issue of censoring. The Committee
noted that the data from approximately 30% of the patients had been censored
and it was unclear whether these data had been censored because of patients
stopping treatment because of adverse events or patients being lost to follow-up.
It heard from the manufacturer that information on the number of patients for
whom data were censored and the reason why, was not available at the time of
the submission. The Committee concluded that, although the trial showed an
increase in PFS for bevacizumab plus gemcitabine and carboplatin compared
with gemcitabine and carboplatin, it was unclear what effect censoring might
have had on these results.

4.7   The Committee considered the most relevant overall survival results for the
clinical effectiveness of bevacizumab plus gemcitabine and carboplatin. It
explored the 3 interim analyses presented by the manufacturer and noted that
none of the analyses showed a statistically significant increase in overall survival
in the bevacizumab-treated group. Although the first interim analysis showed a
trend towards increased overall survival in the bevacizumab arm (35.5 and
29.9 months in the bevacizumab and placebo groups respectively), in the second

and third interim analyses, the difference in median overall survival favoured placebo (1.9 months and 0.3 months respectively). The Committee agreed with the manufacturer's comments that the lack of statistically significant differences between bevacizumab and placebo could have been affected by confounding effects of post-progression treatments. It noted that 18.1% of patients in the bevacizumab arm and 34.7% of patients in the placebo arm received bevacizumab post progression, but also noted that bevacizumab is not licensed for this stage in the treatment pathway because its licence is for first recurrence only. The Committee noted that more than 85% of the patients in both study arms had 3 or more lines of anti-cancer therapy post progression, and it heard from the clinical specialists that it would therefore be very difficult to see any overall survival benefit from bevacizumab with this high level of post-progression treatment without a very much larger trial population. The Committee also heard from the clinical specialists that, although the third interim analysis (March 2012) may be the most reliable because at this stage 59% of patients had died, there could be a bigger issue with confounding. In contrast, the first interim analysis (September 2010) contained overall survival data for only 29% of patients, but may be less confounded by post-progression treatments. The Committee expressed a preference for the more mature and complete overall survival data, but acknowledged that the argument about which were the most reliable data was finely balanced. The Committee concluded that no overall survival benefit for bevacizumab plus gemcitabine and carboplatin had been shown in the OCEANS trial, but the results could have been confounded by post-progression therapies.

4.8   The Committee considered reasons for the discrepancy between the PFS and overall survival results in the OCEANS trial for bevacizumab plus gemcitabine and carboplatin for treating recurrent advanced ovarian cancer. It noted that there were 3 possible underlying causes for the differences:

- the high degree of censoring and the lack of clarity regarding how this might have affected the PFS results (see section 4.6)

- the confounding effects on overall survival results because of the use of post-progression treatments (see section 4.7)

- the potential biological action of bevacizumab.

    The Committee heard from the clinical specialists that, although not

substantiated in clinical practice, it was biologically plausible that
bevacizumab could increase PFS, but once the disease has progressed,
disease progression could be accelerated once bevacizumab is stopped. This
might be an argument for continuing maintenance treatments such as
bevacizumab beyond the stage of progression. Following comments received
from the manufacturer in response to the appraisal consultation document,
the Committee reconsidered the 3 possible underlying causes for the
differences between PFS and overall survival results. It noted the
manufacturer's comment that the overall survival results could have been
affected by confounding effects because of the use of post-progression
treatments. However, the Committee agreed that the high degree of
censoring of PFS estimates and the potential biological action of
bevacizumab could also be explanations for the difference in the results. The
Committee remained unable to draw any firm conclusions as to which of
these issues explained the mismatch, and to what extent.

4.9   The Committee considered the adverse events reported in the OCEANS trial and
noted that more patients in the bevacizumab arm (19.8%) stopped treatment
because of adverse events than in the placebo arm (4.7%). It heard from the
clinical specialists that the discontinuation rate in UK clinical practice would be
expected to be lower than in the clinical trial and that most adverse events can
be satisfactorily managed. The Committee also heard from one of the patient
experts that they had experienced gastrointestinal problems during and after
chemotherapy. However, it heard from the patient experts that these problems
are usually well managed by clinicians and do not necessarily disrupt a patient's
daily life or quality of life. The Committee concluded that the adverse events
related to treatment with bevacizumab plus gemcitabine and carboplatin were
similar to those related to other chemotherapy regimens and that these events
were manageable.

Cost effectiveness

4.10   The Committee discussed the manufacturer's cost-effectiveness estimates,
derived from the manufacturer's economic model based on data from the
OCEANS trial, and the assumptions in the model. The Committee noted the ERG's

comments that it considered the manufacturer's model structure to be generally appropriate, well constructed and transparent. 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 gemcitabine and carboplatin for treating recurrent advanced ovarian cancer.

4.11   The Committee did, however, acknowledge that there were potential shortcomings with some of the assumptions used in the manufacturer's economic model. It noted that health-related quality-of-life data were not collected in the OCEANS trial. The Committee agreed that health-related quality-of-life data collected in the trial would have been preferable for deriving the utilities for the economic model. It noted that the estimates of utility for the PFS and progressed-disease health states were derived from a previous model submitted to NICE (NICE's technology appraisal guidance on trabectedin for the treatment of relapsed ovarian cancer) and that the difference between the utilities for PFS and progressed disease was relatively small (0.718 and 0.649 respectively). The Committee heard from the patient experts that patients may experience a good health-related quality of life while they are progression free. It also noted the comments received from a consultee in response to the appraisal consultation document that reiterated the importance of PFS to patients, and the Committee therefore agreed that it may be plausible for a larger decrement in utility to occur when a person moves from the progression-free health state to a progressed-disease health state and that the difference in utility between the PFS state and progressed state used by the manufacturer could be an underestimate. The Committee also noted that a disutility associated with adverse events was not applied and that there were more serious adverse events in the bevacizumab arm than in the placebo arm. It also discussed how the PFS results were incorporated in the manufacturer's economic model. The Committee noted the ERG's comments on the extrapolation of PFS results by fitting a log-logistic distribution when the Kaplan–Meier data were available. It acknowledged the manufacturer's and ERG's sensitivity and scenario analyses, and concluded that taking all these relevant issues into account (that is, using a higher utility value for the PFS state, including a disutility for adverse events or using the Kaplan–Meier data for PFS) would not be likely to have a significant effect on the incremental cost-effectiveness ratio (ICER).

4.12   The Committee discussed the overall survival data used in the model and noted

the ERG's comments that 90% of the quality-adjusted life years (QALYs) gained in the model were a function of the overall survival. It noted that the overall survival data from the first interim analysis (September 2010), in which bevacizumab showed a non-statistically significant increase in overall survival compared with placebo, had been used by the manufacturer in the model with a resulting ICER of £149,000 per QALY gained. The Committee acknowledged its earlier discussion about the uncertainty around the overall survival estimates (see section 4.7). It noted that the manufacturer was unable to provide the ERG with the March 2012 overall survival data and noted that the ERG scenario analysis, which assumed an equivalent overall survival gain for patients in both treatment arms, had resulted in an ICER of over £1.7 million per QALY gained. The Committee concluded that overall survival was the biggest driver of the cost-effectiveness estimate and that, in principle, it would have liked to have seen a sensitivity analysis from the manufacturer that used the March 2012 data, which would have resulted in a higher ICER than the base case.

4.13   The Committee noted the cost-effectiveness results based on the network meta-analysis presented by the ERG. It noted that there were no significant differences in the ICERs for any of the other comparators listed in the scope. The Committee acknowledged that these analyses were exploratory and the underlying assumption was that all comparators had an efficacy similar to that of gemcitabine and carboplatin. It considered this to be a reasonable assumption (see section 4.5) and therefore concluded that the ICER for other comparators was unlikely to be significantly different from that calculated for gemcitabine and carboplatin.

4.14   The Committee considered the most plausible ICER from the model based on the OCEANS trial presented by the manufacturer and by the ERG in their exploratory analyses. It agreed that the manufacturer's base-case ICER, using the September 2010 overall survival data of £149,000 per QALY gained, was likely to be an optimistic cost-effectiveness estimate and that the most plausible ICER could be much higher than this. The Committee noted that the cost-effectiveness estimates for bevacizumab plus gemcitabine and carboplatin were outside the range normally considered to be a cost-effective use of NHS resources. It therefore concluded that bevacizumab plus gemcitabine and carboplatin would not be a cost-effective use of NHS resources for treating the first recurrence of platinum-sensitive advanced ovarian cancer compared with gemcitabine and

carboplatin alone.

4.15 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of people with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.

- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.

- The treatment is licensed or otherwise indicated for small patient populations.

  In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.16 The Committee discussed whether bevacizumab plus gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer fulfilled the criteria for a life-extending, end-of-life treatment. It noted that bevacizumab is licensed for a relatively large population across a range of indications in the treatment of breast, colorectal, renal and non-small-cell lung cancers. Therefore, it does not meet the criterion of the supplementary advice that the treatment should be licensed for small populations. Having established that bevacizumab did not meet the population criterion, the Committee decided it was not necessary to make a decision about the life-expectancy or extension-to-life criteria. It concluded that, on this basis, bevacizumab plus gemcitabine and carboplatin did not fulfil the criteria for being a life-extending, end-of-life treatment.

4.17 The Committee noted the manufacturer's opinion that bevacizumab was an innovative treatment. It acknowledged that advanced recurrent ovarian cancer is

a disease with limited treatment options, and that bevacizumab represented a
novel biological approach to therapy. It also noted the patient expert comment
(see section 4.3). However, the Committee concluded that all substantial benefits
related to treatment with bevacizumab plus gemcitabine 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

General Practitioner, Heartwood Medical Centre, 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

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

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, Health Economics Research Group, Brunel University

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

General Practitioner, 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 & Dohme

Ms Ellen Rule

Programme Director, NHS Bristol

Dr Peter Sims

General Practitioner, Devon

Mr David Thomson

Lay Member

Dr John Watkins

Clinical Senior Lecturer and Consultant in Public Health Medicine, Cardiff University and 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.

Pilar Pinilla-Dominguez

Technical Lead

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 BMJ Technology Assessment Group (BMJ-TAG):

- Edwards SJ, Barton S, Thurgar E et al. Bevacizumab for the treatment of recurrent advanced ovarian cancer: a single technology appraisal. BMJ-TAG, November 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, 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:

- Ovacome

- Ovarian Cancer Action

- Royal College of Nursing

- Royal College of Pathologists

- Royal College of Physicians

- Target Ovarian Cancer

- United Kingdom Oncology Nursing Society

Other consultees:

- Department of Health

- Welsh Assembly Government

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

- BMJ-TAG

- Commissioning Support Appraisals Service

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

- Eli Lilly (gemcitabine)

- Health Improvement Scotland

- National Institute for Health Research Health Technology Assessment Programme

- Pfizer (pegylated liposomal doxorubicin hydrochloride)

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 initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Professor Jonathan A Ledermann, Professor of Medical Oncology, UCL Cancer Institute and Clinical Director Cancer Services UCL Hospitals, nominated by organisation representing Royal College of Physicians (NCRI, RCP, RCR, ACP, JCCO) – clinical specialist

- Professor Charlie Gourley, Professor of Medical Oncology, nominated by organisation representing Royal College of Physicians (NCRI, RCP, RCR, ACP, JCCO) – clinical specialist

- Mrs Annie Chillingworth, nominated by organisation representing Ovarian Cancer Action – patient expert

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

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