Bevacizumab for the treatment of recurrent advanced ovarian cancer

STA REPORT

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Samantha Barton	Critical appraisal of the manufacturer's submission; critical appraisal of the clinical evidence; carried out exploratory indirect comparison; cross checking of manufacturer's search strategies; and drafted the background and clinical results sections
Elizabeth Thurgar	Critical appraisal of the manufacturer's submission; critical appraisal of the economic model; critical appraisal of the economic evidence; and drafted the economic analysis sections
Leo Nherera	Critical appraisal of the manufacturer's submission; critical appraisal of the economic model; critical appraisal of the economic evidence; and drafted the economic analysis sections
Victoria Hamilton	Critical appraisal of the manufacturer's submission; critical appraisal of the clinical evidence; and validation of the exploratory indirect comparison
Charlotta Karner	Critical appraisal of the manufacturer's submission; and critical appraisal of the clinical evidence
Nicola Trevor	Critical appraisal of the manufacturer's submission; critical appraisal of the economic model; and critical appraisal of the economic evidence

All authors read and commented on draft versions of the ERG report

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Abbreviations

AESI	Adverse events of special interest
AGO	Arbeitsgemeinschaft Gynaekologische Onkologie
AIC	Akaike information criterion
AUC	Area under the curve
BIC	Bayesian information criterion
BNF	British National Formulary
BSA	Body surface area
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMU	Commercial Medicines Unit
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOC	Epithelial ovarian cancer
EQ-5D	EuroQol 5 dimensions questionnaire
ERG	Evidence Review Group
FIGO	International Federation of Gynecology and Obstetrics
FTC	Fallopian tube cancer
G-CSF	Granulocyte colony-stimulating factor
GP	General Practitioner
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IRC	Independent Review Committee
IRFMN	Istituto Mario Negri
ITT	Intention-to-treat
IVRS	Interactive voice response system
kg	Kilogram
LYG	Life-years gained
mg	Milligram
mL	Millilitre
mm	Millimetre
MRC CTU	Medical Research Council's Clinical Trials Unit
MS	Manufacturer's submission

MTA	Multiple Technology Appraisal
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NMA	Network meta-analysis
OCEANS	Ovarian cancer study comparing efficacy and safety of chemotherapy and anti-angiogenic therapy in platinum-sensitive recurrent disease
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PFS	Progression-free survival
PLDH	Pegylated liposomal doxorubicin hydrochloride
PPC	Primary peritoneal cancer
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria for Solid Tumors
SD	Standard deviation
SE	Standard error
SLD	Sum of longest diameters
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal
TTP	Time to progression
UK	United Kingdom
USA	United States of America
VEGF	Vascular endothelial growth factor
vs	versus
WHO	World Health Organization

1 SUMMARY

1.1 Critique of the decision problem in the manufacturer's submission

The manufacturer of bevacizumab (Avastin; Roche) submitted to the National Institute for Health and Clinical Excellence (NICE) clinical and economic evidence in support of the effectiveness of the addition of bevacizumab to gemcitabine and carboplatin in the treatment of first recurrence of platinum-sensitive ovarian cancer.

At the time of writing of the Evidence Review Group's (ERG) report, bevacizumab does not have a European licence for use in recurrent ovarian cancer. However, in September 2012, the Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on the use of bevacizumab in combination with gemcitabine plus carboplatin for the treatment of patients with first-recurrence of platinum-sensitive ovarian cancer (comprising epithelial ovarian cancer [EOC], fallopian tube cancer [FTC], and primary peritoneal cancer [PPC]) who have not received prior therapy with a vascular endothelial growth factor (VEGF) inhibitor or VEGF receptor-targeted agent.

The clinical evidence described in the MS is derived from the OCEANS randomised controlled trial (RCT). OCEANS enrolled patients with histologically confirmed recurrence of ovarian cancer at least 6 months after completion of first-line platinum-based chemotherapy (i.e., platinum-sensitive disease). The ERG considers that the population in OCEANS represents a slightly narrower population than that defined in the final scope issued by NICE, in that the scope did not specify a population of first recurrence of platinum-sensitive ovarian cancer. However, based on the positive opinion issued by the CHMP, it is anticipated that the licence for bevacizumab will restrict its use to treatment of first-recurrence of platinum-sensitive ovarian cancer. With the exception of health-related quality of life (HRQoL), all clinically relevant outcomes were reported within the MS.

The ERG considers that, in the context of the comparisons of interest, the MS does not fully address the decision problem that is the focus of this Single Technology Appraisal (STA). The scope issued by NICE lists comparators of interest as:

- paclitaxel in combination with a platinum compound;
- gemcitabine in combination with carboplatin;
- pegylated liposomal doxorubicin hydrochloride (PLDH) in combination with a platinum compound;
- platinum-based chemotherapy as monotherapy.

The OCEANS trial evaluated adding bevacizumab versus adding placebo to gemcitabine plus carboplatin. Thus, direct evidence is available for only one comparator listed in the final scope. Although gemcitabine plus carboplatin is used in UK clinical practice, at this time, the doublet chemotherapy is not recommended by NICE as a second-line chemotherapeutic treatment for

recurrent platinum-sensitive ovarian cancer. The ERG's clinical expert fed back that paclitaxel plus carboplatin would be the preferred treatment in the UK for patients with recurrent platinum-sensitive ovarian cancer, particularly for patients who relapse >12 months after completion of first-line chemotherapy. At this time, PLDH is unavailable in the UK. Expert opinion is that use of PLDH plus carboplatin in the treatment of recurrent platinum-sensitive ovarian cancer is likely to increase when PLDH becomes available once again. The manufacturer carried out a systematic review of the literature to identify studies that could potentially inform a network meta-analysis (NMA). In addition to the OCEANS trial, the manufacturer identified publications on three other large trials in recurrent platinum-sensitive ovarian cancer that evaluated regimens listed as comparators of interest in the scope. After evaluating the trials and seeking statistical advice on the feasibility of an indirect comparison, the manufacturer decided against carrying out an NMA. However, the ERG considers that an NMA could have been attempted.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The OCEANS trial was a US-based multicentre, double-blind, parallel-group study that included 484 patients with first-recurrence of platinum-sensitive ovarian cancer. Bevacizumab was given initially as a concurrent treatment added to gemcitabine plus carboplatin. After completion of gemcitabine plus carboplatin cycles (maximum of 10 cycles), treatment with bevacizumab was maintained until disease progression or unacceptable toxicity, whichever occurred first. Bevacizumab was administered intravenously at a dose of 15 mg/kg on day 1 of each cycle, before administration of gemcitabine plus carboplatin.

Investigator-assessed progression-free survival (PFS) was the primary outcome evaluated in OCEANS, with PFS defined as the time from random assignment to disease progression (investigator-determined) or death from any cause. Addition of bevacizumab to gemcitabine plus carboplatin was associated with a statistically significant increase in the duration of PFS compared with placebo (Hazard ratio [HR] 0.48; 95% CI: 0.39 to 0.61; p <0.0001). Median duration of PFS was 12.4 months in the bevacizumab group compared with 8.4 months in the placebo group. The manufacturer proposes that strategies that extend duration of PFS, thereby prolonging the platinum-free interval, are important for improving patient outcomes and prognosis in subsequent lines of treatment.

Secondary outcomes evaluated in OCEANS were overall survival (OS), investigator-assessed objective response rate (ORR), and median duration of objective response. Sensitivity analyses included analyses based on evaluation of PFS, ORR, and median duration of response by an independent-review committee (IRC).

ORR was defined as the occurrence of a complete or partial response, and was confirmed by a repeat assessment performed ≥4 weeks after the criteria for response were first met. Based on investigator-assessed ORR, a statistically significant larger proportion of patients achieved an objective response with bevacizumab compared with placebo (190/242 [78.5%] in the bevacizumab group vs 139/242 [57.4%] in the placebo group; p <0.0001). In addition, the proportion of patients achieving a complete response was larger with bevacizumab (42/242 [17.4%] with bevacizumab vs 22/242 [9.1%] with placebo; statistical significance not reported). Of the patients achieving objective response, those in the bevacizumab group had a longer investigator-assessed median duration of response compared with those in the placebo group (10.4 months with bevacizumab group vs 7.4 months with placebo), with a 47% reduction in the risk of disease progression compared with placebo (HR 0.53; 95% CI: 0.41 to 0.67; p <0.0001).

The results of the sensitivity analysis for PFS, ORR, and median duration of response carried out by the IRC seem to support the results of the assessments of the OCEANS investigators.

Within the submitted evidence, the manufacturer presents data from three interim analyses of OS. At the time of writing, OS data from OCEANS are immature. None of the interim analysis found a statistically significant difference between the addition of bevacizumab and the addition of placebo in duration of OS. The direction of effect in the first interim analysis favoured bevacizumab (25% reduction in risk of mortality; HR 0.75; 95% CI: 0.53 to 1.05). The mean effect size generated from the second and third interim analyses approached 1, that is, there was no difference between bevacizumab and placebo in the duration of OS. Moreover, the manufacturer argues that OS data are confounded as a result of administration of bevacizumab post-progression to the placebo group. At the time of the second interim analysis of OS, the manufacturer estimates that 34.7% of patients in the placebo group had received bevacizumab post-progression compared with 18.1% of patients in the bevacizumab group. The ERG agrees with the manufacturer that administration of bevacizumab post-progression is a confounding factor in determination of OS and asserts that confounding of OS data is a well-recognised complexity in clinical trials evaluating treatments for cancer.

The Summary of Product Characteristics (SmPC) for bevacizumab indicates that the most frequently observed adverse effects with bevacizumab are hypertension, fatigue or asthenia, diarrhoea and abdominal pain. Patients with a history of hypertension are at risk of developing proteinuria. In the submitted evidence, a larger proportion of patients in the bevacizumab group experienced an adverse event compared with the placebo group, including various Grade 3 and Grade 4 events, and adverse events of special interest (AESIs). Hypertension, proteinuria, epistaxis, and headache were the adverse effects for which the most substantial difference (>10%) in occurrence was observed between the bevacizumab and placebo groups. In addition, hypertension and proteinuria were two of the AESIs occurring with ≥2% higher incidence in the bevacizumab group compared with the placebo group.

Discontinuation of treatment due to adverse events was higher in the bevacizumab group than in the placebo group. However, statistical analyses comparing the rates of discontinuation or adverse events between the groups were not reported in the MS, and were not provided by the manufacturer during clarification.

1.3 Summary of cost effectiveness submitted evidence by the manufacturer

The manufacturer developed a *de novo* semi-Markov cost-utility model to evaluate the cost-effectiveness of bevacizumab in the treatment of women with recurrent, platinum-sensitive ovarian cancer. The model was constructed with three health states: PFS; progressed disease (PD); and death. The model structure was reflective of previous models developed to assess the cost-effectiveness of interventions in recurrent, advanced ovarian cancer (TA91, TA222).

Rather than estimating the probability of transitioning between health states, the manufacturer estimated the proportion of patients within each of the three health states at each week. Estimates were taken from OCEANS clinical trial data for PFS and OS, using separate parametric models. The data for PFS were taken from September 2010, the final analysis of PFS. The data for OS were also taken from September 2010; this represented the first of three interim analyses of the OS data. Each health state was associated with distinct costs and utility values. Costs captured included drug costs, administration costs, supportive care costs, palliative care costs, post-progression treatment costs, and costs of adverse events. Utilities from a previous technology appraisal in recurrent ovarian cancer (TA222) were applied to the PFS and PD health states (with zero utility applied to the death health state). The model did not consider disutilities, either treatment specific or related to adverse events.

The manufacturer presented both deterministic and probabilistic cost-effectiveness estimates. The manufacturer estimated the incremental cost-effectiveness ratio (ICER) for the bevacizumab group compared with the placebo group to be £149,050 per quality adjusted life year (QALY; deterministic) and £221,750 per QALY (probabilistic). The manufacturer found that the model was sensitive to modelling of OS, the duration of treatment, and the utility of patients in PFS. No deterministic scenario analysis was presented that reduced the ICER to an estimate below £120,000 per QALY. From probabilistic analyses, the manufacturer estimated the probability of the addition of bevacizumab being cost-effective at a willingness-to-pay threshold of £30,000 to be 0%.

1.4 ERG commentary on the robustness of evidence submitted by the manufacturer

1.4.1 Strengths

Clinical

The ERG considers the OCEANS RCT to be a well-designed trial, and considers the results of the submitted evidence to be relevant to the decision problem that is the focus of this STA.

To be eligible for enrolment in OCEANS, patients were required to have first-recurrence of platinum-sensitive ovarian cancer; patients receiving prior chemotherapy in the recurrent setting were excluded. Thus, in terms of number of previous chemotherapeutic treatments, OCEANS includes a clinically homogeneous population.

Economic

The ERG notes that the modelling approach adopted by the manufacturer was reasonable and consistent with previous economic evaluations in recurrent ovarian cancer. The ERG notes that the model was generally well constructed and transparent, although the ERG identified a number of minor errors within the model, and several inconsistencies between the numbers reported in the manufacturer's submission and the model.

1.4.2 Weaknesses

Clinical

Submitted evidence is based on one RCT, which provides direct evidence for only the comparison of adding bevacizumab versus adding placebo to gemcitabine and carboplatin. There is no direct evidence available evaluating the clinical effectiveness of bevacizumab in combination with platinum-based chemotherapy (monotherapy or combination therapy) compared with other platinum-based chemotherapy used in UK clinical practice to treat first-recurrence of platinum-sensitive ovarian cancer. OCEANS allowed patients to receive a maximum of 10 cycles of chemotherapy. Clinical practice in the UK is to administer a maximum of 6 cycles of chemotherapy. There is no evidence to suggest that additional cycles of chemotherapy are associated with increased benefit.

The ERG has concerns around the transparency and consistency in the reporting of the results from the sensitivity analysis based on IRC-determined PFS, ORR, and median duration of response. Within the MS, the manufacturer fully reported data and statistical analyses for the primary analysis of PFS and other investigator-assessed outcomes. By contrast, reporting of corresponding absolute data and results of statistical significance tests for sensitivity analyses was incomplete. The manufacturer was unable to provide all absolute values requested during clarification, indicating that "these data do not appear to be reported in the OCEANS CSR or elsewhere in the relevant publications". Based on the

minimal data provided by the manufacturer at clarification, the ERG has concerns around the considerable discrepancy between the investigator-assessed and IRC-determined proportion of patients having a complete response. The MS states that the investigator-assessed analysis identified that 17.4% and 9.1% of patients in the bevacizumab and placebo group, respectively, achieved a complete response. However, in the IRC-determined analysis, the proportion of patients achieving complete response is reported to be 0.8% and 1.2% for the bevacizumab and placebo groups, respectively.

The ERG has reservations concerning the methods implemented by the manufacturer to systematically identify RCTs relevant to the decision problem. Abstracts were appraised by only one reviewer and the manufacturer specified an inclusion criterion that trials should include a minimum of 200 patients. The ERG suggests that these restrictions limit the robustness of the manufacturer's systematic reviews.

Several inconsistencies and omissions were noted in the reporting of various analyses and number of events in the MS, and in the response to the ERG's requests for clarification. Importantly, the manufacturer was unable to confirm the number of patients lost to follow-up at the time of final PFS analysis, or to provide a mean PFS. In addition, the numbers of patients censored at the time of final PFS analysis and at the time of the three interim OS analyses are unclear. Although reasons for censoring of patients are described in full in the MS, no details on the number of patients censored in each analysis are reported in either the MS or the full publication of OCEANS.

A further limitation to the evidence presented is the lack of an NMA comparing bevacizumab combined with gemcitabine and carboplatin versus other comparators of interest listed in the final scope. The manufacturer cites that the identified RCTs are too clinically heterogeneous as a rationale for not carrying out the NMA. The ERG agrees with the manufacturer that there are differences across the identified trials, but determines that these differences do not preclude comparison of clinical effectiveness through an NMA.

Economic

The ERG identified the following three key limitations within the manufacturer's economic evaluation: date of analysis; estimates of disutility; and comparators evaluated.

Date of analysis

The manufacturer used data from OCEANS to populate the following model parameters: PFS; OS; post-progression treatments; and adverse event incidence. The ERG notes that the data used to populate these parameters were taken from the first interim analysis (carried out in September 2010). The ERG is concerned, in particular, that data on OS were not taken from the latest available analysis

set, the third interim analysis of OS (carried out in March 2012). The ERG considers that use of a less mature dataset introduced additional and unnecessary uncertainty in the extrapolated estimates of OS. Moreover, analysis of OS in September 2010 showed a non-statistically significant OS benefit for the bevacizumab group, which was not sustained in the two later interim analyses; the ERG therefore considers that the OS benefit associated with bevacizumab is likely to be overestimated. The manufacturer notes that OS may be confounded from the use of bevacizumab in the placebo group following progression; however, the degree of bias in OS estimates is uncertain. Overall, the ERG considers that the model is likely to overestimate the OS benefit for the bevacizumab group, although the degree of overestimation is unclear. OS is likely to be of importance to the results of the analysis; this is because OS benefit attributed to bevacizumab was a key driver of model results. For the per patient QALY gain of 0.30 for the bevacizumab group compared with the placebo group in the manufacturer's base case, the ERG estimated that approximately 90% QALYs were a function of the OS gain, and approximately 10% QALYs were a function of PFS gain.

Disutilities

Adverse events experienced by patients in the model were not subject to estimates of disutility. This is likely to favour bevacizumab, because a larger proportion of patients in the bevacizumab group experienced an adverse event compared with the placebo group in OCEANS.

Comparators

The manufacturer compared bevacizumab in combination with gemcitabine plus carboplatin versus placebo in combination with gemcitabine plus carboplatin, and omitted a comparison with: paclitaxel in combination with a platinum compound; PLDH in combination with a platinum compound; platinum-based chemotherapy as monotherapy. Clinical advice suggested that paclitaxel in combination with a platinum compound currently represented the treatment option for approximately 50% of women with recurrent advanced ovarian cancer, and that PLDH in combination with a platinum compound is likely to be increasingly used in clinical practice. Consequently, the ERG considers that the omission of an economic comparison with all comparators outlined in the NICE scope represents an important limitation when considering the cost-effectiveness of bevacizumab in UK clinical practice.

1.4.3 Areas of uncertainty

Results from the OCEANS trial suggest that bevacizumab provides improved PFS when combined with gemcitabine and carboplatin. However, given the lack of supplementary direct evidence evaluating bevacizumab in recurrent platinum-sensitive ovarian cancer, the ERG suggests that there is uncertainty around the comparative clinical benefit of bevacizumab combined with gemcitabine and carboplatin versus alternative platinum-based chemotherapy (monotherapy or combination therapy) currently used in this population. Moreover, it is unclear whether addition of bevacizumab to an

alternative platinum-based chemotherapy would afford a similar level of clinical benefit to that achieved with addition of bevacizumab to gemcitabine and carboplatin.

In addition, the ERG suggests that, at this time, there is uncertainty around the benefit of adding bevacizumab to gemcitabine plus carboplatin in terms of OS. The ERG acknowledges that OS data from OCEANS are immature and that analysis once the defined number of events has occurred will provide more robust evidence on this issue.

1.5 Key issues

The ERG considers the key issues to be:

- lack of clarity in various areas, including the extent of censoring in the final PFS analysis and in the interim OS analyses, the number of patients lost to follow-up at time of final PFS analysis, and the number of events as determined by the IRC for ORR and median duration of response;
- data on mean PFS at time of final analysis not available;
- substantial inconsistency in the proportion of patients achieving complete response reported for the investigator-assessed and IRC-determined analyses;
- lack of comparison of bevacizumab combined with gemcitabine and carboplatin versus all comparators outlined in the NICE scope; in particular paclitaxel in combination with a platinum compound, which represents the treatment choice for approximately 50% patients with first recurrence of platinum-sensitive ovarian cancer, and PLDH in combination with a platinum compound which is likely to be increasingly used in clinical practice when PLDH becomes available once again;
- population of the economic model with data from the first interim analysis (carried out in September 2010) for OS, post-progression treatments and adverse event incidence;
- lack of incorporation of estimates of treatment-related disutility in the economic model.

1.6 Summary of exploratory and sensitivity analyses undertaken by the ERG

1.6.1 Clinical

The ERG carried out a network meta-analysis (NMA) based on data reported in the MS and supplementary data provided by the manufacturer during clarification. The ERG's exploratory analyses suggest that, for the outcome of PFS, addition of bevacizumab to gemcitabine plus carboplatin is associated with a statistically significant improvement in duration of PFS compared with all comparators of interest in the final scope, with a reduction in risk of progression or death from any cause of 53% compared with paclitaxel plus carboplatin (HR 0.47; 95% Credible Interval [CrI]: 0.33 to 0.66) and of 42% compared with PLDH plus carboplatin (HR 0.58; 95% CrI: 0.39 to 0.82). The ERG stresses that its analyses are speculative and, as such, should be interpreted with caution.

1.6.2 Economic

The ERG's revised deterministic and probabilistic base case ICERs were estimated to be £148,360 and £212,079, respectively; these were comparable to the manufacturer's estimates (£149,050 and £221,750, respectively). The base case ICER incorporated a number of model corrections and the following scenarios:

- PFS estimated using Kaplan–Meier data from OCEANS rather than a log-logistic extrapolation of data from OCEANS;
- the cost of gemcitabine taken from the British National Formulary, £162 for 1,000 mg;
- assuming no vial sharing of gemcitabine and carboplatin;
- increasing the pharmacy preparation time to 25 minutes per infusion.

The ERG's revised base case ICER did not incorporate an assumption that OS was the same for both the bevacizumab and the placebo groups or an estimate of adverse event disutility. Although the ERG believes that the OS benefit associated with bevacizumab is likely to be overestimated in the manufacturer's base case, without data from March 2012 or further information around the potential confounding effect of bevacizumab use in the placebo group post-progression, the ERG is unable to comment with confidence on the degree of the overestimate. Similarly for adverse event disutility, because the manufacturer did not account for adverse event disutilities, the ERG believes that the QALY gain for the bevacizumab group was overestimated in the base case but considers that the degree of overestimation is unclear. The ERG, therefore, considers it likely that the "true" ICER is higher than the ERG's revised base case estimate. Incorporation of the assumption of equivalent OS to the ERG's revised base case resulted in a deterministic ICER of £1,826,779 per QALY.

The ERG carried out exploratory cost-effectiveness analyses of bevacizumab in combination with gemcitabine and carboplatin versus: paclitaxel in combination with a platinum compound; PLDH in combination with a platinum compound; platinum-based chemotherapy as monotherapy. Results of the NMA carried about by the ERG suggested that paclitaxel in combination with a platinum compound and PLDH in combination with a platinum compound were not associated with a statistically significantly difference in PFS compared with gemcitabine and carboplatin. The ERG therefore updated the model to reflect drug costs, and assumed comparable treatment effect (PFS and OS) for each comparator as included in the manufacturer's model for gemcitabine and carboplatin. Each analysis produced a deterministic ICER in excess of £140,000 per additional QALY.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problems

In the Context section of the manufacturer's submission (MS; Section 2), the manufacturer provides a brief overview of some of the key characteristics of and issues relating to ovarian cancer, including prevalence, and prognosis. However, there is little discussion of staging of disease, or risk factors associated with ovarian cancer, which the Evidence Review Group (ERG) considers might have been beneficial. The manufacturer gives a detailed description of the involvement of vascular endothelial growth factor (VEGF) – the target of bevacizumab – in angiogenesis, which has an important role in tumour growth and metastasis.

Ovarian cancer, as the manufacturer identifies, is more common in Europe and North America than in other parts of the world.[(1)] In the UK, ovarian cancer is the fifth most common cancer, and is the fourth most common cause of cancer death.[(1)] In 2009, 6,955 women were diagnosed with ovarian cancer, and, in 2010, 4,295 women died from their disease. Ovarian cancer is predominantly a disease of older, post-menopausal women, with over 80% of cases being diagnosed in women over 50 years of age.[(1)] The aetiology of ovarian cancer is not fully understood, but it is thought that various factors either contribute to a woman's risk of developing the condition, or, conversely, act as protective factors and thus reduce risk. It is known that women with mutations in the *BRCA1* and *BRCA2* genes are at an increased risk of developing ovarian cancer; about 10% of ovarian cancers are attributable to mutations in *BRCA1* and *BRCA2*.[(1;2)] In addition to increasing age, other putative factors for increased risk of ovarian cancer include: infertility or having fertility treatment; and using hormone replacement therapy.[(1)] By contrast, lower risk of ovarian cancer might be associated with: use of the contraceptive pill; having children; and breast feeding.[(1)]

Ovarian tumours are classified based on the cell type from which the tumour originates: surface epithelium; germ; or stroma. As reported by the manufacturer, of the different cell types, epithelial tumours are the most common, accounting for about 90% of ovarian cancers;[(3)] epithelial tumours can be further divided based on their histology (serous, mucinous, endometrioid, clear cell, and undifferentiated or unclassifiable). The manufacturer indicates that bevacizumab is intended for use in the most common group of ovarian cancers originating from the epithelium within the ovary (epithelial ovarian cancer; EOC), the fallopian tube (fallopian tube cancer; FTC), or the pelvic peritoneum (primary peritoneal cancer; PPC). FTC and PPC are, in general, histologically serous, and are thus considered to be analogous to EOC, arising from the same pathophysiology. The International Federation of Gynecology and Obstetrics (FIGO) indicates that the management of PPC and FTC should mirror that of EOC, with use of similar chemotherapeutic agents and doses.[(4)] Hereafter, EOC, PPC, and FTC will collectively be referred to as ovarian cancer.

Diagnosing ovarian cancer can be difficult. As noted by the manufacturer, early stage ovarian cancer is generally asymptomatic. Moreover, women frequently present with vague symptoms, such as abdominal bloating, difficulty eating and feeling "full" quickly, that can be suggestive of other, more minor conditions.[1;5] Symptoms such as pelvic pain, low back pain, and an urgency to urinate are more suggestive of pelvic disease.[5] As a consequence, many women (~60%) are diagnosed with ovarian cancer when their disease is in an advanced stage.[3] The manufacturer identifies that advanced stage of ovarian cancer is classified as FIGO Stage III and IV, but did not provide an overview of the FIGO classification system. In brief, the FIGO scale is an internationally agreed surgical staging system based on a scale of I to IV, where Stage I represents early stage disease and Stages III and IV represent advanced disease (summarised in Table 1).

Table 1. FIGO stages for ovarian cancer[4]

Stage	Criteria
1	**Tumour confined to the ovaries**
1A	• Tumour limited to one ovary, and capsule intact; • No tumour on ovarian surface; • No malignant cells in ascites or peritoneal washings.
1B	As for 1A, but tumour limited to both ovaries
1C	Tumour limited to one or both ovaries, with any of the following: • Tumour on ovarian surface; • Ruptured capsule; • Malignant cells in ascites or peritoneal washings.
2	**Tumour involves one or both ovaries with pelvic extension**
2A	Extension and/or metastases in the uterus and/or fallopian tubes but with no malignant cells in ascites or peritoneal washings.
2B	Extension to other pelvic organs but with no malignant cells in ascites or peritoneal washings.
2C	Tumour staged either 2A or 2B with malignant cells in ascites or peritoneal washings.
3	**Tumour involves one or both ovaries with peritoneal metastasis outside the pelvis and/or regional lymph node metastasis** **Liver capsule metastasis equals Stage 3**
3A	Microscopic peritoneal metastasis beyond the pelvis.
3B	Macroscopic peritoneal metastasis beyond the pelvis, none of which exceed 2 cm in greatest dimension.
3C	Peritoneal metastasis beyond the pelvis, larger than 2 cm in greatest dimension and/or regional lymph node metastasis.
4	**Distant metastasis (beyond the peritoneal cavity)**
Abbreviation used in table: FIGO, International Federation of Gynecology and Obstetrics.	

Most women are diagnosed with advanced ovarian cancer, with about 40% of women diagnosed with FIGO Stage III disease and about 15% diagnosed with FIGO Stage IV disease.[1] FIGO stage is a strong predictor of survival in ovarian cancer. According to Cancer Research UK, early stage disease (Stage I) has a 5-year survival rate of about 90%, whereas advanced disease has a 5-year survival of about 20% for women with Stage III disease and about 6% for women with Stage IV disease;[1]

figures are based on data from the cancer registry for the Anglia region (2004–2008). The manufacturer cites an alternative source for 5-year survival rates that are based on data from the USA and are in accordance with the data reported by Cancer research UK; the manufacturer reports 5-year survival rates of 73–93% for early stage disease (FIGO stage I/II) and about 30% for advanced disease.[6] Prognosis is also determined by a woman's age, the grade of her cancer (based on the appearance of the cells), and the extent of residual tumour after initial surgery.[1]

The manufacturer does not describe the role of CA125 as a marker in the diagnosis of ovarian cancer and disease progression within the Context section of the MS. The ERG considers it useful to highlight that CA125 is a protein produced by some ovarian cancers and is measured with a blood test. About 90% of women who have more advanced ovarian cancer have an elevated CA125 level.[1] Normal values of CA125 range from 0 to 35 (U/mL).[7] Raised levels are also correlated with disease progression. However, CA125 is not specific to ovarian tumours, and other conditions of the womb and ovaries also result in elevated CA125 (e.g., endometriosis, fibroids, and pelvic inflammatory disease).[1] Thus, CA125 is generally not used in isolation as a test for ovarian cancer.

First-line treatments for ovarian cancer are given with curative intent. Clinically complete remission is achieved in most patients through a combination of cytoreductive surgery and chemotherapy. However, the risk of disease recurrence is high, and recurrent disease is typically widespread throughout the abdomen and pelvis.[3] The manufacturer identifies that, although up to 70% of patients achieve a response after debulking surgery and first-line chemotherapy, 55–75% of these women will experience a relapse of their cancer within 2 years.[8] A Single Technology Appraisal (STA) evaluating trabectedin for relapsed ovarian cancer reported that, based on expert opinion, about 80% of women with ovarian cancer will relapse and require second-line chemotherapy.[9] The ERG's clinical expert indicated that, based on experience, 75%–80% of women will have recurrence of disease. Although additional chemotherapy in second and subsequent lines can alleviate symptoms and prolong survival, the prognosis for women with relapsed disease is generally poor.

The manufacturer identifies the importance of angiogenesis in the mechanisms involved in tumour growth and metastasis.[10] Angiogenesis stimulates the production of new vessels to provide the nutrients and oxygen essential for growth. VEGF is a cytokine (signal protein) that stimulates vasculogenesis and angiogenesis and is a key regulator of formation of new blood vessels during embryonic development, and after injury, and formation of new vessels to bypass blocked vessels.[11] The receptors for VEGF are primarily expressed by endothelial cells and VEGF has been found to be produced by several types of tumour. The manufacturer gives a detailed description of the rationale for targeting VEGF in ovarian cancer. In brief, studies have reported higher levels of VEGF in ovarian tumours compared with healthy ovaries,[12-14] and it has been proposed that VEGF is involved in several phases of ovarian carcinogenesis. The manufacturer presents evidence from three early

studies of single agent bevacizumab in recurrent ovarian cancer that reported response rates of 16–30% (various measures of response reported).[15-17]

The ERG considers the manufacturer's overview of the underlying health problem to be generally appropriate and relevant to the decision problem that is the focus of this STA. However, expansion of some areas might have aided initial understanding of the proposed position of bevacizumab in the treatment pathway.

2.2 Critique of manufacturer's overview of current service provision

In the Context section, the manufacturer discusses various aspects of current service provision, including National Institute for Health and Clinical Excellence (NICE) guidance, and factors that influence choice of second-line chemotherapy. In addition, the manufacturer outlines the proposed position of bevacizumab in the treatment pathway, and estimates the number of patients in the UK who would be eligible for treatment.

First-line treatment for most women diagnosed with ovarian cancer is combined cytoreductive surgery and chemotherapy. The extent and type of surgery required is determined by the stage of the disease, the histologic cell type, and the patient's age and overall health. In most cases, as it is difficult to excise the tumour completely during surgery, patients will frequently require additional treatment, which, as the manufacturer identifies, is typically first-line platinum-based chemotherapy. In advanced ovarian cancer, first-line chemotherapy (typically 3 cycles) may be administered before cytoreductive surgery, with the goal of shrinking the tumour to facilitate excision. Guidance from NICE on the first-line chemotherapeutic management of ovarian cancer recommends either paclitaxel in combination with a platinum-based chemotherapy (carboplatin or cisplatin) or platinum-based chemotherapy alone.[8] However, as noted earlier, in a large proportion of patients, disease recurs and subsequent treatments are palliative rather than curative.

The manufacturer identifies that a patient's response to first-line platinum-based therapy is a surrogate marker of their response to second-line or subsequent platinum-based treatments, with the length of the treatment-free interval and the extent of relapse (site and number of tumours) being particularly indicative of response. However, most patients will develop resistance to platinum-based chemotherapy over a period of time, and platinum-resistant disease has a poor prognosis; trials suggest a median survival of <12 months.[18] The manufacturer also identifies that current NICE guidance on the choice of chemotherapy in recurrent disease is based on the duration of time since last platinum-based therapy.[19] Recommendations issued by NICE[19] on the treatment of recurrent ovarian cancer are based on a Multiple Technology Appraisal (MTA; TA91) that assessed the clinical effectiveness and cost-effectiveness of paclitaxel, pegylated liposomal doxorubicin hydrochloride (PLDH) and topotecan as treatments (second-line or subsequent) for advanced ovarian cancer.[20] The

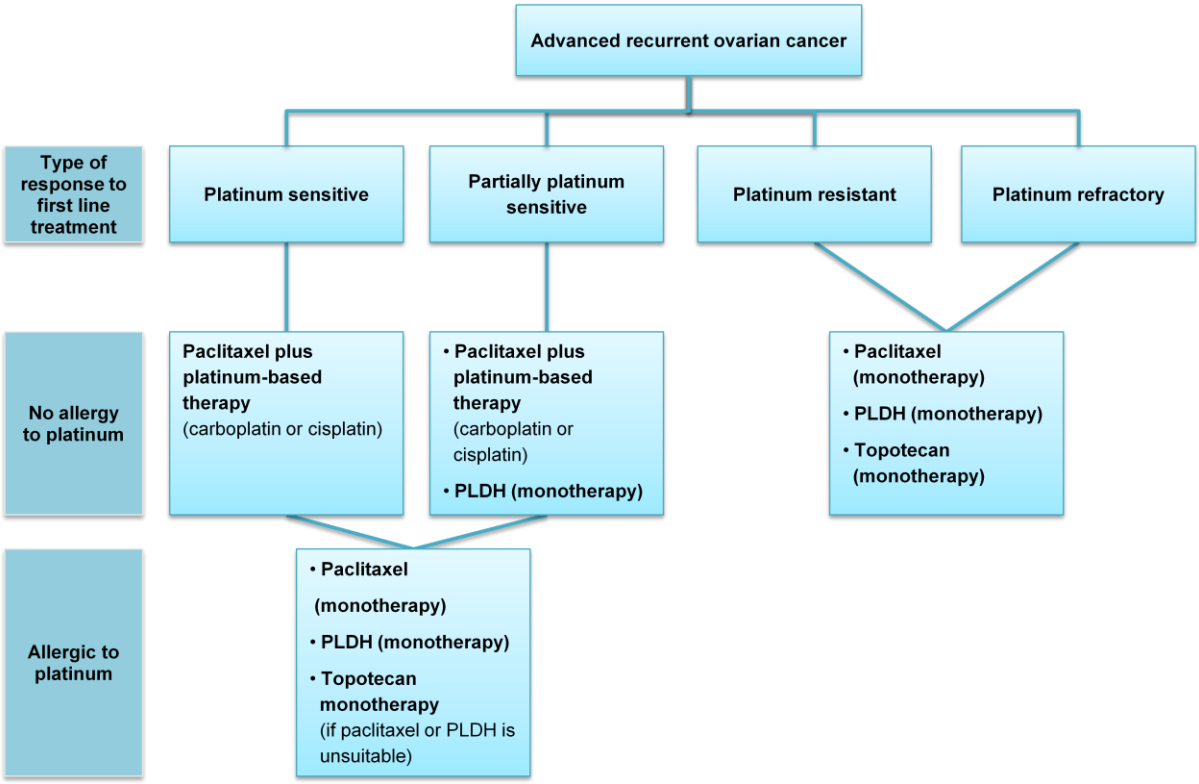
manufacturer lists TA55 and TA222 as other NICE Technology Appraisals relevant to the decision problem. For TA222, NICE issued guidance that trabectedin in combination with PLDH was not recommended for the treatment of relapsed platinum-sensitive ovarian cancer.[21] TA55 evaluated the use of paclitaxel in the treatment of ovarian cancer, and covered first-line and subsequent treatment of ovarian cancer.[8] The ERG notes that TA55[8] is no longer relevant for the treatment of recurrent ovarian cancer, which is the population relevant to the decision problem, as TA55 was partially updated by TA91;[20] recommendations in TA55 are relevant for the first-line treatment of ovarian cancer. TA91 is currently under review, with the report scheduled to be issued in February 2014;[22] the scope of the MTA has been expanded to include trabectedin and gemcitabine.

The manufacturer provides a detailed description of the categorisations used for platinum sensitive (subdivided into sensitive and partially sensitive), resistant and refractory disease (summarised in Table 2), and a brief overview of current NICE guidance for the second-line chemotherapeutic management of ovarian cancer based on these categorisations. A Technology Appraisal evaluating the use of trabectedin in recurrent ovarian cancer presented a flow diagram of NICE recommendations based on TA91, which the ERG has modified and presents in Figure 1.

Table 2. Categorisations of platinum sensitivity used in guidance on second-line and subsequent treatment of ovarian cancer[19]

Categorisation	Definition
Platinum sensitive	Disease that responds to first-line platinum-based therapy but relapses 12 months or more after completion of initial platinum-based chemotherapy
Partially platinum-sensitive	Disease that responds to first-line platinum-based therapy but relapses between 6 and 12 months after completion of initial platinum-based chemotherapy
Platinum resistant	Disease that relapses within 6 months of completion of initial platinum-based chemotherapy
Platinum refractory	Disease that does not respond to initial platinum-based chemotherapy

Figure 1. Treatment options in relapsed ovarian cancer (figure based on NICE guidance[19] and adapted from TA222[9])



NICE guidance recommends paclitaxel plus a platinum-based therapy for patients with any level of sensitivity to platinum-based therapy.[19] However, the manufacturer highlights that patients who relapse after first-line treatment with a paclitaxel–platinum combination regimen are at an increased risk of developing neurotoxicity if re-treated with the same regimen within 12 months of the end of first-line therapy;[23] neurotoxicity is a common adverse effect associated with paclitaxel and carboplatin and can persist for up to 2 years after cessation of treatment.[24] The manufacturer went on to report that, because of the increased risk of neurotoxicity, outside the UK, other guidelines recommend considering the combination of carboplatin with gemcitabine, docetaxel or PLDH.[23;25] The ERG sought clinical advice on the preferred regimen for second-line treatment of platinum-sensitive disease in the UK. The ERG's clinical advisor fed back that paclitaxel plus carboplatin would generally be the preferred second-line treatments in UK clinical practice in recurrent platinum-sensitive cancer, particularly for patients who relapse >12 months after completion of first-line chemotherapy. Carboplatin is chosen over cisplatin because of its more favourable adverse effect profile.[3] The ERG's clinical expert agreed with the manufacturer, commenting that, based on experience, paclitaxel plus carboplatin is unsuitable as a second-line regimen for ~50% of patients because of associated neurotoxicity. The ERG's advisor added that, despite not being formally recommended by NICE, treatment options that would be considered for patients with neurotoxicity are gemcitabine plus carboplatin and PLDH plus carboplatin, which is in agreement with the manufacturer's overview of current service provision. The ERG considers it important to note that, at

the time of writing, as a result of manufacturing difficulties PLDH is not available in the UK. However, the ERG's clinical expert highlighted that, once PLDH becomes available again, it is likely that there will be increased use of PLDH plus carboplatin in the treatment of recurrent platinum-sensitive ovarian cancer.

As indicated in Figure 1, current NICE guidance recommends PLDH monotherapy as a treatment option for patients with partially platinum-sensitive disease (relapse occurs between 6 and 12 months after completion of platinum-based chemotherapy). However, the final scope issued by NICE[26] for this decision problem does not list PLDH monotherapy as a comparator of interest. Moreover, although the manufacturer reports that PLDH is likely to be the monotherapy of choice in UK clinical practice for partially platinum-sensitive patients, the ERG's clinical expert indicated that PLDH monotherapy is unlikely to be considered as a treatment option in this population; current practice supports use of PLDH monotherapy in platinum-resistant disease. The ERG's clinical expert added that degree of sensitivity to platinum (i.e., sensitive [relapse after >12 months] versus partially sensitive [relapse between 6 and 12 months]) is an important prognostic factor and, in addition to residual neurotoxicity, is a consideration in choice of second-line or subsequent treatment.

Overall, the ERG considers the manufacturer's overview of current service provision to be an accurate, relevant representation of current clinical practice in the UK for the treatment of first recurrence of ovarian cancer.

Based on the positive opinion issued by the Committee for Medicinal Products for Human Use (CHMP) in September 2012,[27] the manufacturer states that bevacizumab in combination with gemcitabine plus carboplatin is indicated for the treatment of patients with first-recurrence of platinum-sensitive ovarian cancer (EOC, FTC, or PPC) who have not received prior therapy with a VEGF inhibitor or VEGF receptor-targeted agent. The ERG considers it important to note that the statement issued by the CMHP does not include a definition of platinum-sensitive ovarian cancer. In the key trial that forms the basis of the manufacturer's application to the Technology Appraisal process (OCEANS), platinum-sensitive disease is defined as disease recurrence 6 months or more after previous platinum therapy.[28] The criterion applied in OCEANS encompasses the subgroups of platinum sensitivity defined in NICE guidance.[19]

With reference to additional costs associated with introduction of bevacizumab, the manufacturer anticipates that minimal additional resources will be required to implement treatment with bevacizumab. The manufacturer reports that bevacizumab is administered intravenously every 21 days, and treatment should be continued until disease progression or unacceptable toxicity, whichever occurs first. Additional costs will be incurred for preparation of the intravenous infusion of bevacizumab by a pharmacist, and for administration of bevacizumab in addition to routine

gemcitabine plus carboplatin. The manufacturer also acknowledges that additional resource may be required for monitoring of development of hypertension and proteinuria, which are established adverse effects of treatment with bevacizumab. However, the manufacturer proposes that the evaluation of possible disease progression and the monitoring of blood pressure and for signs of proteinuria typically form part of general follow-up of patients with recurrent ovarian cancer. The ERG's clinical expert indicated that the manufacturer's assumptions around additional resource associated with administration of bevacizumab are appropriate. Additional monitoring would most likely be a component of routine care for patients with recurrent disease, but might not be standard follow-up in all settings.

The manufacturer estimates that about 2,100 patients would be eligible for second-line treatment with bevacizumab in the UK. The manufacturer reports that "about 4,300 patients per year receive first-line chemotherapy for ovarian cancer in the UK and at relapse 79% of these patients will have platinum sensitive or partially sensitive disease. Of this population, about 6% are likely to enter into clinical studies, as many as 30% of the remaining patients may be unsuitable for further chemotherapy and about 4% are likely to have contraindications to bevacizumab". On request, to support the figures presented, the manufacturer provided a summary of data from market research carried out on behalf of the manufacturer that substantiated the estimated rate of relapse of patients with platinum-sensitive and partially platinum-sensitive ovarian cancer, and the proportion of patients likely to enter clinical trials.[29] Data on prevalence of coronary heart disease were taken from the British Heart Foundation and were used to estimate the number of patients contraindicated to bevacizumab.[30] The ERG's clinical expert indicated that it would be difficult to obtain an accurate estimate of the number of patients potentially eligible for treatment with bevacizumab. Overall, the ERG considers the manufacturer's estimate of 2,100 eligible patients in the UK to be reasonable.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

The manufacturer provided a summary of the final decision problem issued by the National Institute for Health and Clinical Excellence (NICE; manufacturer's submission [MS], pg 25),[26] together with a brief description of the rationale for any deviation from the decision problem (Table 3).

Table 3. Summary of decision problem as outlined in the manufacturer's submission (reproduced from MS; pg 25)

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from the scope**
Population	Women with recurrent platinum-sensitive or partially platinum-sensitive advanced epithelial ovarian, fallopian tube or primary peritoneal cancer	As per scope issued by NICE	
Intervention	Bevacizumab in combination with platinum-based therapy	Bevacizumab in combination with gemcitabine and carboplatin	License is expected to be granted in combination only with gemcitabine and carboplatin
Comparator(s)	• Paclitaxel in combination with a platinum compound • Gemcitabine in combination with carboplatin • Pegylated liposomal doxorubicin hydrochloride in combination with a platinum compound • Platinum-based chemotherapy as monotherapy	As per scope issued by NICE	
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	As per scope issued by NICE	
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective	As per scope issued by NICE	

Subgroups to be considered	None specified	• Fully platinum sensitive (relapse >12 months after last platinum therapy) • Partially platinum sensitive (relapse 6–12 months after last platinum therapy)	These sub groups arose from a stratification factor in the OCEANS trial
Special considerations, including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation	–	–
Abbreviations used in table: NHS, National Health Service; NICE, National Institute for Health and Clinical Excellence.			

3.1 Population

The key trial (OCEANS[28]) that forms the basis of the direct clinical evidence submitted by the manufacturer enrolled women with first recurrence of ovarian cancer, occurring at least 6 months after completion of treatment with platinum-based chemotherapy, that is, platinum-sensitive disease. To be eligible for randomisation in OCEANS, patients were required to:

- be ≥18 years of age;
- have histologically confirmed recurrent ovarian cancer;
- have disease progression ≥6 months after completion of front-line platinum-based chemotherapy.

The Evidence Review Group (ERG) considers that the population in OCEANS represents a marginally narrower population than that defined in the final scope issued by NICE,[26] in that the scope did not specify a population of women with first recurrence of their disease. In addition, the positive opinion issued by the Committee for Medicinal Products for Human Use (CHMP) further restricts the population relevant to the decision problem, stating that bevacizumab is indicated for the treatment of patients with first-recurrence of platinum-sensitive ovarian cancer who have not received prior therapy with a VEGF inhibitor or VEGF receptor-targeted agent;[27] prior treatment with agents that either inhibit VEGF or target VEGF receptors were exclusion criteria within OCEANS.[28]

In the MS, platinum-sensitive is defined as disease recurrence more than 6 months after previous platinum therapy (MS; pg 7). However, within OCEANS, eligible patients had disease progression at 6 months or more after completion of front-line platinum-based chemotherapy. Randomisation within OCEANS was stratified by time from last platinum treatment to recurrence:

- between 6 and 12 months (defined within the MS as partially platinum-sensitive);
- >12 months (defined within the MS as fully platinum-sensitive).

In the MS, the manufacturer presents subgroup analyses based on degree of sensitivity to platinum-based chemotherapy. However, subgroups were not identified in the scope issued by NICE.[26] The omission of subgroups from the final scope does not align with current NICE recommendations on second-line chemotherapeutic treatment for recurrent ovarian cancer, which are based on degree of platinum-sensitivity (sensitive [relapse >12 months after platinum-based chemotherapy] versus partially sensitive [relapse 6–12 months after platinum-based chemotherapy]).[22] As noted in Section 2.2, the ERG's clinical advisor indicated that, at this time, clinicians are likely to consider degree of platinum sensitivity an important prognostic factor and a consideration to inform treatment choice. Not all the listed comparators in the scope are currently recommended for the treatment of recurrent platinum-sensitive ovarian cancer, but clinical advice indicates that the listed comparators are the preferred treatments in UK clinical practice. The ERG considers that the scope issued by NICE for this Single Technology Appraisal (STA) perhaps reflects more closely current clinical practice than current NICE guidance.[26]

The OCEANS trial was carried out exclusively in the USA.[28] The ERG's clinical expert stated that, with the exception of baseline weight, the characteristics of the patient population enrolled in OCEANS are representative of women with first recurrence of ovarian cancer in England and Wales.

3.2 Intervention

The ERG notes that the MS provides an appropriate overview of the regulatory status and mode of action of bevacizumab. Bevacizumab does not currently have a UK marketing authorisation for the treatment of recurrent or relapsed ovarian cancer. The manufacturer anticipates that approval will be issued by the European Medicines Agency (EMA) by November 2012 for the use of bevacizumab in the treatment of women with platinum-sensitive or partially platinum-sensitive first recurrence of ovarian cancer (epithelial ovarian cancer [EOC], fallopian tube cancer [FTC], or primary peritoneal cancer [PPC]).

The intervention of interest indicated by the scope is bevacizumab in combination with a platinum-based chemotherapy.[26] Direct evidence submitted in support of the manufacturer's application assesses bevacizumab in combination only with gemcitabine plus carboplatin, which is consistent with the scope, albeit for only one platinum-based regimen. Based on the available direct evidence

evaluating bevacizumab in the treatment of recurrent ovarian cancer, the ERG considers the restriction of the intervention to be appropriate. In addition, as noted in Section 2.2, the positive opinion issued by the CHMP focuses on the use of bevacizumab in combination with gemcitabine plus carboplatin,[27] and thus, as the manufacturer highlights, the licence for bevacizumab is likely to be granted for use in combination only with gemcitabine and carboplatin.

The manufacturer identifies that bevacizumab was first approved by the US Food and Drug Administration (FDA) in 2004 for use in metastatic colorectal cancer in combination with standard chemotherapy. In 2005, bevacizumab was launched in the UK. Since its introduction to the market, bevacizumab has been licensed in the European Union (EU) for use in various cancers in combination with standard chemotherapy regimens:[31]

- metastatic cancer of the colon or rectum (large intestine);
- metastatic breast cancer;
- advanced, metastatic or recurrent non-small cell lung cancer that cannot be removed by surgery alone in patients whose cancer cells are not of the 'squamous' type;
- advanced or metastatic kidney cancer;
- advanced EOC, FTC, and PPC (first-line treatment; not recurrent disease).

Bevacizumab is also licensed in numerous countries outside of the EU for the treatment of relapsed glioblastoma.

Bevacizumab is a humanised monoclonal antibody that inhibits vascular endothelial growth factor (VEGF), and is the first licensed anti-VEGF targeted therapy in ovarian cancer. VEGF is a signal protein that is important in the signalling cascade that stimulates the growth of new blood vessels (angiogenesis).[10] As noted in Section 2.1, angiogenesis has been identified as having an important role in tumour growth and metastasis. VEGF receptors are predominantly expressed by endothelial cells, and VEGF has been found to be produced by several types of tumour, including ovarian tumours. By blocking VEGF-induced signalling, bevacizumab inhibits VEGF-driven angiogenesis, thus reducing vascularisation of tumours and inhibiting tumour growth.

The Summary of Product Characteristics (SmPC) for bevacizumab reports that, in ovarian cancer, the recommended dose of bevacizumab is 15 mg/kg of body weight, given once every 3 weeks as an intravenous infusion.[32] In the first-line treatment of advanced ovarian cancer, the SmPC reports that bevacizumab has been given in addition to carboplatin and paclitaxel for up to 6 cycles of treatment, after which bevacizumab is continued as a single agent until disease progression, or for a maximum of 15 months, or until unacceptable toxicity, whichever occurs first. The ERG considers it important to note that, in the trial evaluating the effectiveness of bevacizumab in the first-line treatment of advanced ovarian cancer (ICON7), bevacizumab was administered at a dose of 7.5 mg/kg of body

weight.[33] The SmPC states that no dose adjustment is necessary for an elderly (>65 years) population.[32] The safety and efficacy of bevacizumab have not been evaluated in patients with renal or hepatic impairment.

In the key trial (OCEANS) from which the direct evidence on the clinical effectiveness of bevacizumab is taken, bevacizumab was administered in combination with gemcitabine and carboplatin for between 6 and 10 cycles (dependent on toxicity), followed by continued bevacizumab as a monotherapy until disease progression or unacceptable toxicity.[28] A maximum duration of administration was not specified. On request, the manufacturer indicated that the maximum duration of administration of bevacizumab, after the period of combination with gemcitabine plus carboplatin, would be determined by the progression-free survival (PFS) of a patient.

In the MS, the manufacturer indicates that, at the time of writing of the submission, bevacizumab was being evaluated by both NICE and the Scottish Medicines Consortium (SMC) for the first-line chemotherapeutic treatment of women with advanced ovarian cancer after surgery. Subsequent to submission of the MS, the SMC has issued guidance recommending against the use of bevacizumab within NHS Scotland for the front-line treatment of advanced ovarian cancer, stating that the "company's base case economic analysis was based on an unlicensed dose of the medicine and this is not within the SMC remit. For the sensitivity analysis using the licensed dose, the submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust economic analysis to gain acceptance by SMC".[34]

3.3 Comparators

The OCEANS[28] trial evaluated adding bevacizumab versus adding placebo to gemcitabine plus carboplatin; for brevity, hereafter the regimens in OCEANS will be referred to as bevacizumab and placebo. In the MS, the manufacturer indicates that gemcitabine plus carboplatin is the most relevant comparator for the decision problem that is the focus of this STA, but does not provide an argument to support this opinion. On request, the manufacturer indicated that gemcitabine plus carboplatin is the most appropriate comparator as "the purpose of the STA is to determine the cost-effectiveness of bevacizumab in this setting" and clinical data are available only for the comparison of addition of bevacizumab versus addition of placebo to gemcitabine plus carboplatin. Although the ERG agrees with the manufacturer that the evidence presented in the MS is the only direct evidence available, the ERG considers it important to present comparisons against other recommended treatment regimens to address as fully as possible the decision problem issued by NICE.

As indicated in Section 2.2, gemcitabine plus carboplatin, although used in clinical practice, is not formally recommended by NICE for the second-line chemotherapeutic treatment of recurrent ovarian cancer. In the response to clarification, the manufacturer states that "...the most popular chemotherapy option for recurrent ovarian cancer, liposomal doxorubicin, is currently unavailable...". The ERG is unclear whether the manufacturer, in this context, is referring to use of pegylated liposomal doxorubicin hydrochloride (PLDH) as monotherapy or in combination with a platinum compound. However, the ERG's clinical expert highlighted that, in UK clinical practice, the preferred treatment for first recurrence of platinum-sensitive ovarian cancer would be paclitaxel plus carboplatin, particularly in patients who relapse >12 months after completion of platinum-based chemotherapy. In addition, use of PLDH plus carboplatin to treat recurrent platinum-sensitive ovarian cancer is likely to increase when PLDH is once again available.

The final scope issued by NICE[26] lists comparators of interest as:

- paclitaxel in combination with a platinum compound;
- gemcitabine in combination with carboplatin;
- PLDH in combination with a platinum compound;
- platinum-based chemotherapy as monotherapy.

The manufacturer carried out a systematic review of the literature to identify studies that could potentially inform a network meta-analysis (NMA). In addition to the OCEANS trial, the manufacturer identified publications on three other large trials (CALYPSO,[35] ICON4/AGO-OVAR-2.2 [hereafter referred to as ICON4],[36] and AGO-OVAR-2.5[37]) in recurrent ovarian cancer that evaluated regimens listed as comparators of interest in the scope. After evaluating the trials and seeking statistical advice on the feasibility of an indirect comparison, the manufacturer decided against carrying out an NMA, indicating that the clinical heterogeneity in population baseline prognostic factors across the identified trials was too high to generate results that would be informative. The ERG notes that the manufacturer imposed an inclusion criterion for their systematic review of trial size of 200 people or more. The ERG has concerns that restricting inclusion to larger studies potentially excluded evidence that could inform the network. As part of the clarification process, the manufacturer provided reference details for studies excluded on the basis of too few people. The ERG independently reviewed the full publications of the excluded studies; further details of the ERG's appraisal are provided in Section 4.3.

The ERG sought clinical advice on the appropriateness of comparing the populations in the four large trials identified by the manufacturer in an NMA. The ERG's clinical experts indicated that, although there are differences across the populations included in the identified trials, in their opinion, the differences do not preclude comparison in an NMA. In the absence of head-to-head trials evaluating the additional comparisons of interest listed in the scope, the ERG considers that an adjusted indirect

comparison could be performed to inform how addition of bevacizumab to gemcitabine plus carboplatin compares in terms of clinical effectiveness with regimens currently used in clinical practice in the UK. Based on the evidence presented in the MS, and additional details provided by the manufacturer during clarification, the ERG has carried out exploratory analyses; the appropriateness and potential biases in the ERG's exploratory analyses are discussed in further detail in Section 4.3.

In summary, the ERG considers that the MS does not fully address the scope issued by NICE in the context of the comparisons of interest to the decision problem.

3.4 Outcomes

In the clinical section of the MS, with the exception of health-related quality of life (HRQoL), the manufacturer has provided direct evidence on the outcomes listed in the final scope issued by NICE, which were:[26]

- overall survival (OS);
- PFS;
- objective response rate (ORR);
- adverse effects of treatment;
- HRQoL.

The pre-specified primary outcome reported in OCEANS[28] was investigator-determined PFS, with PFS defined as the time from random assignment to disease progression or death from any cause. PFS was determined using RECIST (Response Evaluation Criteria for Solid Tumors) modified v1.0 criteria. OCEANS enrolled only those patients with measurable disease at baseline. Scans for progression were performed at baseline and every 9 weeks until disease progression. RECIST criteria are used to categorise patients as responding to treatment (complete or partial response), having stable disease, or having disease progression (criteria presented in Table 4).

Table 4. Definition of RECIST criteria[38]

Response	Definition
Complete response	Disappearance of all target lesions; confirmed at 4 weeks
Partial response	At least a 30% decrease in the SLD of target lesions (taking as reference the baseline SLD); confirmed at 4 weeks
Disease progression	At least a 20% increase in the SLD of target lesions (taking as reference the smallest SLD recorded since treatment started); no documentation of complete response, partial response or stable disease before disease progression
Stable disease	Neither sufficient decrease in SLD to meet criteria for partial response nor sufficient increase in SLD to meet criteria for disease progression
Abbreviations used in table: RECIST, Response Evaluation Criteria for Solid Tumors; SLD, sum of longest diameters.	

OS is regarded to be the most reliable endpoint in trials evaluating interventions in cancer, and is generally the preferred endpoint.[39] However, long follow-up periods and potential confounding from post-progression therapies hinder the collection and analysis of survival data. Guidance from the US Food and Drug Administration (FDA) on choice of clinical trial outcomes for the approval of cancer drugs indicates that PFS may be an adequate surrogate endpoint for accelerated approval. As PFS includes death from any cause, it may correlate with OS.[39] However, it is also noted that it may be difficult to validate PFS as an intermediate for OS for a specific type of cancer as data are typically insufficient to enable a rigorous assessment of the correlation between effects on OS and PFS.

In OCEANS,[28] ORR was also defined based on the modified RECIST criteria. ORR was defined as the occurrence of a complete or partial response, and was confirmed by a repeat assessment performed ≥4 weeks after the criteria for response were first met. The guidance from the FDA states that, when complete and partial responses are combined, ORR is a direct measure of antitumor activity of a drug.[39]

PFS, ORR, and median duration of response were also evaluated by an Independent Review Committee (IRC). In the IRC-determined analysis, PFS was defined as the time from random assignment to disease progression (IRC determined) or on-study death (death within 9 weeks of the last dose of protocol treatment).[28]

Various data on safety and tolerability are presented within the MS, including data based on rates of Grade 3, 4, and 5 adverse events (graded using National Cancer Institute Common Terminology Criteria for Adverse Events v3.0). The manufacturer also presented data on patients experiencing at least one adverse event by treatment group and by toxicity term.

Cost-effectiveness was assessed using incremental cost per quality adjusted life year, as recommended in the NICE reference case.

Other than HRQoL, which was not recorded during OCEANS, the ERG considers the outcomes reported to be appropriate and clinically meaningful to the decision problem.

3.5 Other relevant factors

The median duration of follow-up in the OCEANS trial was 24 months.[28] The mean duration of follow-up in the trial was not reported in the MS. As part of the clarification process, the ERG requested that the manufacturer provide the mean PFS and mean OS based on analyses performed at clinical data cut-off. The manufacturer reported that the analyses of "PFS and OS were conducted before all patients had progressed or died", and, "therefore the maximum PFS and OS values are unknown and a mean cannot be calculated". The ERG acknowledges that the data are immature, but

considers that mean values for PFS and OS for the primary analysis at clinical data cut-off could have been provided.

The ERG notes that the manufacturer reports several values for mean treatment duration with bevacizumab: 7.5 months, which equates to 10.8 cycles on a 21-day cycle (MS; Table A1, pg 13); 42 weeks (ERG calculates this to equate to 9.8 months), with a mean number of cycles of bevacizumab of 13.6 (MS; Table 16, pg 88); and 11.71 months (MS; Table 42, pg 152). On request, the manufacturer agreed that there is a discrepancy in the mean treatment durations reported in Table 16 of the MS, which is taken from the Clinical Study Report (CSR), and Table 42 of the MS, which is taken from the economic model. The manufacturer commented that the variation "...is likely due to minor differences in patient numbers and the methodology followed to calculate these times. If the CSR treatment duration reflects a more accurate calculation of the true treatment duration, then the data used in the economic model is likely to overestimate time spent on bevacizumab in the trial and therefore result in an inflated ICER". The manufacturer stated that the value reported in Table A1 was generated from adjustment of the mean treatment duration for bevacizumab in OCEANS to account for different patient populations and differences in routine UK clinical practice. Despite the manufacturer's response, the ERG remains uncertain as to which is the most robust value for mean treatment duration with bevacizumab.

For adverse events, the manufacturer reported the mean duration of follow-up in the bevacizumab group and the placebo group to be 10.7 months and 8.8 months, respectively.

The ERG considers the duration of follow-up to be sufficient to assess the effects of bevacizumab on PFS in the second-line treatment of recurrent ovarian cancer.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

The manufacturer's submission (MS) presents the search terms and strategies implemented in the manufacturer's review of the literature in August 2012. The manufacturer searched the literature to identify relevant randomised controlled trials (RCTs) and non-randomised studies assessing the clinical effectiveness of bevacizumab in the treatment of patients with recurrent ovarian cancer. Additionally, the MS presents search terms and strategies used to identify studies reporting on the safety and tolerability of bevacizumab, as well as terms for a search of studies to inform an indirect comparison of bevacizumab plus gemcitabine and carboplatin against other interventions of interest. The manufacturer highlights that the searches to identify RCT and non-RCT studies on clinical effectiveness and studies on safety and tolerability used the same initial search strategy.

The manufacturer listed the specific databases searched, the time period covered by the searches, and the date the searches were run. For the review of the literature on the clinical effectiveness of bevacizumab in combination with gemcitabine and carboplatin, the manufacturer supplemented the search by reviewing clinical abstracts from relevant conferences covering, as a minimum, the past 2 years (American Society of Clinical Oncology, Society of Gynecologic Oncology, European Cancer Organisation, European Society for Molecular Oncology, and European Society of Gynecological Oncology). As a result of the volume of studies evaluating comparators of interest listed in the scope issued by NICE, conference abstracts were not searched in the review to identify studies to inform the indirect comparison. Clinical trial registries and company databases were not searched. Within the searches, the manufacturer used multiple search terms for recurrent ovarian cancer and for bevacizumab. However, in the search strategy designed for the indirect comparison, search terms of comparators of interest were predominantly limited to the common drug name. It is not clear whether reference lists of identified RCTs were evaluated for additional suitable studies. The manufacturer restricted the search for studies on the clinical effectiveness of bevacizumab to citations published after 1st January 2001; restriction applied to all databases, with the exception of the Cochrane Library, for which there was no limitation on date. As bevacizumab was first approved in 2004, the Evidence Review Group (ERG) considers that the imposed restriction of the span of the search is unlikely to have resulted in relevant publications being missed.

In summary, the ERG considers that the manufacturer searched the key electronic databases, including MEDLINE, EMBASE, and the Cochrane Library, and that the search strategies used were appropriate for the decision problem that is the focus of this Single Technology Appraisal (STA).

Due to time constraints, the ERG was unable to replicate the manufacturer's search and appraisal. However, the ERG carried out a separate search of MEDLINE and the Cochrane Library in November 2012 using the manufacturer's search terms, and considers that all studies relevant to the clinical effectiveness of bevacizumab in the treatment of recurrent ovarian cancer are likely to have been identified.

4.1.2 Inclusion/exclusion criteria used in study selection

Inclusion/exclusion criteria applied by the manufacturer for the systematic review of the literature to identify RCT evidence on the clinical effectiveness of bevacizumab and to identify studies to inform an indirect comparison are summarised in Table 5. In the MS, the table presenting inclusion/exclusion criteria (Table B1, pg 30) for the clinical effectiveness of bevacizumab is labelled as "Eligibility criteria used in search strategy". However, the table is presented within the section detailing study selection (MS, Section 6.2) and the ERG considers it to be transparent that the manufacturer has applied the listed criteria during study appraisal.

Table 5. Eligibility criteria for the review of clinical effectiveness studies and for the indirect comparison applied by the manufacturer (reproduced from the MS; Table B1, pg 30, and Table 11, pg 75)

Characteristic	Inclusion criteria	Exclusion criteria
Direct comparison		
Population	Platinum-sensitive, second line relapsed/recurrent ovarian cancer	Patients with first-line or platinum resistant/refractory ovarian cancer
Intervention(s)	Bevacizumab in combination with carboplatin and gemcitabine	Anything other than bevacizumab in combination with carboplatin and gemcitabine
Outcomes	Standard efficacy (e.g., PFS, ORR, OS) and safety assessments	None
Study design	Large RCT studies (≥200 patients)	Small scale (<200 patients) or non-RCT
Language restriction	None	None
Indirect comparison		
Population	Platinum-sensitive, recurrent ovarian cancer	Patients with any other disease than platinum-sensitive, recurrent ovarian cancer
Intervention(s)	Studies evaluating any of: • paclitaxel; • platinum-based therapy (carboplatin or cisplatin); • gemcitabine; • PLDH.	Any study not evaluating any of the interventions specified in the inclusion criteria (in either experimental or control arms)
Outcomes	PFS	No assessment of PFS
Study design	Large RCT studies (≥200 patients)	Non-RCT or small RCT (<200 patients)
Language restriction	None	None
Abbreviations used in table: ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; RCT, randomised controlled trial.		

Eligibility criteria for the review of non-RCT evidence were the same as that for RCT evidence, with the exception of study design, as would be expected, which specified inclusion of non-RCT studies (≥200 patients).

For the review of the literature evaluating direct comparisons, the manufacturer restricted the population of interest to patients with platinum-sensitive disease that was the first recurrence of disease (i.e., treatment would be second-line). The final scope issued by NICE specified the population of interest to be women with recurrent platinum-sensitive or partially platinum-sensitive advanced ovarian cancer,[26] whereas the positive opinion issued by the Committee for Medicinal Products for Human Use (CHMP) states that bevacizumab may be indicated as a treatment in first-recurrence of platinum-sensitive ovarian cancer.[27] The MS indicates that the literature search was carried out on 12 August 2012, whereas the CHMP's opinion was published in September 2012. Despite the deviation in the inclusion criteria for population from the population of interest outlined by NICE, and the disparity between the manufacturer's search date and the date of issue of the positive opinion, based on the statement from the CHMP, the ERG considers the restriction to be appropriate. However, the CHMP further specifies that bevacizumab (in combination with gemcitabine plus carboplatin) may be indicated for the treatment of patients with ovarian cancer who have not received prior therapy with a vascular endothelial growth factor (VEGF) inhibitor or VEGF receptor-targeted agent. On this basis, the ERG considers that it might have been consistent to specify an inclusion criterion of no prior treatment with a VEGF inhibitor or VEGF-receptor targeted agent.

The intervention of interest is that specified in the statement issued by the CHMP, that is, bevacizumab in combination with gemcitabine and carboplatin. However, the ERG notes that eligibility criteria for comparators of interest are not listed for any of the literature reviews. The manufacturer does not indicate whether a trial evaluating any comparator would have been included. The manufacturer does state that, for the purposes of the review of clinical effectiveness, carboplatin plus gemcitabine is the main comparator (MS, pg 21). The ERG considers that specifying *a priori* comparators of interest, or stating that any comparator would be considered, would have added methodological rigour. However, the ERG acknowledges that its search identified only one RCT evaluating bevacizumab plus gemcitabine plus carboplatin in the specified population and thus considers that non-specification of criteria for comparators has not influenced the identification of relevant studies.

The ERG has concerns around the limitation placed on study design, in that only studies randomising a minimum of 200 patients would be included. On request, the manufacturer clarified that the rationale behind this decision was to focus on studies with a sufficient population size (i.e., at least 100 patients per arm) to provide robust efficacy data. The manufacturer noted that this criterion was of particular importance to "the non-RCT literature search, where small-scale uncontrolled

retrospective/observational studies may not provide particularly informative data, and the network meta-analysis (NMA), where the comparison of numerous small-scale trials may result in an even larger level of heterogeneity". The fundamental aim, and requirement, of a systematic review is to identify all original studies of acceptable quality that evaluate the defined therapeutic question. The ERG considers that applying the criterion of a minimum of 200 people would, thus, not fulfil the core requirement of a systematic review.

With reference to the criteria for outcomes, the ERG notes that the manufacturer has not listed health-related quality of life (HRQoL) as criteria for either inclusion or exclusion, which is listed as an outcome of interest to the decision problem. In the inclusion criteria for the indirect comparison, the manufacturer indicates that the only outcome of interest is PFS. Although the ERG considers that it would have been appropriate to include the other outcomes listed in the final scope, the ERG notes that information on reasons for exclusion provided within the MS suggests that no study was excluded based on outcomes reported.

Considering the methodology implemented to identify relevant studies from the searches, recommended practice for carrying out systematic reviews, as outlined by the Centre for Reviews and Dissemination,[40] is for two reviewers to apply independently pre-specified inclusion and exclusion criteria to identified studies. Where consensus cannot be reached, disagreements should be resolved by discussion with a third reviewer. The methods implemented by the manufacturer for screening of identified studies were not reported in the MS. On request, the manufacturer indicated that study selection and data extraction were carried out by only one reviewer.

Although the ERG is satisfied that all relevant studies evaluating the clinical effectiveness of bevacizumab in combination with gemcitabine plus carboplatin in the treatment of first-recurrence of platinum-sensitive ovarian cancer have been identified, the ERG considers that the methods implemented by the manufacturer did not fully adhere to recommended practice, and asserts that the imposed trial size has resulted in exclusion of studies that could inform an indirect comparison; this issue is discussed in further detail in Section 4.3.

4.1.3 Included and excluded studies in review of clinical effectiveness

The manufacturer provided appropriate PRISMA diagrams for the systematic reviews of the literature for evidence on the direct (MS; Figure 1, pg 31), and indirect comparison (MS; Figure 9, pg 76), which outlined the number of studies included and excluded at each stage.

Direct comparison

The manufacturer's search identified one RCT (OCEANS[28]) evaluating adding bevacizumab versus adding placebo to a combination of gemcitabine plus carboplatin in women with first-recurrence of platinum-sensitive ovarian cancer. The PRISMA diagram indicates that six articles were identified as relevant for inclusion in the review. The MS lists details of the full publication of OCEANS[28] and five associated conference abstracts.[41-45] The direct evidence reported in the MS is appropriately derived from OCEANS, which is a Phase III, randomised, double-blind, placebo controlled study;[28] key characteristics of OCEANS are summarised in Table 6.

The MS states that 14 full-text articles were evaluated and excluded. Full reference details for the excluded studies were not provided. In addition, the tables in the MS detailing reasons for exclusion list 13 excluded studies, rather than 14; reasons for exclusion were evaluation of lines other than second-line treatment (11 studies), population other than platinum-sensitive ovarian cancer (one study), and not relevant comparator (one study). Despite this discrepancy in reporting of number of studies excluded, the ERG is satisfied that the manufacturer has identified all relevant trials for the direct comparison relevant to the decision problem. The ERG's search identified the full publication of the OCEANS trial,[28] and associated conference abstracts.[41-45] The ERG identified one additional OCEANS-related abstract that reports on a second interim analysis of overall survival (OS).[46]

Table 6. Key trial characteristics of OCEANS[28]

Study: Design and patients	Intervention/comparator	Key inclusion criteria	Key exclusion criteria	Outcomes
484 patients with platinum-sensitive first recurrence of ovarian cancer Double blind, placebo controlled RCT Two-armed RCT assessing the effectiveness of adding bevacizumab to gemcitabine plus carboplatin compared with adding placebo Event-driven US-based RCT; 96 sites Patients randomised 1:1 to addition of bevacizumab or placebo to gemcitabine plus carboplatin Randomisation stratified by: • time from last platinum treatment to recurrence (6 to 12 vs >12 months);	Intervention: intravenous bevacizumab Comparator: placebo Bevacizumab or placebo 15 mg/kg was administered intravenously on day 1 of each cycle, before administration of gemcitabine plus carboplatin. After completion of gemcitabine plus carboplatin, bevacizumab or placebo was continued until disease progression or unacceptable toxicity. Gemcitabine plus carboplatin cycles: Patients received gemcitabine 1,000 mg/m^2 on days 1 and 8 and carboplatin AUC 4 on day 1 (based on the Calvert formula). Cycles were repeated every 21 days. The RCT was designed so that patients would receive six cycles of gemcitabine plus carboplatin but would be allowed to receive up to 10 cycles if continued response was documented. Patients were followed for survival every 3 months until death, withdrawal of consent,	Eligible patients were women: • ≥18 years of age; • histologically confirmed recurrent ovarian cancer; • disease progression ≥6 months after completion of front-line platinum-based chemotherapy. No prior chemotherapy in the recurrent setting was allowed. Patients were required to have measurable disease according to RECIST version 1.0. Other key eligibility criteria included: • Eastern Cooperative Oncology Group performance status of 0 or 1; • life expectancy of at least 12 weeks; • adequate bone marrow, coagulation, renal, and hepatic function; • signed, approved informed consent in	Main exclusion criteria were: • prior treatment with bevacizumab or other VEGF pathway-targeted therapy; • other malignancies within 5 years (unless low risk of recurrence); • history of abdominal fistula, GI perforations, or intra-abdominal abscess; • clinical signs or symptoms of GI obstruction and/or requirement for parenteral hydration or nutrition; • non-healing wound, ulcer, or bone fracture; • bleeding diathesis or significant coagulopathy; • known CNS disease (except for treated brain metastases); • clinically significant cardiovascular disease; • a major surgical procedure within 28 days of enrolment or anticipated to occur while participating in study.	Primary endpoint: • Investigator determined progression-free survival according to the RECIST modified v1.0 criteria • Scans for progression were performed at baseline and every 9 weeks until progression. Secondary endpoints: • Objective response rates (partial response or complete response as defined by the investigator, per RECIST); • Overall survival; • Duration of objective response; • Safety assessments evaluated the incidence of all adverse events (according to NCI CTCAE v3), serious adverse events, and selected adverse events. Scans for response were performed at baseline and every 9 weeks until progression. Assessment of adverse events was conducted pre-dose at each study visit (days 1 and 8 during

• cytoreductive surgery for recurrent ovarian cancer (yes/no). Duration of study: 17th April 2007 (1st patient enrolment) to 17th September 2010 (clinical data cut-off for progression-free survival)	loss to follow-up or study termination. At the time of the final analysis of progression-free survival (338 events), the median follow-up was 24 months.	accordance with federal, state, and local requirements as well as authorisation permitting the release of personal health information.		the chemotherapy phase, day 1 during the bevacizumab/placebo extension phase) and at the termination of carboplatin plus gemcitabine and bevacizumab or placebo. Survival was assessed at follow-up.
Abbreviations used in table: AUC, area under the curve; CNS, central nervous system; GI, gastrointestinal; kg, kilogram; mg, milligram; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; RCT, randomised controlled trial; RECIST, Response Evaluation Criteria for Solid Tumors; US, United States; VEGF, vascular endothelial growth factor; vs, versus.				

Indirect comparison

In addition to gemcitabine plus carboplatin, the final scope issued by NICE identified three other comparators of interest:[26]

- paclitaxel in combination with a platinum compound;
- pegylated liposomal doxorubicin hydrochloride (PLDH) in combination with a platinum compound;
- platinum-based chemotherapy as monotherapy.

The manufacturer's search identified publications relating to three trials (CALYPSO,[35] ICON4,[36] and AGO-OVAR-2.5[37]) that could potentially facilitate comparison of bevacizumab in combination with gemcitabine plus carboplatin versus all the comparators of interest listed in the final scope. All three trials evaluated treatments in recurrent platinum-sensitive ovarian cancer. As noted in Section 3.3, after seeking statistical advice the manufacturer decided against carrying out a network meta-analysis (NMA), commenting that population baseline prognostic factors were considered to be too heterogeneous for the results to be robust. Although the ERG agrees with the manufacturer that there are differences in patient baseline characteristics among the four identified studies, after consultation with clinical experts, the ERG is of the opinion that the differences are sufficiently minor such that their inclusion would have a minimal impact on clinical heterogeneity; the NMA is discussed in greater detail in Section 4.3. A summary of the key characteristics of CALYPSO, ICON4, and AGO-OVAR-2.5 are presented in Table 7; full details are provided in Appendix 1.

Furthermore, the ERG notes that the manufacturer imposed an inclusion criterion for their systematic review of trial size of 200 people or more. The ERG asserts that application of this criterion led to the exclusion of studies potentially relevant to the NMA, and, thus, studies that, although smaller, may be more clinically similar to the trials reported. The MS states that four full-text articles were evaluated and excluded based on trial size. However, the list of studies excluded from the indirect comparison indicates that seven studies were excluded based on trial size. On request, the manufacturer helpfully provided the full references for the seven studies. The ERG independently evaluated these studies for inclusion in an exploratory NMA; the characteristics of the additional included studies, together with results of the NMA, are discussed in more detail in Section 4.3.

The ERG sought advice from clinical experts as to whether they were aware of any additional trials that could inform either the direct or indirect comparison. The clinical experts indicated that they were unaware of any additional relevant trials.

No relevant non-RCTs on clinical effectiveness of bevacizumab were identified by the manufacturer.

Table 7. Summary of trials identified by the manufacturer as potentially relevant for an indirect comparison

Study	Population	Intervention	Number randomised	Median follow up (months)	Outcomes assessed (all)	Trial design
CALYPSO[35]	Platinum-sensitive relapsed/recurrent ovarian (included women who had received two previous lines of chemotherapy [~15% of women])	• PLDH (30 mg/m^2 intravenously on day 1) plus carboplatin (AUC 5 intravenously on day 1)[a] • Paclitaxel (175 mg/m^2 intravenously on day 1) plus carboplatin (AUC 5 intravenously on day 1)[a]	976	49	• PFS	Phase III, RCT, parallel group, open-label, international, multicentre
ICON4[36]	Platinum-sensitive relapsed/recurrent ovarian (included women who had received two previous lines of chemotherapy [~9% of women])	*Note: there were three protocols for this trial (additional details are given in Appendices).* Core interventions: • Paclitaxel plus platinum-based chemotherapy • Conventional platinum-based chemotherapy	802	42	• OS (primary outcome) • PFS • Quality of life	RCT, parallel group, international, multicentre
AGO-OVAR-2.5[37]	Platinum-sensitive relapsed/recurrent ovarian	• Gemcitabine 1,000 mg/m^2 on days 1 and 8 plus carboplatin (AUC 4 on day 1) • Carboplatin at AUC 5 on day 1	356	17	• PFS • Duration of response • OS	Phase III, RCT, parallel group, open label, international, multicentre

[a] Based on the Calvert formula using glomerular filtration rate calculated from serum creatinine values according to the method of Cockroft and Gault.

Abbreviations used in table: AUC, area under the curve; mg, milligram, m, metre; OS, overall survival; PFS, progression-free survival; PLDH, pegylated liposomal doxorubicin hydrochloride.

4.1.4 Details of relevant studies that were not included in the submission

The ERG considers that all studies relevant to the direct comparison of bevacizumab in combination with gemcitabine and carboplatin were included in the MS. The ERG repeated the manufacturer's searches for the review of RCT data on clinical effectiveness in MEDLINE and the Cochrane Library. However, due to time constraints, the ERG was unable to repeat the manufacturer's search to identify RCTs relevant to the indirect comparison. The ERG sought clinical advice on the studies identified within the MS and the additional studies provided by the manufacturer during the clarification process. The ERG's clinical experts indicated that they consider no relevant studies have been omitted from either the direct or indirect comparison.

4.1.5 Description and critique of manufacturer's approach to quality assessment

Direct comparison

The manufacturer assessed the OCEANS[28] trial against criteria adapted from guidance for undertaking reviews in health care issued by the Centre for Reviews and Dissemination,[40] as provided in NICE's template for manufacturer/sponsor submission of evidence to the Single Technology Appraisal (STA) process.[47] The ERG independently validated OCEANS and predominantly agrees with the manufacturer's assessment; the manufacturer's assessment, with accompanying minor comments from the ERG, is presented in Appendix 2. Evidence on the clinical effectiveness of bevacizumab is appropriately derived from OCEANS. A more detailed critique of the conduct of OCEANS is presented in Section 4.1.6.

Indirect comparison

Although the manufacturer decided against carrying out an NMA, quality assessments for the three additional trials identified were provided within the MS: CALYPSO; ICON4; and AGO-OVAR-2.5. The ERG independently validated the trials and agrees with the manufacturer's assessments of the quality of the trials; the manufacturer's assessments, with accompanying minor comments from the ERG, are presented in Appendix 3. The manufacturer's rationale for not carrying out an NMA is discussed in greater detail in Section 4.3.

4.1.6 Summary and critique of submitted clinical effectiveness evidence

The OCEANS trial was designed to assess the effectiveness of adding bevacizumab compared with adding placebo to the combination of carboplatin and gemcitabine in patients with platinum-sensitive first recurrence of ovarian cancer.[28] Bevacizumab and placebo were initially given concomitantly with gemcitabine plus carboplatin, and, subsequent to completion of 6–10 cycles of gemcitabine plus carboplatin, were given as maintenance treatments until either disease progression or unacceptable toxicity; key characteristics of the OCEANS trial are presented in Table 6.

Trial conduct

Initiated as a Phase II study, OCEANS was converted to a Phase III trial after more than 10 weeks' follow-up (approximately 20 patients accrued to each arm) with no reported gastrointestinal perforations; in an earlier study in platinum-refractory and platinum-resistant recurrent ovarian cancer, bevacizumab was associated with a higher than expected rate of gastrointestinal perforation.[15] In OCEANS, during the Phase II portion of the trial, a data monitoring committee regularly reviewed unblinded safety summaries and additional extensive reviews were planned if more gastrointestinal perforations were observed in the bevacizumab versus placebo group after at least 10 weeks of treatment. Data for patients enrolled in the Phase II portion of OCEANS remained blinded.

OCEANS was a multicentre (96 sites), parallel-group, double-blind RCT carried out in the USA. A total of 484 patients were enrolled over a period of 33 months and randomised (1:1) to bevacizumab versus placebo. Randomisation occurred through a telephone interactive voice response system (IVRS) and was stratified by two factors: (i) time to recurrence since last platinum therapy (recurrence 6–12 months after platinum based treatment vs recurrence >12 months after platinum based treatment); and (ii) cytoreductive surgery for recurrent ovarian cancer (surgery performed vs surgery not performed). The manufacturer indicates that two randomisation audits were performed by an external data co-ordinating centre to ensure that the randomisation had been carried out correctly. The ERG considers the method of randomisation to be robust.

The ERG notes that baseline characteristics, including prognostic factors (e.g., age, Eastern Cooperative Oncology Group [ECOG] score, and platinum-free interval), are reasonably well balanced across the bevacizumab and placebo groups (baseline characteristics presented in Table 8). The mean age of patients in OCEANS was 61 years, with the largest proportion of patients categorised as age 40–64 years. The ERG observes that the population in OCEANS is younger than patients with ovarian cancer typically seen in UK clinical practice. However, the ERG's clinical expert indicated that a comparatively younger population is characteristic of trials evaluating treatments for ovarian cancer.

In advanced ovarian cancer, mucinous and clear-cell carcinomas have been reported to be associated with a poorer prognosis for PFS and OS when compared with carcinomas of serous histology.[48] The ERG notes that the proportion of patients with mucinous and clear cell histological subtypes is small and is similar across the two groups (Table 8).

An inclusion criterion of OCEANS was ECOG score of 0 or 1, although one patient (0.2% of full population) with an ECOG classification of 2 was included. The ECOG scale (score of 0–5) is used to assess disease progression and how a patient's daily living abilities are affected by their disease. The lower a patient's ECOG score, the greater their capacity for physical activity. Low ECOG scores (0 and 1) indicate good performance status, and performance status has been shown to be an important prognostic factor in several types of cancer.[49]

Table 8. Baseline characteristics of patients in OCEANS[28]

Characteristic	Bevacizumab (N = 242)	Placebo (N = 242)	All patients
Age (years)			
Mean (SD)	60.5 (9.8)	61.6 (10.2)	61.0 (10.0)
Median	60.0	61.0	61.0
25th and 75th percentiles	53.0, 68.0	55.0, 68.0	54.0, 68.0
Range	38.0–87.0	28.0–86.0	28.0–87.0
Number (%) of patients by age (years)			
<40	2 (0.8)	2 (0.8)	4 (0.8)
40–64	155 (64.0)	147 (60.7)	302 (62.4)
≥65	85 (35.1)	93 (38.4)	178 (36.8)
Number (%) of patients by race			
American Indian or Alaska Native	2 (0.8)	0 (0.0)	2 (0.4)
Asian	9 (3.7)	6 (2.5)	15 (3.1)
Black or African American	8 (3.3)	7 (2.9)	15 (3.1)
Native Hawaiian/other Pacific Islander	1 (0.4)	1 (0.4)	2 (0.4)
White	218 (90.1)	222 (91.7)	440 (90.9)
Not available	4 (1.7)	6 (2.5)	10 (2.1)
Number (%) of patients by ECOG at baseline			
0	182 (75.2)	185 (76.4)	367 (75.8)
1	59 (24.4)	57 (23.6)	116 (24.0)
2	1 (0.4)	0 (0.0)	1 (0.2)
Weight (kg) at baseline			
Mean (SD)	75.5 (17.9)	75.8 (19.1)	75.7 (18.5)
Median	71.5	73.5	73.0
25th and 75th percentiles	64.0, 84.5	62.1, 84.0	63.0, 84.0
Range	41.9–159.6	43.6–163.9	41.9–163.9
Number (%) of patients by primary site			
Fallopian tube carcinoma	14 (5.8)	15 (6.2)	29 (6.0)
Ovarian carcinoma	200 (82.6)	207 (85.5)	407 (84.1)
Primary peritoneal carcinoma	28 (11.6)	20 (8.3)	48 (9.9)
Number (%) of patients by histology subtype			
Serous	189 (78.1)	202 (83.5)	391 (80.8)
Mucinous	3 (1.2)	1 (0.4)	4 (0.8)
Endometrioid	13 (5.4)	16 (6.6)	29 (6.0)
Transitional cell	2 (0.8)	2 (0.8)	4 (0.8)

Clear cell	9 (3.7)	6 (2.5)	15 (3.1)
Other	20 (8.3)	10 (4.1)	30 (6.2)
Serous, clear cell	2 (0.8)	1 (0.4)	3 (0.6)
Serous, endometrioid	2 (0.8)	4 (1.7)	6 (1.2)
Serous, transitional cell	2 (0.8)	0 (0.0)	2 (0.4)
Number (%) of patients by cytoreductive surgery for recurrent disease			
Yes	30 (12.4)	24 (9.9)	54 (11.2)
No	212 (87.6)	218 (90.1)	430 (88.8)
Number (%) of patients by time to recurrence since the last platinum-based therapy			
6–12 months	100 (41.3)	102 (42.1)	202 (41.7)
>12 months	142 (58.7)	140 (57.9)	282 (58.3)
Baseline SLD of target lesions (mm)			
Mean (SD)	73.8 (53.0)	72.4 (52.4)	73.1 (52.7)
Median	60.0	58.0	59.0
25th and 75th percentiles	36.0, 100.0	34.0, 95.0	35.0, 98.0
Range	10.0–285.0	11.0–307.8	10.0–307.8
Number (%) of patients by baseline SLD category			
≤Median (59.0 mm)	118 (48.8)	126 (52.1)	244 (50.4)
>Median	124 (51.2)	116 (47.9)	240 (49.6)
Number (%) of patients by baseline CA125			
≤35 U/mL	57 (25.0)	63 (27.4)	120 (26.2)
>35 U/mL	171 (75.0)	167 (72.6)	338 (73.8)
Abbreviations used in table: ECOG, Eastern Cooperative Oncology Group; kg, kilogram; mm, millimetre; mL, millilitre; SD, standard deviation; SLD, sum of longest diameters.			

Within the manufacturer's quality assessment of OCEANS, in response to the question on concealment of treatment allocation, the ERG determines that the manufacturer described who was blinded to treatment rather than how treatment allocation was concealed. In response to the ERG's request for further details on concealment of treatment allocation, the manufacturer stated that "treatment assignment was carried out using an Interactive Voice Response System (IVRS). Using this system, study centres obtained an identification number and treatment assignment for each patient". The ERG considers that the manufacturer's response does not fully clarify the methods implemented to allocate treatment. It is unclear how the allocation sequence was generated.

OCEANS is described as placebo-controlled, but the MS and full publication did not include a description of how placebo was matched to bevacizumab to maintain blinding of treatment allocation. As part of the clarification process, the ERG asked the manufacturer to make available the Clinical Study Report (CSR) for OCEANS. In the response, the manufacturer indicated that the full CSR was not available at this time. Instead, the manufacturer provided a short report used in the preparation of the submission. The report stated that the placebo consisted of the vehicle used for bevacizumab. With regards to level of blinding, the MS indicates that the Sponsor's personnel, the Clinical Research Organisation, investigators, and patients were blinded to treatment allocation. The Sponsor's personnel remained blinded until the database lock for the final analysis of progression-free survival

(PFS). The protocol allowed unblinding at progression of disease, and, therefore, investigators and patients may have been unblinded to treatment allocation at the time of investigator-assessed disease progression. The ERG is satisfied that OCEANS was adequately blinded.

Intervention

Bevacizumab (or placebo) was administered intravenously on day 1 of each cycle before gemcitabine plus carboplatin at a dose of 15 mg/kg of body weight, which is the recommended dose of bevacizumab when used in combination with paclitaxel plus carboplatin in the first-line treatment of advanced ovarian cancer (FIGO stages IIIB, IIIC and IV).[32] As noted earlier, in ICON7, the trial that evaluated the effectiveness of bevacizumab in the first-line treatment of advanced ovarian cancer, bevacizumab was administered at a dose of 7.5 mg/kg of body weight.[33] After completion of gemcitabine plus carboplatin, bevacizumab (or placebo) was continued at the same dose as a monotherapy until either disease progression or unacceptable toxicity, whichever occurred first. Gemcitabine (1,000 mg/m^2 on days 1 and 8) and carboplatin (area under the curve [AUC] 4 on day 1) were given intravenously for 6–10 cycles. Cycles were repeated every 21 days. Treatment on day 1 of each cycle was held if the absolute neutrophil count was <1,500/μL, haemoglobin was <8.5 g/dL, or platelet count was <100,000/μL within 24 hours of scheduled treatment. Cycles could be delayed for a maximum of 3 weeks until these values were achieved. Bevacizumab or placebo could be held for up to 3 weeks if carboplatin and gemcitabine were held, to allow for administration of study drug on the same day as administration of gemcitabine and carboplatin. In addition, bevacizumab or placebo could be held for toxicity for a maximum of 6 weeks to allow recovery; the trial protocol specified that cessation of treatment for longer than 6 weeks required the discontinuation of bevacizumab. Should a component of therapy be discontinued because of toxicity, the patient was eligible to continue with the other components per protocol.

OCEANS was designed such that patients would receive six cycles of gemcitabine plus carboplatin but, if the assessing investigator deemed it necessary, and the study Sponsor approved, patients could receive up to 10 cycles.[28] It has been reported that the number of cycles of chemotherapy does not influence median OS but longer durations of chemotherapy are associated with greater toxicity compared with shorter durations.[23] At this time, there is consensus that patients should receive a maximum of six cycles of chemotherapy.[23] The ERG's clinical expert indicated that more than six cycles of chemotherapy is unlikely to be given in UK clinical practice as there is no evidence to indicate that a higher number of cycles is associated with an increase in clinical benefit. Although patients could receive up to a maximum of 10 cycles, data presented within the MS indicate that the mean number of cycles (based on the safety evaluable population) received was about six cycles each of gemcitabine and carboplatin (summarised in Table 9). However, as a percentage, ~50% of patients received 4–6 cycles of gemcitabine and of carboplatin. Of the remaining patients, ~40% received 7–

10 cycles of each treatment. Other trials identified as potentially relevant to an NMA also allowed more than six cycles of chemotherapy. Thus, the ERG considers that, in this regard, OCEANS is comparable with other key trials evaluating efficacy of treatments in recurrent platinum-sensitive ovarian cancer. However, the ERG considers it important to reiterate that there is no evidence to suggest that increased number of chemotherapy cycles has an effect on OS, and that a maximum of six cycles of chemotherapy would likely be given in UK clinical practice.

Table 9. Summary of dosing of gemcitabine and carboplatin in OCEANS (adapted from MS; Table 15, pg 85)

Measure	Exposure to gemcitabine		Exposure to carboplatin	
	Bevacizumab (N = 246)	Placebo (N = 233)	Bevacizumab (N = 246)	Placebo (N = 233)
Dose				
Mean total dose (mg) (SD)	20,317.0 (8,802.6)	20,743.1 (8,600.9)	2,395.7 (1,017.1)	2,475.8 (1,033.2)
Median dose (mg)	18,580.0	20,176.0	2,298.6	2,358.0
25th and 75th percentiles	15,090.0 / 24,820.0	14,421.5 / 26,280.0	1,776.0 / 3,077.2	1,850.0 / 3,150.0
Range in dose (mg)	1,600.0–46,850.0	1,780.0–44,800.0	260.0–5,920.0	383.0–6,552.0
Number of cycles				
Mean (SD)	7.0 (2.3)	7.0 (2.2)	6.3 (2.4)	6.6 (2.4)
Median	6.0	6.0	6.0	6.0
25th and 75th percentiles	6.0 / 9.0	6.0 / 9.0	5.0 / 8.0	6.0 / 9.0
Range	1.0–10.0	1.0–10.0	1.0–10.0	1.0–10.0
Estimated dose intensity (%)				
Mean (SD)	70.7 (17.1)	71.8 (16.9)	88.5 (11.7)	89.0 (11.3)
Median	74.0	74.2	89.4	88.9
25th and 75th percentiles	57.1 / 85.7	60.0 / 86.0	80.5 / 100.0	82.5 / 100.0
Range	29.3–95.4	31.5–95.4	58.7–111.0	57.7–118.6
Number of patients based on number of cycles received (%)				
1–3	18 (7.3)	19 (8.2)	34 (13.8)	32 (13.7)
4–6	127 (51.4)	108 (46.4)	130 (52.8)	107 (45.9)
7–10	102 (41.3)	106 (45.5)	82 (33.3)	94 (40.3)
Data based on safety evaluable population, which included patients who received at least one dose of protocol treatment. Abbreviations used in table: mg, milligram; SD, standard deviation.				

4.1.7 Description and critique of manufacturer's outcome selection

The primary efficacy outcome of OCEANS was investigator-assessed PFS based on the Response Evaluation Criteria for Solid Tumors (RECIST modified v1.0).[28] Secondary outcomes measured were OS, objective response rate (ORR; based on RECIST criteria), and median duration of objective response. The MS indicated that, to evaluate the robustness of the primary endpoint, a sensitivity analysis was added in which an independent-review committee (IRC) assessed PFS. The IRC also assessed ORR and duration of response based on radiographic and clinical evidence; the IRC did not evaluate OS. On request, the manufacturer clarified that the IRC reviewed data for all patients randomised. The outcomes assessed in OCEANS are standard outcomes in RCTs evaluating

treatments for cancer, and are in accord with the outcomes specified in the final scope issued by NICE.[26] However, HRQoL data were not collected during OCEANS.

The ERG notes a minor disparity between the definition of PFS in the investigator-assessed analysis and that in the IRC-determined analysis:

- investigator assessed: time from random assignment to disease progression or death as a result of any cause;
- IRC-determined: time from random assignment to disease progression (IRC determined) or on-study death (i.e., death within 9 weeks of the last dose of protocol treatment).

During clarification, the ERG asked the manufacturer for the rationale behind the difference in definition. The manufacturer indicated that the reason for the discrepancy in definitions in the protocol was unclear, but stated that it was assumed that the difference arose "because the remit of the IRC was to examine data collected for patients only while they were on study." The ERG discusses this in further detail in Section 4.2.1.

The ERG notes that there are differences in the number of recorded events for PFS between the investigator-assessed and IRC-determined analyses. However, the median durations of PFS, and resultant hazard ratios (HRs), are similar for the analyses; clinical effectiveness results are discussed in more detail in Section 4.2.1.

ORR was defined as partial response or complete response as defined by the investigator and based on RECIST criteria. Duration of objective response was evaluated for those achieving an objective response, and was defined as the time from initial complete or partial response until documented disease progression or death.

Analyses of PFS, OS, and ORR were based on the intention-to-treat (ITT) population, which was defined as "all patients randomised to protocol treatment, irrespective of whether the assigned treatment was actually received". The primary analysis of PFS censored patients without disease progression or death at time of last tumour assessment, and those patients who received non-protocol-specified therapy.

As highlighted in Section 3.4, OS is widely accepted as the preferred outcome in cancer trials.[39] At the time of clinical data cut-off in OCEANS, OS data were immature. Within the MS, the manufacturer presents three interim analyses of OS. The first interim analysis was planned for the time of initial PFS clinical data cut-off and was based on 141 (29.1%) deaths. A second interim analysis was planned when approximately 214 deaths had occurred. The subsequent second and third interim analyses were carried out after 235 (48.6%) and 286 (59.1%) deaths. The MS states that the final analysis of OS is planned when 353 (73%) deaths have occurred.

4.1.8 Description and critique of the statistical approaches used

The manufacturer presented comprehensive details in the MS on the statistical approaches used in the OCEANS trial. The primary analysis was the comparison of PFS between the two treatment groups in OCEANS: bevacizumab added to gemcitabine and carboplatin versus placebo added to gemcitabine plus carboplatin. The manufacturer calculated that approximately 317 events would have had to occur at the time of final analysis to test a statistical difference between groups in PFS, based on assumptions of:[28]

- a two-sided log-rank test at the 5% level of significance;
- 80% power to reject the null hypothesis;
- an HR of 0.73 for the bevacizumab group relative to the placebo group;
- a median PFS in the placebo group of 8.6 months.

Based on estimates of rate of enrolment, ramp-up period, and drop-out rate, the manufacturer calculated that it would be necessary to randomise 480 patients (484 patients were randomised in OCEANS). It was anticipated that enrolment would be complete approximately 2.5 years after study initiation, with full information on PFS available approximately 1 year later.

OS was a pre-specified secondary outcome. Based on the assumption that bevacizumab decreases mortality by 25.9% (i.e., HR 0.74) and that median OS in the placebo group is 18 months, the manufacturer calculated that 353 deaths would provide 80% power for a two-sided test conducted at 0.048 significance level to classify that bevacizumab is superior to placebo. The final analysis of OS is planned when 353 deaths have occurred. For the interim OS analysis conducted at the time of the final PFS analysis, OS was tested at a 0.001 significance level. Based on input from the FDA in 2008, an additional interim OS analysis was planned when approximately 214 deaths had occurred and was also tested at a 0.001 significance level. The remaining α of 0.048 is allocated for the final OS analysis. A third interim analysis of OS was carried out at the request of the EMA, and is based on 286 events.

Median PFS and duration of response for the bevacizumab and placebo groups were estimated with the Kaplan–Meier method. The 95% Confidence Intervals (95% CIs) for median values were computed using methods of Brookmeyer and Crowley methodology. The stratified HR was estimated using a Cox regression model. Stratification factors were time to recurrence since the last platinum therapy (6–12 months vs >12 months) and cytoreductive surgery for recurrent disease (yes vs no). Results from an unstratified log-rank test were also presented in the MS. A two-sided stratified log-rank test was used to compare the two groups. ORRs were compared by the Cochran-Mantel-Haenszel test. Final analyses of ORR and duration of objective response occurred at the time of final PFS analysis.

Analyses of PFS, OS, and ORR were based on an ITT population. For PFS, data for patients who did not have investigator-determined disease progression and who had not died were censored at the time of their last tumour assessment. For patients with no assessment of their tumour after the baseline visit, PFS was censored at the date of randomisation plus 1 day. PFS data for patients receiving non-protocol cancer therapy before documented disease progression were censored at the time of the last tumour assessment before commencement of non-protocol therapy. The manufacturer presents analyses of PFS including patients receiving non-protocol therapy as a sensitivity analysis.

To investigate any potential effect of individual demographic and baseline characteristics on prognosis, several subgroup analyses were carried out in OCEANS. Pre-specified subgroups based on baseline characteristics were:

- platinum sensitivity (6–12 months vs >12 months);
- occurrence of cytoreductive surgery (yes vs no);
- age (<65 years vs ≥65 years);
- race (white vs non-white);
- ECOG performance status (0 vs 1);
- histopathological cell type (fallopian tube vs ovarian vs primary peritoneal);
- sum of longest diameters (SLD) of target lesions at baseline (≤median [59.0 mm] vs >median);
- baseline CA125 (≤35 vs >35 U/ml);
- prior biologic therapy (yes vs no);
- prior hormonal therapy (yes vs no);
- prior myeloablative therapy (yes vs no).

The ERG notes that separate power calculations were not carried out to determine the number of events required to detect a statistically significant difference in outcomes for the subgroups reported.

4.1.9 Summary statement

The ERG determines that the manufacturer's search strategies were generally appropriate and is satisfied that all relevant evidence was identified on the direct comparison of bevacizumab in combination with platinum-based therapy versus other chemotherapy regimens in recurrent platinum-sensitive ovarian cancer. The ERG notes that, within the MS, the level of reporting of methodology followed to carry out the systematic review was limited. On request, the manufacturer reported that only one reviewer appraised abstracts and extracted data. In addition, it is not clear whether reference lists of identified RCTs were evaluated for additional suitable studies. More importantly, the ERG has concerns around the inclusion criterion that limited eligible studies to those involving a minimum of 200 patients. Although the ERG appreciates the manufacturer's rationale that their goal was to focus

on studies with a sufficient population size, and that this is particularly relevant to the non-RCT literature search, the ERG asserts that studies that could potentially inform an indirect comparison were excluded from the review. The manufacturer provided details of excluded studies on request during the clarification process.

The submitted direct clinical evidence is based on a large, multicentre trial (OCEANS[28]), which the ERG considers to be well-designed. The primary objective of OCEANS was to evaluate the efficacy of bevacizumab over placebo in extending PFS in women with recurrent ovarian cancer. With the exception of HRQoL, which was not collected in OCEANS, the outcomes assessed in the trial and presented in the MS are clinically relevant and address the decision problem as outlined in the final scope issued by NICE.[26] After seeking clinical advice, the ERG determines that, with the exception of baseline weight, the baseline characteristics of the population in OCEANS are representative of women seen in UK clinical practice who have first recurrence of platinum-sensitive ovarian cancer.

OCEANS was designed such that patients would receive between six and 10 cycles of gemcitabine plus carboplatin.[28] There is little evidence that the number of cycles of chemotherapy influences median OS but there is evidence that longer durations of chemotherapy are associated with greater toxicity compared with shorter durations. At this time, consensus is that patients should receive a maximum of six cycles of chemotherapy,[23] which the ERG's clinical expert indicated reflects UK clinical practice. In OCEANS, about 40% of patients in both the bevacizumab and placebo group received 7–10 cycles of chemotherapy. The ERG is unsure of the relevance to UK clinical practice of the additional cycles of chemotherapy.

As well as gemcitabine plus carboplatin, the final scope issued by NICE listed paclitaxel plus a platinum compound, PLDH plus a platinum compound, and platinum-based chemotherapy as monotherapy as comparators of interest to this decision problem. The manufacturer's systematic review for studies to inform an indirect comparison of bevacizumab identified three trials that could be used to form a linear NMA. After consulting with a statistician, the manufacturer decided against carrying out an NMA, indicating that the level of clinical heterogeneity across the trials was too high. The ERG independently reviewed the publications identified by the manufacturer, and the publications initially excluded based on trial size. Based on its review of the studies and comments from clinical experts, the ERG concluded that the manufacturer excluded studies that could inform an indirect comparison. The ERG considers that, in terms of comparison against other treatments used in UK clinical practice, the evidence submitted did not fully address the decision problem outlined in the final scope.

4.2 Summary of submitted evidence

As discussed earlier, the primary efficacy outcome of OCEANS was investigator-assessed PFS based on RECIST criteria.[28] Secondary outcomes analysed were OS, ORR, and median duration of objective response. Sensitivity analyses included analyses based on evaluation of results by an IRC (PFS, ORR, and median duration of response) and analysis of PFS that included patients who received non-protocol therapies. Within the MS, the manufacturer fully reported data and statistical analyses for the primary analysis of PFS and other investigator-assessed outcomes. By contrast, reporting of corresponding absolute data and results of statistical significance tests for sensitivity analyses was incomplete. The inconsistent reporting of data and analyses in the MS prompted the ERG to request the CSR for OCEANS as part of the clarification process. The manufacturer was unable to provide the full CSR, and instead made available a copy of the report used when preparing the submission, adding that "while the core report refers to additional sections, these were not available prior to submission of the MS and are not provided in this version". Individual outcomes and the manufacturer's responses are discussed separately in the sections that follow.

4.2.1 Summary of results on clinical effectiveness

Primary outcome: progression-free survival

Addition of bevacizumab to gemcitabine and carboplatin was associated with a statistically significant increase in duration of PFS compared with addition of placebo (HR 0.48; 95% CI: 0.39 to 0.61; p <0.0001): summary of PFS analysis is presented in Table 10 and the Kaplan–Meier analysis for the primary outcome is provided in Appendix 4. Median duration of PFS was 12.4 months in the bevacizumab group compared with 8.4 months in the placebo group. The manufacturer proposes that strategies that extend duration of PFS, thereby prolonging the platinum-free interval, are important for improving patient outcomes and prognosis in subsequent lines of treatment.

For completeness, during clarification, the ERG asked the manufacturer to provide the mean duration of PFS in each group based on analyses of data at clinical cut-off. The manufacturer did not provide the mean PFS, stating that the analysis of PFS was conducted before all patients had progressed, and, therefore, the maximum PFS value is unknown and a mean cannot be calculated. The ERG acknowledges that not all patients had progressed, but asserts that the reported analysis is likely to be the sole analysis of PFS and a mean duration based on the data collected could have been provided.

The IRC-determined sensitivity analysis supports the findings of the investigator-assessed result for PFS, with median durations of PFS of 12.3 months and 8.6 months for the bevacizumab and placebo groups, respectively (HR 0.45; 95% CI: 0.35 to 0.58; Table 10); Kaplan–Meier analysis of IRC-determined PFS is presented in Appendix 5.

The ERG observes that there is a minor difference in the time to death component of the PFS definition that was followed by the OCEANS investigators and that followed by the IRC. In the investigator-assessed analysis, PFS included time to death from any cause, whereas the IRC analysis of PFS was based on time to on-study death (i.e., death within 9 weeks of the last dose of protocol treatment). As noted earlier, on request, the manufacturer indicated that it was assumed that the difference arose "because the remit of the IRC was to examine data collected for patients only while they were on study". To verify that the number of deaths included in each analysis was similar, the ERG requested a breakdown of events by disease progression or death for the IRC-determined sensitivity analysis (not reported in the MS). The manufacturer was unable to provide these data during clarification. Based on the low number of deaths from any cause contributing to the investigator-assessed analysis of PFS, the ERG does not consider that any potential difference in number of deaths in the IRC-determined analysis would have a considerable impact on the analysis.

The ERG notes that the number of recorded events is higher in the investigator-assessed analysis than in the IRC-determined analysis. Diagnosis of disease progression in both analyses was based on standard RECIST criteria (summarised in Table 4), and, thus, the ERG is unclear as to why there is a considerable variation in the number of recorded events. The MS did not provide a detailed description of the processes followed by the IRC, or of the experts who comprised the IRC. The additional short report provided by the manufacturer indicates that two radiologists reviewed data, and assessments were adjudicated by a third radiologist if necessary. An oncologist then initially reviewed clinical data and subsequently reviewed both the radiological and clinical evidence to make a final determination of response and progression status. Radiologists and oncologists were blinded to treatment allocation. The MS does not discuss the variation in event rate across the investigator-assessed and IRC-determined analysis of PFS.

Table 10. Results of the primary analysis of progression-free survival

	Investigator-assessed[a]		**Independent review committee-determined**		**Sensitivity analysis (includes patients censored for receiving non-protocol therapies)**	
Outcome	**Bevacizumab (N = 242)**	**Placebo (N = 242)**	**Bevacizumab (N = 242)**	**Placebo (N = 242)**	**Bevacizumab (N = 242)**	**Placebo (N = 242)**
Number (%) of patients with an event	151 (62.4)	187 (77.3)	119 (49.2)	148 (61.2)	174 (71.9)[b]	203 (83.9)[b]
Disease progression	146 (60.3)	185 (76.4)	NA	NA	146 (60.3)[b]	185 (76.4)[b]
Death	5 (2.1)	2 (0.8)	NA	NA	5 (2.1)[b]	2 (0.8)[b]
Number of patients not known to have an event	91 (37.6)	55 (22.7)	NA	NA	NA	NA

Progression-free survival, months						
Median (95% CI)	12.4 (11.40 to 12.71)	8.4 (8.31 to 9.66)	12.3 (10.7 to 14.6)	8.6 (8.3 to 10.2)	12.4	8.4
HR (relative to placebo) (95% CI)	*Stratified analysis*:[c] 0.48 (0.39 to 0.61) p <0.0001		*Stratified analysis*:[c] 0.45 (0.35 to 0.58) p <0.0001		0.52 (0.43 to 0.65) p <0.0001	
	Unstratified analysis: 0.49 (0.40 to 0.61) p <0.0001		NA		NA	

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

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

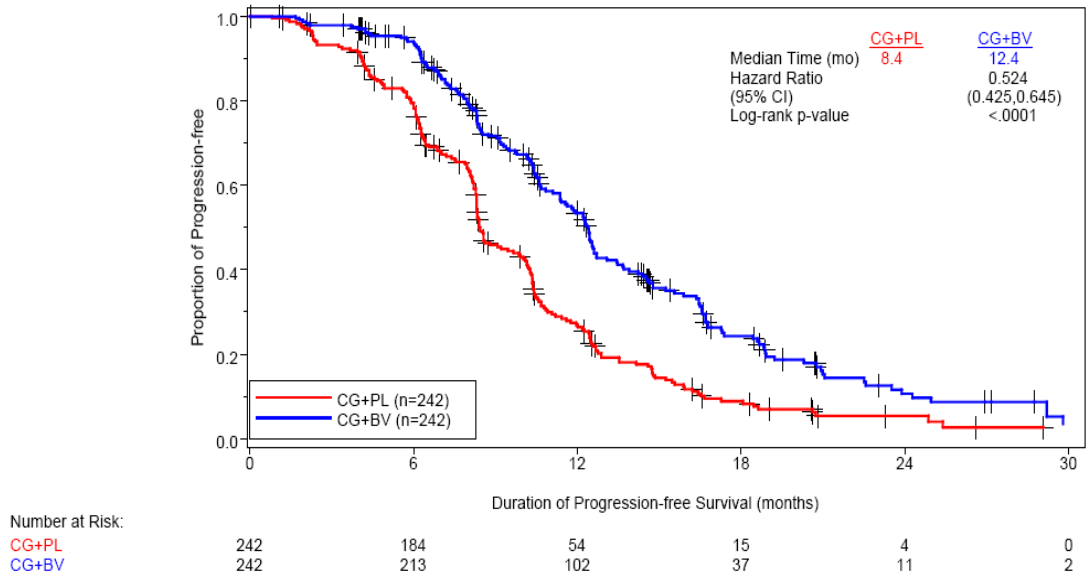
[b] Data provided by the manufacturer during the clarification process.

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

Abbreviations used in table: CI, confidence interval; ERG, Evidence Review Group; HR, hazard ratio; NA, not available.

In the primary analysis of PFS, patients who received non-protocol specified cancer therapy before documented disease progression were censored at the time of the last tumour assessment before initiation of non-protocol therapy. Sensitivity analysis including these patients generated similar results to those of the investigator-assessed primary analysis of PFS (HR 0.52; 95% CI: 0.43 to 0.65; p <0.0001). Within the MS, the manufacturer provided only the Kaplan–Meier data for this analysis (presented in Figure 2). During clarification, the ERG requested the total number of events in each group in this sensitivity analysis, together with a breakdown of events by disease progression or death. The manufacturer helpfully provided these data, which are summarised in Table 10. The ERG notes that the breakdown of events in the sensitivity analysis mirrors that in the primary analysis, but the total number of events differs. The ERG considers that the total number of events is likely to be correct, and the breakdown by event erroneous.

Figure 2. Kaplan–Meier estimates of investigator-assessed progression-free survival without censoring for non-protocol specified therapy (reproduced from MS; Figure 7, pg 66)



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

For standard survival analysis techniques to be valid, it is important that censored patients are representative of those patients that remain at risk, that is, censoring at specific time point should not influence the prognosis of patients alive at that time. Censoring at random and censoring at a fixed time point ensure the validity of the analysis. However, censoring because of worsening condition or discontinuation due to adverse effects of treatment can lead to a biased estimate of the survival probability. Although the MS describes the pre-specified reasons for censoring of patients, and the methods to analyse the data for censored patients, neither the MS nor the full publication of OCEANS[28] specifies the number of patients censored in each group at the time of final PFS analysis in the investigator-assessed or IRC-determined analysis. Moreover, the patient flow diagram presented in the MS, and which is also in the full publication of OCEANS,[28] does not report the number of patients lost to follow-up at the time of the primary analysis.

During clarification, in an attempt to ascertain whether the number of patients censored was skewed at any time point, for each group in OCEANS, the ERG requested a monthly breakdown of number of patients censored because they did not have disease progression or they were still alive, in addition to the number patients censored because they received non-protocol specified therapy. The ERG also requested details of the number of patients who discontinued due to an adverse effect each month and those that were lost to follow-up. The manufacturer was unable to provide the requested data. The ERG appreciates that providing a breakdown of censoring by month may have proved challenging in the timeframe for clarification, but the ERG would expect the manufacturer to be able to report the number of patients lost-to follow-up at final analysis of PFS (i.e., clinical data cut-off).

During clarification, the manufacturer reproduced data from the MS to illustrate the number of patients who remained at risk at 6-monthly time points for the PFS analysis. The ERG considers that these data do not provide information on the number of patients censored.

In addition, as discussed earlier, UK clinical practice is to administer no more than 6 cycles of chemotherapy, whereas OCEANS protocol allowed a maximum of 10 cycles of gemcitabine plus carboplatin; ~40% of patients in OCEANS received more than 6 cycles of chemotherapy. In an attempt to investigate any potential impact of additional chemotherapy cycles, the ERG requested an analysis of PFS based on patients who received up to 6 cycles of chemotherapy. The manufacturer was unable to provide this analysis. The ERG appreciates that this may have proved challenging in the timeframe for clarification.

Overall survival

The manufacturer presents data from three interim analyses of OS (summarised in Table 11). As noted in Section 4.1.8, the manufacturer's power calculations indicate that data will be mature with respect to OS when 353 events have occurred. The first interim analysis of duration of OS was carried out at the time of final PFS analysis. In the full publication of OCEANS, the authors highlight that, at the time of the second interim analysis, median OS was longer than anticipated in both the bevacizumab and placebo group and that there was a high degree of censoring beyond 18 months.[28] At the last interim analysis, 286 events had occurred and thus OS data remain immature and should be interpreted with caution.

None of the interim analysis found a statistically significant difference between bevacizumab and placebo in duration of OS. The direction of effect in the first interim analysis favoured bevacizumab (25% reduction in risk of mortality). The effect size generated from the second and third interim analyses approaches 1, that is, there is no difference between bevacizumab and placebo in duration of OS.

The manufacturer states that, due to post-progression treatment, OS data are confounded. The manufacturer highlights that fewer patients in the bevacizumab group received post-progression bevacizumab compared with the placebo group (37/242 [18.1%] in the bevacizumab group compared with 74/242 [34.7%] in the placebo group). However, the manufacturer also presents data that indicate a similar proportion of women in each group went on to receive any subsequent anticancer therapy (based on data-set used for second interim analysis of OS; 204/242 [84.3%] in the bevacizumab group compared with 213/242 [88.0%] in the placebo group; taken from MS; Table 9, pg 71).

The ERG agrees with the manufacturer that confounding due to post-progression treatment is a well-recognised difficulty associated with interpretation of OS data, but considers that this issue is common to trials evaluating cancer treatments, as highlighted in FDA guidance.[39]

Table 11. Interim analyses of overall survival

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

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

[b] HR reported in the manufacturer's submission to be relative to placebo. However, the quoted HR is for placebo relative to bevacizumab.[50]

Abbreviations used in table: CI, confidence interval; HR, hazard ratio; OS, overall survival.

Objective response rate and duration of response

ORR was defined as the occurrence of a complete or partial response, and was confirmed by a repeat assessment performed ≥4 weeks after the criteria for response were first met; criteria for response were assessed based on the modified RECIST criteria (presented in Table 4).

In investigator-assessed ORR, a statistically significant larger proportion of patients achieved an objective response with bevacizumab compared with placebo (190/242 [78.5%] in the bevacizumab group vs 139/242 [57.4%] in the placebo group; $p<0.0001$); results summarised in Table 12. In addition, the proportion of patients achieving a complete response was larger with bevacizumab (42/242 [17.4%] with bevacizumab vs 22/242 [9.1%] with placebo; statistical significance not reported). The results of the sensitivity analysis for ORR carried out by the IRC are in agreement with the results of the investigator-assessed analysis (summarised in Table 12). The ERG notes that the proportion of patients classified as achieving an objective response is comparable for the investigator-

assessed and IRC-determined analyses. However, as the manufacturer notes, there is disparity between the analyses in the proportion of patients classified as achieving a complete, and, as a consequence, a partial response (presented in Table 12). The IRC seemingly classified most patients as achieving partial response, and the proportion of patients achieving a complete response is larger in the placebo group (0.8% with bevacizumab vs 1.2% with placebo; statistical significance not reported). There is no discussion in the MS of potential reasons for the difference between the analyses. Absolute event rate and results of the statistical significance between groups for the IRC-determined analysis are not reported in the MS.

Of the patients achieving objective response, those in the bevacizumab group had a longer median duration of response than those in the placebo group (10.4 months with bevacizumab group vs 7.4 months with placebo). In addition, bevacizumab was associated with a 47% reduction in the risk of disease progression compared with placebo (HR 0.53; 95% CI: 0.41 to 0.67; p <0.0001). The duration of response in each group as determined by the IRC is not reported within the MS. The manufacturer states that the "IRC-assessed duration of response was consistent with investigator-assessed duration of response".

As part of the clarification process, the ERG requested the absolute event rates for ORR and duration of response as determined by the IRC. The manufacturer was unable to provide these data during clarification, stating that "these data do not appear to be reported in the OCEANS CSR or elsewhere in the relevant publications".

The guidance from the FDA indicates that, when complete and partial responses are combined, ORR is a direct measure of antitumor activity of a drug.[39] Based on this guidance, the ORR for the investigator-assessed and IRC-determined analyses are comparable and suggest that bevacizumab is associated with a statistically significant improvement in objective response compared with placebo. However, the ERG has concerns around the considerable difference between the two analyses in the classification of patients as having either a complete or partial response.

Table 12. Analysis of objective response rate (adapted from MS; Table 6, pg 66)

	Investigator-assessed		**Independent-review committee**	
Outcome	**Bevacizumab (N = 242)**	**Placebo (N = 242)**	**Bevacizumab (N = 242)**	**Placebo (N = 242)**
Number (%) of patients with objective response	190 (78.5)	139 (57.4)	74.8%	53.7%
Best objective confirmed response				
Complete response	42 (17.4)	22 (9.1)	0.8%	1.2%
Partial response	148 (61.2)	117 (48.3)	NA	NA

Difference in objective response rates (%, relative to placebo) (95% CI)	21.1 (13.0 to 29.2) p <0.0001[a,b]		28.9 (95% CI NA) p value NA	
Duration of response (months) (for those patients achieving objective response)	10.4 (9.36 to 11.83)	7.4 (6.31 to 8.31)	NA	NA
HR for risk of disease progression (relative to placebo) (95% CI)	Stratified analysis:[b] 0.53 (0.41 to 0.70) p <0.0001		NA	
	Unstratified analysis: 0.54 (0.41 to 0.70) p <0.0001		NA	

[a] p value reported for both the stratified and the unstratified analysis. p value for the stratified analysis is from the Cochran–Mantel–Haenszel test, and the p value for the unstratified analysis is from the Pearson's X^2 test.

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

Abbreviations used in table: CI, confidence interval; NA, not available.

4.2.2 Subgroup analysis

The final scope issued by NICE specified no subgroup as being of interest to the decision problem.[26] However, the manufacturer specified *a priori* subgroup analyses to investigate further the clinical effect of bevacizumab based on baseline prognostic factors. Pre-specified subgroup analyses in the OCEANS trial were:

- platinum-sensitivity (6–12 vs >12 months);
- occurrence of cytoreductive surgery (yes vs no);
- age (<65 vs ≥65 years);
- race (white vs non-white);
- ECOG performance status (0 vs 1);
- histopathological cell type (fallopian tube vs ovarian vs primary peritoneal);
- sum of longest diameters (SLD) of target lesions at baseline (≤median [59.0 mm] vs >median);
- baseline CA125 (≤35 vs >35 U/ml);
- prior biologic therapy (yes vs no);
- prior hormonal therapy (yes vs no);
- prior myeloablative therapy (yes vs no).

Randomisation in OCEANS was stratified by platinum-sensitivity (6–12 vs >12 months) and occurrence of cytoreductive surgery (yes vs no).

Based on clinical expert advice and the scope issued by NICE, the ERG considers that none of the subgroup analyses is of particular relevance to this decision problem that is the focus of this STA, and thus the results are not discussed in detail. Across most subgroups, bevacizumab was associated with

a reduced risk of progression compared with placebo that was consistent with the overall result for the ITT population (schematic of PFS by subgroup and absolute numbers of events in each subgroup are presented in Appendix 6 and Appendix 7, respectively). In terms of stratified subgroups, it is noteworthy that, compared with placebo, bevacizumab improved PFS in the subgroups of patients based on degree of platinum-sensitivity and status of cytoreductive surgery:

- 6–12 months since last platinum therapy: HR 0.41; 95% CI: 0.29 to 0.58;
- >12 months since last platinum therapy: HR 0.55; 95% CI: 0.41 to 0.73;
- patients having cytoreductive surgery: HR 0.50; 95% CI: 0.24 to 1.01;
- patients not having cytoreductive surgery: HR 0.49; 95% CI: 0.39 to 0.62.

4.2.3 Adverse effects

The Summary of Product Characteristics (SmPC) for bevacizumab reports that the overall safety profile of bevacizumab is based on data from 3,500 patients with various cancers.[32] The SmPC states that the most serious adverse effects observed with bevacizumab treatment were gastrointestinal perforations, haemorrhage, and arterial thromboembolism. The most frequently observed adverse effects were hypertension, fatigue or asthenia, diarrhoea and abdominal pain. Patients with a history of hypertension are at risk of developing proteinuria. Increased monitoring of patients for hypertension and proteinuria is identified in the MS as a potential additional resource associated with administration of bevacizumab. The SmPC notes that the occurrence of hypertension and proteinuria is likely to be dose-dependent.

In the MS, the manufacturer also recognises that varying levels of gastrointestinal perforations were observed during Phase II trials of bevacizumab in recurrent ovarian cancer. For this reason, the manufacturer carried out a literature search for prospective trials reporting adverse events with bevacizumab, with a focus on gastrointestinal perforations. The manufacturer identified 10 studies in which bevacizumab was predominantly used in combination with various agents (one trial evaluated single-agent bevacizumab) in the treatment of recurrent ovarian cancer. In the identified studies, the range in incidence of gastrointestinal perforations was 0–15.4% (summarised in MS; Table 24, pg 95). A systematic review identified by the ERG reported that bevacizumab was associated with a significantly increased risk of gastrointestinal perforation compared with control treatments (Relative risk 2.14; 95% CI: 1.19 to 3.85; p = 0.011).[51] The meta-analysis is based on data from 17 prospective RCTs that evaluated a total of 12,294 patients with various types of cancer, including ovarian cancer.

The manufacturer presented adverse event data from the "safety-evaluable" population of the OCEANS trial, which comprised patients who received at least one dose of protocol treatment (i.e., one dose of bevacizumab, placebo, gemcitabine, or carboplatin). Information provided in the patient flow diagram (MS; Figure 3, pg 57), together with the manufacturer's responses to clarification,

indicate that five patients in the placebo group received bevacizumab in error and, for the purposes of the analysis of adverse effects, were included in the bevacizumab group. In addition, four patients in the placebo group did not receive a dose of protocol therapy. All patients in the bevacizumab group received at least one dose of protocol treatment. Thus, the safety-evaluable population comprised 247 patients in the bevacizumab group and 233 patients in the placebo group.

The mean and median doses of bevacizumab were higher than the corresponding 'dose' of placebo (Table 13). Median estimated dose intensity was 92.3% of intended dose for both groups. Patients received a median of 12 cycles and 10 cycles of bevacizumab and placebo, respectively. Median duration of treatment was 37.3 weeks in the bevacizumab group compared with of 32.1 weeks in the placebo group. Summary of exposure to gemcitabine and carboplatin is provided in Table 9.

Table 13. Summary of dosing of bevacizumab and placebo in OCEANS (safety evaluable patients) (adapted from MS; Table 16, pg 88)

Measure	Exposure to bevacizumab (N = 246)[a]	Exposure to placebo (N = 233)
Dose		
Mean total dose (mg) (SD)	15,332.8 (10,179.1)	12,748.2 (7,812.6)
Median dose (mg)	13,220.0	11,190.0
25th and 75th percentiles	7,856.0 / 20,790.0	7,640.0 / 16,353.0
Range in dose (mg)	855.0–60,375.0	750.0–41,910.0
Number of cycles		
Mean (SD)	13.6 (8.5)	11.2 (6.2)
Median	12.0	10.0
25th and 75th percentiles	8.0 / 18.0	6.0 / 14.0
Range	1.0–43.0	1.0–36.0
Estimated dose intensity (%)		
Mean (SD)	91.4 (8.3)	91.7 (8.4)
Median	92.3	92.3
25th and 75th percentiles	87.5 / 100.0	86.7 / 100.0
Range	60.0–100.6	60.0–108.7
Number of patients based on number of cycles received (%)		
1–3	17 (6.9%)	19 (8.2%)
4–6	37 (15.0%)	40 (17.2%)
7–10	57 (23.2%)	63 (27.0%)
11–20	90 (36.6%)	93 (39.9%)
21–30	34 (13.8%)	15 (6.4%)
31–40	9 (3.7%)	3 (1.3%)
41–50	2 (0.8%)	0 (0.0%)

Data based on safety evaluable population, which included patients who received at least one dose of protocol treatment.

[a] One patient in the bevacizumab group did not receive bevacizumab, but received a dose of another protocol treatment.

Abbreviations used in table: mg, milligram; SD, standard deviation.

The manufacturer presented various assessments of adverse event data derived from OCEANS,[28] including analysis based on all adverse events (Table 14), adverse events (any Grade) that occurred with a ≥5% incidence in the bevacizumab group compared with the placebo group (Table 15), and Grade 3–5 adverse events occurring with a ≥2% higher incidence in the bevacizumab group (Table 16).

The mean duration of follow-up for the safety assessment in OCEANS was 10.7 months (median of 9.6 months) in the bevacizumab group and 8.8 months (median of 8.4 months) in the placebo group.

All patients in the safety-evaluable population experienced an adverse effect of treatment (Table 14). Adverse events were categorised based on, amongst others, Grade of event, adverse event leading to discontinuation, and adverse events of special interest (AESIs). In most classifications, a larger proportion of patients in the bevacizumab group experienced the event(s) compared with the placebo group, although it should be noted that there are only minor differences between groups for some categories. Hypertension, proteinuria, epistaxis, and headache were the adverse effects for which the most substantial difference (>10%) in occurrence was observed between the bevacizumab and placebo groups (Table 14). In addition, hypertension and proteinuria were two of the AESIs occurring with ≥2% higher incidence in the bevacizumab group compared with the placebo group (Table 16). The proportion of patients experiencing an adverse effect known to be related to chemotherapy, for example, neutropenia and febrile neutropenia, was comparable between the two groups. Of note, no patients in OCEANS experienced a gastrointestinal perforation (Table 14).

No statistical analysis of difference between groups for adverse effects is provided in the MS. The manufacturer did not provide the statistical analysis as requested during clarification, indicating that the analyses had not previously been undertaken and, furthermore, could not be undertaken during clarification as the manufacturer did not have access to the raw data. As part of the clarification process, the ERG also requested statistical analysis for the bevacizumab-specific adverse events. The manufacturer highlighted that it was not possible to determine whether the differences between groups were statistically significant for all adverse events for methodological reasons (multiple testing on a single database). However, the ERG considers that, as there are statistical methods available to counteract the problem of multiple comparisons, supplementary analyses could potentially have been carried out.

Table 14. Summary of the safety analyses from OCEANS (safety-evaluable patients; adapted from MS; Table 18, pg 90)

Adverse event	**Number of patients experiencing adverse event (%)**	
	Bevacizumab (N = 247)	**Placebo (N = 233)**
Any adverse event	247 (100)	233 (100)
Grade 3–5 adverse event	221 (89.5)	192 (82.4)
Serious adverse event	86 (34.8)	58 (24.9)
Serious adverse event (Grade 3–5)	72 (29.1)	47 (20.2)
Adverse event leading to study drug (bevacizumab or placebo) discontinuation	49 (19.8)	11 (4.7)
All deaths	63 (25.5)	78 (33.5)
Grade 5 adverse event	1 (0.4)	1 (0.4)
Adverse events of special interest (any Grade)	233 (94.3)	198 (85.0)
Adverse events of special interest (Grade 3–5)	182 (73.7)	144 (61.8)
Arterial thromboembolic event (any Grade)	7 (2.8)	2 (0.9)
Bleeding (CNS) (any Grade)	2 (0.8)	1 (0.4)
Bleeding (non-CNS; Grade ≥3)	14 (5.7)	2 (0.9)
LV systolic dysfunction/CHF (Grade ≥3)	3 (1.2)	2 (0.9)
Febrile neutropenia (any Grade)	4 (1.6)	4 (1.7)
Fistula/abscess[a] (any Grade)	4 (1.6)	1 (0.4)
Gastrointestinal perforation (any Grade)	0 (0.0)	0 (0.0)
Hypertension (Grade ≥3)	43 (17.4)	1 (0.4)
Neutropenia (Grade ≥4)	51 (20.6)	51 (21.9)
Proteinuria (Grade ≥3)	21 (8.5)	2 (0.9)
RPLS (any Grade)	3 (1.2)[b]	0 (0.0)
Wound healing complication (Grade ≥3)	2 (0.8)	0 (0.0)
Venous thromboembolic event (Grade ≥3)	10 (4.0)	6 (2.6)

[a] Includes all fistula/abscess events: anal fistula, female genital tract fistula, pelvic abscess, perirectal abscess, rectal abscess (narratives provided only for gastrointestinal-related events [anal fistula, perirectal abscess, and rectal abscess])

[b] Two were MRI-confirmed RPLS cases.

Abbreviations used in table: CHF, coronary heart failure; CNS, central nervous system; LV, left ventricular; MRI, magnetic resonance imaging; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; RPLS, reversible posterior leukoencephalopathy syndrome.

Table 15. Adverse events with ≥5% higher incidence in the bevacizumab group versus placebo group (safety-evaluable patients) (adapted from MS; Table 19, pg 91)

Adverse effect	**Number of patients experiencing adverse effect (%)**	
MedDRA System Organ Class MedDRA Preferred Term	**Bevacizumab (N = 247)**	**Placebo (N = 233)**
Any adverse event	247 (100)	233 (100)
Blood and lymphatic system disorders		
Thrombocytopenia	143 (57.9)	119 (51.1)
Gastrointestinal disorders		
Diarrhoea	92 (37.2)	67 (28.8)
Gingival bleeding	17 (6.9)	1 (0.4)
Nausea	177 (71.7)	153 (65.7)
Stomatitis	37 (15.0)	15 (6.4)
General disorders/administration site conditions		
Fatigue	201 (81.4)	175 (75.1)
Mucosal inflammation	38 (15.4)	22 (9.4)
Infections and infestations		
Sinusitis	36 (14.6)	20 (8.6)
Injury, poisoning, and procedural complications		
Contusion	42 (17.0)	21 (9.0)
Musculoskeletal/connective tissue disorders		
Arthralgia	68 (27.5)	44 (18.9)
Back pain	49 (19.8)	30 (12.9)
Nervous system disorders		
Dizziness	55 (22.3)	39 (16.7)
Headache	120 (48.6)	70 (30.0)
Psychiatric disorders		
Insomnia	50 (20.2)	35 (15.0)
Renal and urinary disorders		
Proteinuria	41 (16.6)	9 (3.9)
Respiratory, thoracic, mediastinal disorders		
Cough	62 (25.1)	42 (18.0)
Dysphonia	32 (13.0)	8 (3.4)
Dyspnoea	72 (29.1)	56 (24.0)
Epistaxis	134 (54.3)	33 (14.2)
Oropharyngeal pain	40 (16.2)	23 (9.9)
Rhinorrhoea	23 (9.3)	8 (3.4)
Sinus congestion	19 (7.7)	4 (1.7)
Vascular disorders		
Hypertension	100 (40.5)	20 (8.6)

Table 16. Adverse events (Grade 3–5) with ≥2% higher incidence in the bevacizumab group versus placebo group (safety-evaluable patients) (adapted from MS; Table 20, pg 92)

Adverse event	**Number of patients experiencing adverse event (%)**	
MedDRA System Organ Class MedDRA Preferred Term	**Bevacizumab (N = 247)**	**Placebo (N = 233)**
Any adverse event	221 (89.5)	192 (82.4)
Grade 5	1 (0.4)[a]	1 (0.4)[b]
Grade 4	115 (46.6)	93 (39.9)
Grade 3	105 (42.5)	98 (42.1)
Blood and lymphatic system disorders		
Thrombocytopenia (total)	99 (40.1)	79 (33.9)
Grade 4	70 (28.3)	44 (18.9)
Grade 3	29 (11.7)	35 (15.0)
Gastrointestinal disorders		
Nausea (total)	10 (4.0)	3 (1.3)
Grade 4	1 (0.4)	0 (0.0)
Grade 3	9 (3.6)	3 (1.3)
General disorders/administration site conditions		
Fatigue (total)	16 (6.5)	10 (4.3)
Grade 3	16 (6.5)	10 (4.3)
Nervous system disorders		
Headache (total)	9 (3.6)	2 (0.9)
Grade 4	1 (0.4)	0 (0.0)
Grade 3	8 (3.2)	2 (0.9)
Renal and urinary disorders		
Proteinuria	20 (8.1)	1 (0.4)
Grade 4	1 (0.4)	0 (0.0)
Grade 3	19 (7.7)	1 (0.4)
Respiratory, thoracic, mediastinal disorders		
Dyspnoea	11 (4.5)	4 (1.7)
Grade 3	11 (4.5)	4 (1.7)
Epistaxis	12 (4.9)	1 (0.4)
Grade 3	12 (4.9)	1 (0.4)
Vascular disorders		
Hypertension	40 (16.2)	1 (0.4)
Grade 4	2 (0.8)	0 (0.0)
Grade 3	38 (15.4)	1 (0.4)

[a] Intracranial haemorrhage.

[b] Acute myocardial infarction.

Discontinuation due to an adverse effect

More patients in the placebo group discontinued treatment for any reason (88.0% in the bevacizumab group vs 91.7% in the placebo group; Table 17). The most reported reason for discontinuation of treatment was disease progression.

Considering discontinuation due to an adverse effect, a considerably larger proportion of patients in the bevacizumab group experienced a treatment-related adverse event that led to discontinuation, with most patients stopping treatment early in their chemotherapy (Table 17).

Absolute numbers of patients discontinuing due to an adverse effect varied within the MS. The patient flow diagram indicated that 55 patients and 12 patients in the bevacizumab and placebo groups, respectively, discontinued treatment primarily as a result of adverse event. However, in all tables within the MS presenting adverse effect data, the numbers of patients discontinuing due to an adverse event are reported to be 49 and 11 in the bevacizumab and placebo group, respectively. At clarification, the ERG asked the manufacturer to verify which set of absolute event rates is correct. The manufacturer provided an updated patient flow diagram, which reported that 55 and 12 patients discontinued treatment due to an adverse event (Appendix 8). However, the manufacturer also provided a table presenting a breakdown of adverse effects leading to discontinuation, which indicated that 49 and 11 patients discontinued for this reason (Appendix 9). The ERG remains unclear as to the correct number of patients discontinuing treatment because of an adverse event.

In the bevacizumab group, the most frequent treatment-related adverse effect leading to discontinuation was hypertension (9 patients [3.6%]). In the short report supplied by the manufacturer at clarification, it is stated that the high incidence of study drug discontinuation because of hypertension was likely as a result of protocol-defined study drug discontinuation criteria that included Grade 4 or Grade 3 hypertension not controlled with medication.

Table 17. Summary of information provided on rates of discontinuation due to an adverse event (based on information in MS; Figure 3, pg 54, and Table 23, pg 94)

	Bevacizumab (N = 242)	**Placebo (N = 242)**
Primary reason for discontinuation (Figure 3, pg 57)		
Disease progression (%)	104 (43.0)	160 (66.1)
Adverse event (%)	55 (22.7)	12 (5.0)
Investigator/patient decision (%)	54 (22.3)	50 (20.7)
Total patients discontinued because of adverse event (Table 23, pg 94)		
Total number of patients (%)	49 (19.9)	11 (4.7)
Concurrent chemotherapy plus bevacizumab or placebo (%)	*36 (14.6)*	*8 (3.4)*
Cycles 1–6 (%)	26 (10.5)	7 (3.0)
Cycles 7–10 (%)	10 (4.0)	1 (0.4)
Single-agent bevacizumab or placebo (%)	*13 (5.3)*	*3 (1.3)*
Cycles 7–10 (%)	2 (0.8)	2 (0.9)
Cycles 11–20 (%)	8 (3.2)	1 (0.4)
Cycles 20 + (%)	3 (1.2)	—

4.3 Indirect comparisons between bevacizumab chemotherapy regimen and comparators listed in the final scope (exploratory work on clinical effectiveness undertaken by the ERG)

As discussed in Section 3.3, in their systematic review of the literature, the manufacturer identified three large RCTs (CALYPSO, ICON4, and AGO-OVAR-2.5) that, when combined with OCEANS, could potentially be used to construct a linear NMA (summarised in Table 18). Detailed descriptions of the trials are provided in Appendix 1, and patient baseline characteristics are presented in Appendix 10.

Table 18. Summary of the trials identified by the manufacturer as relevant to the indirect comparison (reproduced from the MS; Table 12, pg 77)

Number of trials	Trial name	Platinum plus PLDH	Paclitaxel plus platinum	Platinum monotherapy	Platinum plus gemcitabine	Platinum plus gemcitabine plus bevacizumab
1	CALYPSO[35]	✓	✓			
1	ICON4[36]		✓	✓		
1	AGO-OVAR-2.5[37]			✓	✓	
1	OCEANS[28]				✓	✓

Adapted from Caldwell et *al*.[52]
Abbreviations used in table: PLDH, pegylated liposomal doxorubicin hydrochloride.

In the MS, the manufacturer discusses the feasibility of conducting an indirect comparison of bevacizumab in combination with gemcitabine and carboplatin versus the comparators listed in the final scope.[26] After taking statistical advice, the manufacturer decided against carrying out the NMA, indicating that the "that the levels of heterogeneity between the 4 studies were too high for an indirect comparison". The points raised by the manufacturer against inclusion of the individual trials are outlined below, together with the ERG's opinions.

Baseline characteristics: platinum-sensitivity

The manufacturer identifies that ICON4 included patients with a platinum-free interval of >12 months. Results in the full publication of ICON4 come from two trials that were run in parallel – ICON4 and AGO-OVAR-2.2.[36] ICON4 was coordinated by the Istituto Mario Negri (IRFMN), and the Medical Research Council's Clinical Trials Unit (MRC CTU), and AGO-OVAR-2.2 was coordinated by Arbeitsgemeinschaft Gynaekologische Onkologie (AGO). Each co-ordinating unit had its own protocol, with minor differences in eligibility criteria. As the manufacturer identifies, in centres co-ordinated by the MRC CTU and AGO, patients were eligible for enrolment if the interval since their last platinum-based therapy was greater than 6 months, whereas the IRFMN protocol specified a treatment-free duration of >12 months. Thus, compared with the other trials, ICON4 includes a smaller proportion of patients with partially platinum-sensitive disease (23–29% in ICON4 vs 35–42% in CALYPSO, AGO-OVAR-2.5, and OCEANS).

The ERG acknowledges that ICON4 includes fewer patients who were partially platinum sensitive but considers that inclusion of ICON4 would introduce bias against bevacizumab in the indirect comparison. As the manufacturer highlights, the improved prognosis of patients who are platinum sensitive compared with those who are partially platinum-sensitive is likely to have resulted in the significantly longer PFS and OS for both arms of ICON4 compared with the other studies.[53] The ERG considers that the variation in baseline characteristics in terms of platinum sensitivity is small and is unlikely to have a considerable impact on heterogeneity. Moreover, as the result taken from the trial and used in the NMA is a relative treatment effect, the inclusion of this trial could have a minimal impact on the overall result.

Baseline characteristics: previous lines of chemotherapy

The manufacturer identifies that ICON4 and CALYPSO included patients who had received more than one line of previous chemotherapy. Again, the ERG agrees with the manufacturer that the populations are clinically heterogeneous, but argues that the proportion of patients receiving two or more lines of previous chemotherapy in each trial is small (8% in ICON4 and 16% in CALYPSO). Increasing number of previous chemotherapy regimens is associated with a decrease in response to treatment. The ERG considers that inclusion of trials in which patients received two or more chemotherapy regimens is likely to underestimate the effects of the evaluated treatments in patients with first recurrence of disease, and thus potentially bias the results of an indirect comparison towards bevacizumab. Again, as the HR used in the NMA is a relative treatment effect, the ERG considers that the impact of inclusion of this trial on the overall result could be minimal.

Baseline characteristics: performance status

The manufacturer stated that no notable differences between AGO-OVAR-2.5 and OCEANS were identified, with the exception of baseline ECOG status. The manufacturer highlights that AGO-OVAR-2.2 included fewer than 50% of patients of ECOG score of 0, compared with 75% of patients in OCEANS. As noted earlier, low ECOG scores (0 and 1) indicate good performance status, and performance status has been shown to be an important prognostic factor in several types of cancer.[49] Of the four trials identified by the manufacturer to inform the indirect comparison, the ERG considers OCEANS to be the least comparable in terms of baseline performance score. OCEANS was designed to include patients with an ECOG score of 0 or 1, whereas CALYPSO, ICON4, and AGO-OVAR-2.5 included patients with a performance score of 2. However, the proportion of patients with baseline performance score of 2 is small, ranging from 4.8% to 6.2% across the three trials. Moreover, the proportion of patients with performance score of 1 is similar across CALYPSO, ICON4, and AGO-OVAR-2.5. The ERG considers that the inclusion of patients with performance score 2 is likely to underestimate the effect of the evaluated treatments in those trials and thus potentially bias the results of an indirect comparison towards bevacizumab.

Baseline characteristics: diagnosis of recurrence

In ICON4, the manufacturer identifies that a small proportion of patients (18 [2.2%]) in centres co-ordinated by the MRC CTU was diagnosed to have recurrent disease based on raised CA125 levels alone.[36] Remaining patients were diagnosed as having recurrent disease based on clinical or radiological criteria. The manufacturer does not discuss this issue further. Although raised levels of CA125 are frequently associated with advanced ovarian cancer and are correlated with disease progression, CA125 is not specific to ovarian tumours and it is not recommended that CA125 levels alone be used to diagnose advanced ovarian cancer or disease progression. The ERG acknowledges that there is uncertainty as to whether the small subset of patients in ICON4 had recurrent ovarian cancer.

Interventions assessed

The manufacturer highlights that ICON4 evaluated the efficacy of adding paclitaxel to "conventional" chemotherapy. The manufacturer identifies that 20% of patients randomised to paclitaxel plus platinum-based therapy and 29% of patients randomised to the conventional chemotherapy group did not receive carboplatin. Based on these data, the manufacturer argues that patients in ICON4 are not comparable with patients in other studies. The ERG considers it important to note that 10% of patients in the paclitaxel group received paclitaxel in combination with cisplatin, and 5% of patients received paclitaxel plus carboplatin or cisplatin, switching between the two platinum monotherapies. In the conventional chemotherapy group, 4% of patients received cisplatin alone, and a further 2% received either carboplatin or cisplatin monotherapy, switching between the two platinum monotherapies. Moreover, 17% of patients in the conventional chemotherapy group received the triple therapy of cyclophosphamide, doxorubicin, and cisplatin, which the ICON investigators had compared against carboplatin in an earlier trial and found no statistically significant difference between the treatments in effect on OS.[54] In summary, the ERG considers that, although a minority of patients received different treatments, there is evidence that the regimens received have similar efficacy to the treatments received by the majority of patients.

The manufacturer recognises that the chemotherapy regimens in the remaining trials are predominantly consistent with the decision problem and NICE recommendations for the treatment of platinum-sensitive recurrent ovarian cancer.[22]

The ERG considers it important to note that the treatment schedules of CALYPSO, ICON4, and AGO-OVAR-2.5 all permitted administration of more than 6 cycles of chemotherapy (schedules summarised in Appendix 1). In CALYPSO, like OCEANS, the median number of cycles was 6 in both treatment groups. A slightly larger proportion of patients in PLDH plus carboplatin group completed 6 cycles of treatment compared with the paclitaxel plus carboplatin group (85% vs 77%). In ICON4, a larger proportion of patients in the conventional chemotherapy group received less than 6

cycles of therapy. Although the ERG has previously suggested that patients would receive no more than 6 cycles of chemotherapy, the ERG considers that, for the purposes of the NMA, the treatment schedules of the four trials are highly similar.

Overall, the ERG agrees with the manufacturer that there are differences across the key trials identified, but asserts that the trials are sufficiently comparable to facilitate an adjusted indirect comparison, with accompanying critical assessment of the impact that any potential bias may have on the results. Based on the evidence presented in the MS, and supplementary information provided by the manufacturer during clarification, the ERG performed an exploratory analysis for the outcome of PFS. As data on OS in OCEANS are immature, the ERG decided against carrying out this analysis.

Trials excluded by the manufacturer based on trial size

As discussed in Section 3, the manufacturer applied an inclusion criterion of trial size of a minimum of 200 people. The ERG considers this approach would potentially exclude smaller studies that could inform the network. On request, the manufacturer provided the reference details for the studies listed in the MS as excluded based on number (details provided in Appendix 11). The ERG independently reviewed (two reviewers) the identified studies and excluded all but two studies;[55;56] ERG's reasons for exclusion are provided in Appendix 11.

One trial enrolled patients with recurrent stage III or IV ovarian carcinoma (61 patients) and a progression-free and platinum-free interval of 6–24 months after first-line platinum-based chemotherapy.[55] Patients were randomised to PLDH plus carboplatin or carboplatin alone. The ERG notes that enrolment was closed early as a result of slow patient accrual. PFS was listed a secondary outcome. The study included some patients who had measurable disease determined by only elevated CA125 (9.8%).

The second trial enrolled patients with recurrent ovarian carcinoma (81 patients) a minimum of 6 months after treatment with a platinum-based regimen and with no more than two previous chemotherapy lines.[56] Patients were randomised to either paclitaxel plus carboplatin or carboplatin alone. The proportion of patients with two previous lines of chemotherapy was 16%. The ERG notes that the outcome assessed in the trial is time to progression (TTP), rather than PFS. TTP was defined as the time from date of randomisation to date of documentation of tumour progression. TTP was listed as a secondary outcome and the study was neither designed nor powered to detect a significant difference between treatments in TTP.

A sensitivity analysis excluding the two small trials generated similar results to the primary exploratory analysis. Full details on the characteristics of the additional trials and the ERG's quality assessments of the full publications of the trials are provided in Appendix 12 and Appendix 13, respectively.

Results of the exploratory network meta-analysis

The ERG used a Bayesian Markov Chain Monte Carlo simulation in WinBUGS to conduct the NMA. The median HRs and accompanying CIs for PFS used in the analysis were taken from the full publications of the identified trials and are reported in Table 19 (RCTs described in the MS) and Table 20 (RCTs initially excluded by the manufacturer based on trial size). The linear NMA was carried out using a fixed effects model. The ERG chose a fixed effects model because of the limited data available. In a random effects model, the between study heterogeneity generated would reflect the prior value inputted into the model as there are insufficient trial data to further inform this estimate.

The ERG's exploratory analyses suggest that, for the outcome of PFS, addition of bevacizumab to gemcitabine plus carboplatin is associated with a statistically significant improvement in duration of PFS compared with all comparators of interest in the final scope, including paclitaxel plus carboplatin (HR 0.47; 95% Credible Interval [CrI]: 0.33 to 0.66); results of the linear NMA are presented in Table 21.

The ERG's exploratory analysis also suggests that doublet chemotherapy regimens are of similar efficacy, with most differences between treatments not reaching statistical significance (Table 21). PLDH plus carboplatin was found to be statistically significantly more effective than paclitaxel plus carboplatin (HR 0.82; 95% CrI: 0.72 to 0.94).

Although the ERG considers the analysis to represent a methodologically robust assessment, it should be stressed that the analysis is exploratory, and, as such, the results should be interpreted with caution. In addition, the ERG is uncertain about the direction of overall bias in the analysis.

Table 19. Data on progression-free survival reported in trials identified in the manufacturer's submission as potentially relevant to a network-meta-analysis

PFS	**CALYPSO[35;57]**		**ICON4[36]**		**AGO-OVAR-2.5[37]**		**OCEANS[28]**	
	PLDH + carboplatin	**Paclitaxel + carboplatin**	**Paclitaxel + platinum-based chemotherapy**	**Platinum-based chemotherapy**	**Gemcitabine + carboplatin**	**Carboplatin alone**	**Bevacizumab + gemcitabine + carboplatin**	**Placebo + gemcitabine + carboplatin**
Median duration (months)	11.3	9.4	13	10	8.6	5.8	12.4	8.4
Median duration of follow-up	49 months		42 months		17 months		24 months	
Number of events: disease progression (RECIST criteria)	301/466 (64.6%)	363/507 (71.6%)	50% (at 1 year)	40% (at 1 year)	NR	NR	146/242 (60.3%)	185/242 (76.4%)
HR (95% CI)	**0.82 (0.72 to 0.94)** favours PLDH plus carboplatin		**0·76 (0·66 to 0·89)** favours paclitaxel plus platinum-based therapy		**0.72 (0.58 to 0.90)** favours gemcitabine plus carboplatin		**0.48 (0.39 to 0.61)** favours bevacizumab plus gemcitabine plus carboplatin	

Abbreviations used in table: HR, hazard ratio; NR, not reported; PFS, progression-free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 20. Data on progression-free survival reported in additional trials used by ERG to inform network meta-analysis

PFS	Alberts *et al*.[55]		Gonzalez-Martın *et al*.[56]	
	PLDH plus carboplatin	**Carboplatin alone**	**Paclitaxel + carboplatin**	**Carboplatin alone**
Median duration (months)	12	8	49.1 weeks	33.7 weeks
Median duration of follow-up	22.4 months		67.7 weeks	
Number of events: disease progression (RECIST criteria)	NR	NR	NR	NR
HR (95% CI)	**0.54 (0.32 to 0.93)** favours PLDH plus carboplatin		**0.54 (0.32 to 0.92)**[a] favours paclitaxel plus carboplatin	

[a] Outcome reported is time to progression rather than progression-free survival.

Abbreviations used in table: HR, hazard ratio; NR, not reported; PFS, progression-free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; RECIST, Response Evaluation Criteria in Solid Tumors; vs, versus.

Table 21. Hazard ratios for progression-free survival based on an adjusted indirect comparison

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

Abbreviations used in table: CrI, Credible Interval; HR, hazard ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.

4.4 Conclusions of the clinical effectiveness section

4.4.1 Clinical results

- The submitted evidence is derived from the OCEANS trial.[28]
- OCEANS assessed the effects of adding bevacizumab versus adding placebo to gemcitabine plus carboplatin for the treatment of first-recurrence of platinum-sensitive ovarian cancer. In terms of number of previous chemotherapeutic treatments, OCEANS includes a clinically homogeneous population.
- Bevacizumab does not have a European licence at this time for use in recurrent ovarian cancer. However, the CHMP has issued a positive opinion on the use of bevacizumab in combination with gemcitabine plus carboplatin for the treatment of patients with first-recurrence of platinum-sensitive ovarian cancer who have not received prior therapy with a VEGF inhibitor or VEGF receptor-targeted agent.[27]
- In the investigator-assessed analysis, addition of bevacizumab was associated with a statistically significant improvement in the primary outcome of PFS (HR 0.48; 95% CI: 0.39 to 0.61).
- The manufacturer proposes that strategies that extend the duration of PFS during second-line treatment will improve treatment outcome and maintain the platinum-sensitivity of patients, thereby improving patient outcomes and prognosis in subsequent lines of treatment.
- Secondary outcomes assessed were OS, ORR, and median duration of response. Bevacizumab was associated with statistically significant improvements across all outcomes.
- Sensitivity analysis included an independent analysis of PFS, ORR and duration of response by an IRC, and an analysis including patients censored for receipt of non-protocol specified therapies. Based on data presented within the MS, the IRC analyses support the investigator-assessed analyses, generating similar results for PFS, ORR and median duration of response.
- At the time of writing this report, OS data from OCEANS are immature. The manufacturer has carried out three interim analyses for OS, all of which found no significant difference between bevacizumab and placebo. Moreover, the HR for the second and third analyses approached 1, indicating no difference in effect between treatments.
- Adverse effects associated with bevacizumab were hypertension and proteinuria, both of which are recognised adverse effects of treatment. Bevacizumab has been reported to increase the risk of gastrointestinal perforation. However, during OCEANS, no cases of gastrointestinal perforation were reported in either group.
- Exploratory NMA carried out by the ERG for the outcome of PFS found that bevacizumab plus gemcitabine and carboplatin is statistically significantly more effective at improving PFS compared with NICE recommended platinum-based chemotherapy regimens.

4.4.2 Clinical issues

- Only one RCT is available for the comparison of adding bevacizumab versus adding placebo to gemcitabine and carboplatin. In addition, this is the only direct comparison reported.
- OCEANS allowed patients to receive a maximum of 10 cycles of chemotherapy. The ERG's clinical expert indicated that patients in the UK are likely to receive a maximum of 6 cycles of chemotherapy. Within OCEANS, ~40% of patients received between 7 and 10 cycles of chemotherapy. The ERG is unclear as to whether the additional cycles of chemotherapy are likely to have an impact on the overall results.
- The reporting of the results from the IRC is not transparent.

- There is uncertainty around the level of censoring within OCEANS. Although reasons for censoring of patients are described in full, number of patients censored at the time of final PFS analysis is not reported.
- The number of patients lost to follow-up at time of final PFS is unclear.

5 COST EFFECTIVENESS

5.1 Introduction

The manufacturer developed a *de novo* semi-Markov cost-utility model to evaluate the cost-effectiveness of bevacizumab in combination with gemcitabine and carboplatin (bevacizumab group), versus placebo in combination with gemcitabine and carboplatin (placebo group) in the treatment of women with advanced, recurrent, platinum-sensitive, ovarian cancer. In addition to the economic evidence provided in the manufacturer's submission (MS) (Table 22), the manufacturer submitted a Microsoft© EXCEL-based economic model.

The manufacturer presents both deterministic and probabilistic cost-effectiveness estimates in terms of an incremental cost per additional quality adjusted life year (QALY). The manufacturer estimated the incremental cost-effectiveness ratio (ICER) for the bevacizumab group compared with the placebo group to be £149,050 per QALY (deterministic) and £221,750 per QALY (probabilistic) (Section 5.3.12).

The following sections (Section 5.2 and Section 5.3) provide a summary and critique of the economic evidence submitted by the manufacturer in support of this Single Technology Appraisal. Table 23 provides an overview of the sections covered in this ERG report.

Table 22. Summary of key information within the manufacturer's submission

Information	Section (MS)
Details of the systematic review of the economic literature	7.1
Population	7.2.1
Model structure	7.2.2
Technology	7.2.7
Treatment continuation rules	N/A
Clinical parameters and variables	7.3
Measurement and valuation of health effects and adverse events	7.4
Resource identification, valuation and measurement	7.5
Sensitivity analysis	7.6
Results	7.7
Validation	7.8
Subgroup analysis	N/A
Interpretation of economic evidence	7.10
Strengths and weaknesses of economic evaluation	7.10.3
Abbreviations used in table: MS, manufacturer's submission; N/A, not applicable.	

Table 23. Overview of the ERG report

Information	Section
Details of the systematic review of the economic literature	5.2
Summary and critique of manufacturer's submitted economic evaluation	5.3
NICE reference case checklist	5.3.1
Model structure	5.3.2
Population	5.3.3
Interventions and comparators	5.3.4
Summary of model parameters	5.3.5
Perspective and time horizon	5.3.6
Discounting and half-cycle correction	5.3.7
Treatment effectiveness and extrapolation	5.3.8
Adverse events	5.3.9
Health-related quality of life	5.3.10
Resources and costs	5.3.11
Cost-effectiveness results	5.3.12
Sensitivity analysis	5.3.13
Model validation and face validity check	5.3.14
Abbreviations used in table: ERG, Evidence Review Group.	

5.2 ERG comment on manufacturer's review of cost-effectiveness evidence

The manufacturer carried out a systematic review of the literature to identify cost-effectiveness publications and economic evaluations on the use of bevacizumab in the treatment of relapsed or recurrent ovarian cancer from the perspective of the UK National Health Service (NHS). The electronic databases searched were: ProQuest MEDLINE and MEDLINE in-process; ProQuest MEDLINE; EconLit; and NHS EED. In addition, the manufacturer searched the TUFTS CEA registry, a database of 3,115 cost-utility analyses.[58] The search was carried out in August 2012 and was not restricted by date, publication type, or study design. The manufacturer provided details of the search strategy, inclusion and exclusion criteria, and data extraction tables (MS; pgs 245–253).

The manufacturer's review identified a total of nine publications, of which two were considered initially relevant for the submission (Fuh *et al.*[59] and Chan *et al.*[60]). Both of the identified studies were only available as abstracts; details of the studies are summarised in Table 24. The manufacturer concluded that neither study was relevant for the purposes of the submission. Fuh *et al.*[59] was not considered relevant on the basis that the study used first-line bevacizumab data to assess the cost-effectiveness of bevacizumab in a recurrent setting. In addition, both Fuh *et al.*[59] and Chan *et al.*[60] used US rather than UK cost data. The Evidence Review Group (ERG) notes that the studies did not report sufficient details of modelling methods or sources of data used, and were, therefore, of limited use to inform the economic evaluation.

Table 24. Summary of cost-effectiveness studies identified by the manufacturer

Study (Country)	Overview	Costs and outcomes	ICER	Author conclusions	Manufacturer's assessment of relevance
Fuh *et al*.[59] (USA)	Comparison of the cost-effectiveness of bevacizumab in the primary versus recurrent setting in patients with first occurrence of or first recurrence of advanced ovarian cancer	***Costs*** Cost of drugs, rate of complication ***Outcomes*** PFS Taken from a clinical trial of bevacizumab as a first-line therapy[33]	Cost per life year saved; estimated at $270,900 per life year saved for first-line bevacizumab versus $361,100 for second-line bevacizumab	The authors concluded that in this economic model bevacizumab at first occurrence may be more cost-effective	Not relevant as analysis was based entirely on data from first-line treatment with bevacizumab; no rationale was reported for the assumptions around additional PFS from addition of bevacizumab or the basis of costs of complications
Chan *et al*.[60] (USA)	An economic analysis of the two arms of the OCEANS trial:[28] placebo added to gemcitabine and carboplatin versus concurrent and maintenance bevacizumab added to gemcitabine and carboplatin in patients with first recurrence of ovarian cancer	***Costs*** Cost of drugs, administration, and complications ***Outcomes*** Rate of bowel perforation, and PFS Taken from the OCEANS trial	Cost per life year saved; estimated at $677,250 for bevacizumab added to gemcitabine and carboplatin versus placebo added to gemcitabine and carboplatin	The authors ran a series of scenario analyses to investigate the impact of PFS, cost of bevacizumab, and risk of intestinal perforation and concluded that the addition of bevacizumab to combination chemotherapy for the treatment of recurrent ovarian cancer was associated with significant costs and potential benefits	Not relevant as the costs were based on a US setting, details were not provided for the costs or the basis of the assumption regarding increase of PFS to 15 months for the bevacizumab arm
Abbreviations used in table: ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; USA, United States of America.					

The ERG notes that the search terms used in the manufacturer's searches of the cost-effectiveness literature limited results to studies that included bevacizumab as an intervention. The ERG considers that this restriction was likely to have limited the cost-effectiveness evidence retrieved. A search without restriction on therapy would have ensured the identification of previous economic evaluations within recurrent ovarian cancer, and, in particular, previous health technology appraisals (HTAs) that could inform model structure and parameters.

To supplement the search carried out by the manufacturer, the ERG conducted a basic search of Ovid MEDLINE, Ovid EMBASE, EconLit and NHS EED for cost effectiveness studies in relapsed or recurrent ovarian cancer using simple terms for recurrent ovarian cancer and economic evaluation. The search did not limit inclusion to studies that included bevacizumab as an intervention. The ERG's search identified seven additional studies (Havrilesky *et al*.[61], Papaioannou *et al*.[62], Havrilesky *et al*.[63], Case *et al*.[64], Rocconi *et al*.[65], Main *et al*.[66], Ojeda *et al*.[67]), which are summarised in Table 25.

Of the seven identified studies, two studies considered the cost-effectiveness of interventions in relapsed or recurrent ovarian cancer from a UK perspective. Four studies were carried out from the perspective of the USA, and the final study from the perspective of Spain. Both of the UK studies represented published summaries of previous National Institute for Health and Clinical Excellence (NICE) Technology Appraisals in relapsed or recurrent ovarian cancer:

- Papaioannou *et al*.[62]: Technology Appraisal 222. Trabectedin for the treatment of relapsed ovarian cancer (STA)[21];
- Main *et al*.[66]: Technology Appraisal 91. Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for the treatment of advanced ovarian cancer (Multiple Technology Appraisal).[19]

Main *et al*.[66] reported the development of a cost utility model developed for NICE Multiple Technology Appraisal 91 (TA91) that represented relapsed or recurrent ovarian cancer and used three health states (progression-free survival [PFS], progressed disease [PD], and death). The probability of being in each health state was estimated from PFS and overall survival (OS) trial data. The analysis considered in Papaioannou *et al*.[62] was based on a manufacturer's submission to NICE for Single Technology Appraisal 222 (TA222); the model developed by the manufacturer within the MS for TA222 was derived from the TA91 model.

Table 25. Summary of cost-effectiveness papers identified by the ERG's literature search

Study (Country)	Overview/patient population	Model type and time horizon	Costs	Outcomes and data sources	ICER	Author conclusions
Havrilesky *et al*.[61] (USA)	An assessment of the cost-effectiveness of sequential versus concurrent docetaxel and carboplatin for the management of patients with recurrent platinum-sensitive ovarian cancer from the perspective of the third party payer	Cost-utility analysis Markov simulation model with a 2-year time horizon	Costs of chemotherapy, management of adverse events, and costs of cancer recurrence	PFS Data taken from a Phase II RCT	An incremental cost per QALY was estimated with an ICER of $25,239 for concurrent docetaxel and carboplatin versus sequential docetaxel and carboplatin	Authors concluded that combined weekly concurrent docetaxel and carboplatin appeared to be cost-effective compared with sequential docetaxel and carboplatin as treatment strategy for patients with platinum-sensitive ovarian cancer, even when accounting for slightly lower QoL during treatment
Papaioannou *et al*.[62] (UK)	A summary of the ERG report into the clinical effectiveness and cost-effectiveness of trabectedin for the treatment of relapsed platinum-sensitive ovarian cancer, based on a review of the manufacturer's submission to NICE as part of the STA process	Cost-utility analysis The model evaluated two distinct periods: the progression-free period; and the time from progression to death The time horizon is lifetime	Costs of therapy, management, and adverse events	OS and PFS	The ERG base case estimate of the cost per QALY of trabectedin in combination with PLDH ranged from £46,503 to £54,607 in the partially platinum-sensitive population	Trabectedin in combination with PLDH for the treatment of women with relapsed platinum-sensitive ovarian cancer is not recommended by NICE

Havrilesky *et al*.[63] (USA)	An assessment of the cost-effectiveness of three chemotherapy regimens for patients with recurrent platinum-sensitive ovarian cancer: carboplatin alone, paclitaxel plus carboplatin, and gemcitabine plus carboplatin from the perspective of the third party payer	Cost-effectiveness analysis Markov model with a 42-month time horizon, and three month cycles Health states: "no evidence of disease"; "no evidence of disease with neurotoxicity"; and "recurrence"	Costs related to treatment and adverse events, professional fees, and infusion costs	PFS, risk of recurrence, risk of death, and adverse events Data take from RCTs and an indirect comparison	Incremental cost per progression free month ($1,297 paclitaxel plus carboplatin compared with carboplatin alone; $23,199 gemcitabine plus carboplatin compared with paclitaxel plus carboplatin), and incremental cost per progression free year ($15,564 paclitaxel plus carboplatin compared with carboplatin alone; $278,388 gemcitabine plus carboplatin compared with paclitaxel plus carboplatin), and incremental cost per QALY in sensitivity analysis	Paclitaxel plus carboplatin appeared to be relatively cost-effective compared with carboplatin for the treatment of recurrent platinum-sensitive ovarian cancer. Gemcitabine plus carboplatin appeared to be less cost-effective compared with paclitaxel plus carboplatin, with an ICER ten times higher
Case *et al*.[64] (USA)	An assessment of several strategies for the treatment of patients with recurrent platinum-sensitive advanced epithelial ovarian cancer including best supportive care, carboplatin monotherapy, carboplatin and paclitaxel, and several third and fourth line therapies, from the perspective of a third party payer	Cost effectiveness analysis Decision analysis model with a hypothetical cohort of 10,000 eligible women	Clinical visits, hospitalisations, tests, and cost of chemotherapy	PFS, and OS Data taken from studies published between 1998 and 2005	Incremental cost per life year gained: $24,228 for second-line monotherapy versus best supportive care; £46,068 for second-line combination therapy versus second-line monotherapy	Second-line chemotherapy was cost-effective for patients with platinum-sensitive recurrent epithelial ovarian cancer. Due to minimal improvements in overall survival, third- and fourth-line chemotherapy were not cost-effective strategies

Rocconi *et al*.[65] (USA)	An assessment of several strategies for the treatment of women with recurrent platinum-resistant epithelial ovarian cancer including best supportive care, second line monotherapy, second line combination therapy and third line therapies from the perspective of the third party payer	Cost-effectiveness analysis Decision analysis model with a hypothetical cohort of 4,000 eligible women	Direct medical costs (clinical visits, medication, and palliative care)	OS and PFS Data taken from studies published between 1996 and 2005 and synthesised with supplementation by author opinions	Incremental cost per life-year gained with second-line monotherapy over best supportive care was $64,104. The incremental cost-effectiveness ratios of the other strategies (with respect to the next most effective strategy) were greater than $100,000 per life-year gained	The authors stated that the analysis was intended to be thought-provoking and bring awareness to the high costs of subsequent chemotherapy with limited effectiveness in patients with recurrent platinum-resistant epithelial ovarian cancer
Main *et al*.[66] (UK)	An assessment of the clinical effectiveness and cost-effectiveness of intravenous formulations of topotecan monotherapy, PLDH monotherapy and paclitaxel used alone or in combination with a platinum-based compound for the second-line or subsequent treatment of advanced ovarian cancer, from the perspective of the UK NHS	Cost-utility analysis The model evaluates OS in relation to two distinct periods: progression free period; and time from progression to death	Costs of therapy, management, and adverse events	PFS and OS Electronic databases covering publication years 2000–2004. Manufacturer submissions	Incremental cost per QALY in analysis 1: PLDH versus paclitaxel: £7,033 in the overall patient population; £5,777 in the platinum-sensitive population; and £9,555 in the platinum-refractory/resistant population Incremental cost per QALY in analysis 2 (platinum-sensitive patients): £16,421 for cyclophosphamide, doxorubicin and cisplatin versus platinum monotherapy; and £20,950 for paclitaxel–platinum combination therapy compared with cyclophosphamide, doxorubicin and cisplatin	PLDH appeared to be cost-effective compared with topotecan and paclitaxel monotherapy (WTP threshold £20,000–£40,000). For platinum-sensitive patients, the combination of paclitaxel plus platinum appeared to be cost-effective (WTP threshold £20,000–£40,000)

Ojeda *et al*.[67] (Spain)	A cost-minimisation analysis of PLDH versus topotecan in the treatment of patients with recurrent epithelial ovarian cancer in Spain	Cost minimisation analysis	Direct medical costs (drug, drug administration, and managing adverse events)	Data taken from a Phase III clinical trial	The total cost per patient was estimated to be 9,614.72 Euros for PLDH and 11,824.69 Euros for topotecan	The findings suggested that PLDH can be used as a cost-saving option for treatment of patients with recurrent epithelial ovarian cancer who have failed a first-line platinum-containing regimen
Abbreviations used in table: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Clinical Excellence; OS, overall survival; PFS, progression-free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; QALY, quality adjusted life year; QoL, quality of life; RCT, randomised controlled trial; STA, Single Technology Appraisal; UK, United Kingdom; USA, United States of America; WTP, willingness to pay.						

5.3 Summary and critique of manufacturer's submitted economic evaluation by the ERG

5.3.1 NICE reference case checklist

Table 26 and Table 27 summarise the ERG's quality assessment of the manufacturer's economic evaluation. Table 26 summarises the ERG's appraisal of the manufacturer's economic evaluation against the requirements set out in the NICE reference case checklist for a base case analysis. Table 27 summarises the ERG's appraisal of the quality of the manufacturer's economic evaluation using the Philips checklist.[68]

The ERG's main criticism of the submitted economic evaluation was the use of September 2010 OCEANS clinical effectiveness, cost, and adverse event incidence data, rather than data from March 2012 (where available). The ERG believes that the use of data from September 2010 may have introduced uncertainty in the estimates of the ICER and, in particular, may have overestimated the OS benefit associated with bevacizumab. In addition, the ERG notes that omission of comparison with the full list of comparators outlined in the NICE scope was a key limitation of the analysis.

Table 26. NICE reference case

Attribute	**Reference case**	**Does the *de novo* economic evaluation match the reference case?**
Decision problem	The scope developed by NICE	Broadly yes, but omits comparison versus: • paclitaxel in combination with a platinum compound; • PLDH in combination with a platinum compound; • platinum-based chemotherapy as monotherapy.
Comparator(s)	Alternative therapies routinely used in the NHS	The manufacturer addressed one of four comparators listed within the scope (gemcitabine in combination with carboplatin). However, the manufacturer did not consider the remaining three comparators outlined in the scope: • paclitaxel in combination with a platinum compound; • PLDH in combination with a platinum compound; • platinum-based chemotherapy as monotherapy.
Perspective costs	NHS and Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-utility analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes
Synthesis of evidence on outcomes	Systematic review	Yes, however the only trial identified was OCEANS and a network meta-analysis was not carried out

Outcome measure	Quality adjusted life years	Yes
Health states for QALY	Described using a standardised and validated instrument	Yes
Benefit valuation	Time-trade off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes The manufacturer carried out deterministic sensitivity analysis, scenario analysis and probabilistic sensitivity analysis. However, not all inputs were varied in these analyses.
Abbreviations used in table: HRQoL, health-related quality of life; QALY, quality adjusted life year; NHS, National Health Service; NICE, National Institute for Health and Clinical Excellence; PLDH, pegylated liposomal doxorubicin hydrochloride.		

Table 27. Philips checklist[68]

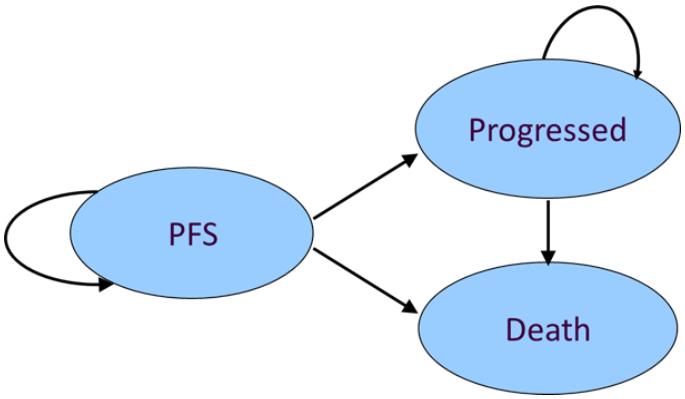
Dimension of quality	Comments
Structure	
S1: Statement of decision problem/objective	Clearly stated
S2: Statement of scope/perspective	Clearly stated (UK NHS)
S3: Rationale for structure	Clearly stated
S4: Structural assumptions	Appropriate
S5: Strategies/comparators	The following comparators were not included in the analysis: • paclitaxel in combination with a platinum compound; • PLDH in combination with a platinum compound; • platinum-based chemotherapy as monotherapy.
S6: Model type	Appropriate; cost-utility analysis
S7: Time horizon	Appropriate: 10 years was considered sufficient
S8: Disease states/pathways	Appropriate
S9: Cycle length	Appropriate; the ERG considers one week to be a reasonable cycle length to capture the consequences of model events

Data	
D1: Data identification	The manufacturer's literature searches for cost-effectiveness analyses, resource use and cost, and utilities were clearly described. However, the utilities used within the model were not identified from the literature search, and the manufacturer did not describe how these utilities were identified.
D2: Premodel data analysis	The manufacturer analysed patient level data from OCEANS for inclusion in the analysis for: OS; PFS; adverse events; and post-progression treatments. The manufacturer extrapolated data on OS and PFS, and the results of the survival analyses were presented within the economic model. The manufacturer justified the use of the selected extrapolation methods (log-logistic) via statistical tests.
D2a: Baseline data	The manufacturer used data from September 2010 to inform a number of model parameters including PFS, OS, adverse events, and post-progression treatments. The ERG considers that use of data from March 2012 would have been more appropriate for data that was collected at that time point, in particular OS data. The ERG considers the use of less mature data in the model, where more recent data were available, to be a major weakness of the analysis.
D2b: Treatment effects	Treatment effects presented in the analysis were PFS and OS. The ERG has concerns about the use of both measures of treatment effect within the model. The ERG does not consider that it was necessary to use parametric extrapolation for PFS as Kaplan–Meier data were relatively mature. The ERG additionally believes that the use of September 2010 data to inform OS within the model may have resulted in an overestimate of the effectiveness of bevacizumab.
D2d: Quality of life weights (utilities)	Appropriate; derived from TA222.
D3: Data incorporation	The use of unpublished survival analyses from patient level data prevented validation of the estimates of PFS and OS.
D4: Assessment of uncertainty	
D4a: Methodological	Appropriate; scenario analyses with alternative values for the discount rate were considered.
D4b: Structural	The manufacturer considered multiple alternative parametric extrapolations of the PFS and OS data.
D4c: Heterogeneity	Not addressed; the ERG considers this to be appropriate as no subgroups were defined within the scope.
D4d: Parameter	Parameter uncertainty was assessed through deterministic and probabilistic sensitivity analyses; however, the manufacturer did not vary all inputs in these analyses, in particular costs of palliative care, post-progression treatments, and adverse events were not varied.
Consistency	
C1: Internal consistency	The model seems to be mathematically sound with the exception of a few minor errors. In addition, the model results up to September 2010 are comparable with the clinical trial data. However, the ERG is unable to comment on whether the model results are comparable with clinical trial data up to March 2012 as this information was not supplied.
C2: External consistency	The ERG considers that the use of data from September 2010 makes it difficult to assess the external consistency of the data.
Abbreviations used in table: ERG, Evidence Review Group; NHS, National Health Service; OS, overall survival; PFS, progression-free survival.	

5.3.2 Model structure

The manufacturer developed a *de novo* semi-Markov cost-utility model with three health states (PFS, progressed disease [PD], and death), which used a cycle length of 1 week (Figure 3). The model was populated with clinical trial data from OCEANS and compared the addition of bevacizumab to gemcitabine and carboplatin in the treatment and maintenance of women with recurrent, platinum-sensitive ovarian cancer. The model followed an average cohort through a base case model time horizon of 10 years. The model was constructed in Microsoft© EXCEL.

Figure 3. Model structure (reproduced from MS; Figure 11, pg 110)



Rather than estimating the probability of transitioning between health states, the manufacturer estimated the proportion of patients located in the PFS and PD health states each week from OCEANS clinical trial data for PFS and OS. The manufacturer fitted two separate parametric functions to the PFS and OS data, respectively. The data for PFS were from September 2010 (the final analysis of PFS). The data for OS were also from September 2010; this analysis represents the first of three interim analyses of the OS data.

The proportion of patients within the PFS health state was estimated from the parametric function for PFS and applied within the model at each corresponding week. The proportion of patients within the PD health state was estimated by subtracting the proportion of patients with PFS from the proportion of patients with OS, and was applied within the model at the corresponding week. For example, in week 10, the manufacturer estimated from the PFS parametric function that 99.4% patients in the bevacizumab group were in the PFS health state. The manufacturer also estimated from the OS parametric function that OS for the bevacizumab group in week 10 was 99.9%. The proportion of patients within the PD health state at week 10 for bevacizumab was therefore calculated to be 0.5% (99.9% – 99.4% = 0.5%). Implicitly, the manufacturer also estimated the proportion of patients within the death health state to be 0.1% (100% – 99.9% = 0.1%).

Each health state was associated with a cost and a utility. Costs captured included costs of: drug; administration; supportive care; palliative care; post-progression treatment; and adverse events

(Section 5.3.11). Utilities from a previous Technology Appraisal in recurrent ovarian cancer (TA222) were applied to the PFS and PD health states (with zero utility applied to the death health state) (Section 5.3.10). The model did not consider disutilities specific to treatment or those associated with adverse events.

The manufacturer stated that "the model structure is fully aligned with two of the primary objectives of treatment in advanced ovarian cancer; namely, prolonging life [and] delaying disease progression" (MS; pg 111). The manufacturer also adds that "this model structure and the health states utilised are typical of modelling in metastatic oncology and have been utilised in numerous NICE appraisals including those specifically in advanced ovarian cancer" (MS; pg 111). The ERG notes that this conclusion is consistent with the findings from the supplementary cost-effectiveness literature search conducted by the ERG (Section 5.2), and the ERG agrees that this model structure is appropriate to describe the decision problem.

5.3.3 Population

The manufacturer's base case analysis was based on clinical effectiveness results from the OCEANS trial. However, baseline characteristics (age, weight and body surface area [BSA]) of the population in the base case were taken by the manufacturer from a UK study by Sacco *et al* to reflect UK baseline characteristics.[69] Sacco *et al*.[69] reported the age and BSA of 321 women who were treated for ovarian cancer in three UK-based centres in 2005. No details of the methods used to identify the study by Sacco *et al*.[69] were provided in the MS.

Within the model, patient age, weight and BSA were used to estimate doses and average costs of treatment (Section 5.3.11). As the OCEANS study was conducted in US ovarian cancer patients, the manufacturer asserted that "it is likely that the patients enrolled had baseline demographic characteristics different from counterparts in the UK" (MS; pg 109). To estimate costs reflective of those experienced by women with ovarian cancer in UK clinical practice, the manufacturer used baseline characteristics data from Sacco *et al*.[69] rather than OCEANS. Baseline age, body weight, height and BSA of patients from OCEANS and Sacco *et al*.[69] are presented in Table 28. The ERG notes that the manufacturer refers to the ranges presented within Table 28 as 95% Confidence Intervals (95% CIs). However, review of the model identifies these ranges as 2.5% and 97.5% percentiles.

Table 28. Patient base line characteristics in OCEANS and Sacco *et al*.[69] (adapted from MS; Table 27, pg 109)

Characteristic	Sacco *et al*.[69] (N = 321) Mean (2.5% and 97.5% percentiles)	OCEANS (N = 484) Mean (2.5% and 97.5% percentiles)
Age (years)	61.37 (37–79)	61.02 (43–81)
Body weight (kg)	69.35[a] (41.70–107.65)	75.68 (48.91–117.93)
Height (cm)	160.05[b] (N/A)	161.4 (147-175.3)
BSA (m^2)	1.71 (1.39–2.08)	1.79[c] (1.40–2.22)

[a] Body weight was calculated from BSA.

[b] Height assumed to be 160.05 cm for all patients.

[c] BSA calculated from weight and height data.

Abbreviations used in table: BSA, body surface area; cm, centimetre; kg, kilogram; N/A, not applicable.

Within the MS, the manufacturer stated that the overall survey female population weight (68.15 kg) reported in Sacco *et al*.[69] was used to estimate individual body weight (Section 5.3.11). The ERG was unable to locate the overall survey population weight of 68.15 kg within Sacco *et al*.[69] During the clarification process, the ERG asked the manufacturer to identify the source of the data; however, the manufacturer did not provide an additional reference.

The ERG notes that patients within OCEANS reflect the anticipated licensed population (patients with first recurrence of platinum-sensitive, recurrent epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer) and largely reflect the population outlined in the final scope issued by NICE. However, the ERG notes that the population described in Sacco *et al*.[69] may not fully reflect the anticipated licensed population as first-line ovarian cancer patients may have been included in the study.

However, the ERG considers that the use of BSA data from Sacco *et al*.[69] was reasonable to more accurately reflect the likely chemotherapy doses, and therefore costs, in UK clinical practice, despite potential inclusion of first-line ovarian cancer patients in the estimates of BSA and age. In addition, the ERG notes that the manufacturer presented results using OCEANS baseline characteristics in sensitivity analysis (Section 5.3.11). As the ERG was unable to locate the reference for overall population body weight (68.15 kg), the impact of varying this parameter was investigated in deterministic and probabilistic sensitivity analysis (Section 6.1.4).

5.3.4 Interventions and comparators

The manufacturer considered the clinical and cost-effectiveness of adding bevacizumab or placebo to gemcitabine and carboplatin combination chemotherapy in the treatment and maintenance of women with recurrent ovarian cancer. The ERG notes that gemcitabine and carboplatin combination therapy represents one of four comparators defined as relevant in the final scope issued by NICE for this STA; the three therapies that follow were also listed:

- paclitaxel in combination with a platinum compound;
- pegylated liposomal doxorubicin hydrochloride (PLDH) in combination with a platinum compound;
- platinum-based chemotherapy as monotherapy.

The manufacturer did not present clinical or cost-effectiveness evidence for bevacizumab in combination with platinum-based therapy compared with the above three comparators. Furthermore, the ERG notes that no rationale was provided for the exclusion of these comparators from the cost-effectiveness analysis.

Clinical advice indicated that paclitaxel in combination with a platinum compound is likely to represent the first choice treatment option for women with advanced recurrent ovarian cancer, with approximately 50% of patients treated using this combination therapy. When paclitaxel cannot be tolerated (e.g., as a result of neuropathy), gemcitabine and carboplatin combination therapy or PLDH in combination with a platinum compound are likely to be considered as alternative treatment options, with PLDH in combination with a platinum compound likely to be increasingly used in clinical practice. The ERG considers that the omission of an economic comparison with all comparators outlined in the NICE scope, and in particular paclitaxel in combination with a platinum compound, represents an important limitation when considering the cost-effectiveness of bevacizumab in UK clinical practice.

Consequently, for the outcome of PFS, the ERG conducted a network meta-analysis (NMA) to compare clinical effectiveness of bevacizumab in combination with gemcitabine plus carboplatin versus the three treatment regimens for which there is no direct clinical evidence. The ERG's exploratory analyses suggest that, for the outcome of PFS, addition of bevacizumab to gemcitabine plus carboplatin is associated with a statistically significant improvement in duration of PFS compared with all comparators of interest in the final scope, including paclitaxel plus a platinum compound (carboplatin) (HR 0.47; 95% Credible Interval [CrI]: 0.33 to 0.66). The NMA is discussed in more detail in Section 4.3.

The ERG explored the impact of the NMA results in terms of the cost-effectiveness of adding bevacizumab to gemcitabine and carboplatin versus: paclitaxel in combination with a platinum

compound; PLDH in combination with a platinum compound; and a platinum compound as monotherapy. The results of these exploratory analyses are presented in Section 6.1.5.

5.3.5 Model parameters

All parameters used within the manufacturer's model are summarised in Table 29.

Table 29. Summary of the manufacturer's model parameters

Parameter type	Parameter	Mean value (95% CI)	Source
General parameters	Discount rate (costs)	3.5%	NICE guide to the methods of technology appraisal (2008) [70]
	Discount rate (benefits)	3.5%	
	Time horizon	10 years	Assumption
	Cycle length	1 week	Assumption
Drug cost	Bevacizumab 400 mg vial	£924.40	British National Formulary 63 [71]
	Bevacizumab 100 mg vial	£242.66	
	Gemcitabine 1,000 mg vial	£12.57 (£12.47 to £12.67)	CMU eMit[27] CIs calculated by ERG
	Carboplatin 600 mg vial	£260.00	British National Formulary 63 [71]
Patient demographics	Average age	61.37 years (60.17 years to 62.57 years)	Sacco *et al.*[69] CIs calculated by ERG
	Average body weight	69.35 kg (67.43 kg to 71.27 kg)	Sacco *et al.*[69] Assumption CIs calculated by ERG
	Average BSA	1.71 m^2 (1.69 m^2 to 1.73 m^2)	Sacco *et al.*[69] CIs calculated by ERG
Administration cost	First cycle, bevacizumab, carboplatin and gemcitabine administration	£279.17 Cost of administration: £265.37 (£172.20 to £298.10[a]) plus cost of pharmacy preparation £13.80	National reference costs (2010/11); Unit Costs of Health and Social Care (2011)[72;73]
	Subsequent cycles, bevacizumab, carboplatin and gemcitabine administration	£98.87 Cost of administration: £85.07 (£0 to £95.52[a]) plus cost of pharmacy preparation £13.80	
	Cost of administering gemcitabine alone (day 8)	£89.67 Cost of administration: £85.07 (£0 to £95.52[a]) plus cost of pharmacy preparation £4.60	

	Cost of bevacizumab administration alone (cycles 7 onwards)	£89.67 Cost of administration: £85.07 (£0 to £95.52[a]) plus cost of pharmacy preparation £4.60		
	First cycle, carboplatin and gemcitabine administration	£274.57 Cost of administration: £265.37 (£172.20 to £298.10[a]) plus cost of pharmacy preparation £9.20		
	Subsequent cycles, carboplatin and gemcitabine administration	£94.27 Cost of administration: £85.07 (£0 to £95.52[a]) plus cost of pharmacy preparation £9.20		
Supportive care cost	Weekly supportive care of PFS	£44.08		Assumption
	Weekly supportive care of progressed disease	£10.31		Assumption
Cost of post-progression treatment	Cost of post-progression treatment (bevacizumab group)	£1,558.58		Various (see Section 5.3.11)
	Cost of post-progression treatment (placebo group)	£2,827.74		Various (see Section 5.3.11)
Cost of palliative care	Cost of palliative care	£6,726.53		Guest *et al.*[74]
Utility	Utility associated with PFS	0.72 (0.70 to 0.74)		TA222[9]
	Utility associated with progressed disease	0.65 (0.61 to 0.69)		
Treatment effectiveness	Estimates of PFS	Log-logistic extrapolation based on data from OCEANS		OCEANS[28]
	Estimates of OS	Log-logistic extrapolation based on data from OCEANS		OCEANS[28]
Incidence of adverse events costed in the model. Patient numbers (%)		Bevacizumab	Placebo	
	Thrombocytopenia (Grade 3)	15 (6.15%)	14 (5.58%)	Manufacturer's model
	Thrombocytopenia (Grade 4)	15 (6.15%)	8 (3.19%)	
	Leukopenia (Grade 3)	8 (3.28%)	7 (2.79%)	
	Neutropenia (Grade 3)	40 (16.39%)	30 (11.95%)	
	Neutropenia (Grade 4)	14 (5.74%)	9 (3.59%)	
	Hypertension	33 (13.52%)	1 (0.4%)	
	Anaemia (Grade 3)	14 (5.74%)	13 (5.18%)	
	Platelet count decreased (Grade 4)	5 (2.05%)	3 (1.20%)	
	White blood cell count decreased (Grade 3)	1 (0.41%)	6 (2.39%)	

Adverse event costs	Thrombocytopenia (Grade 3)	£58	National reference costs (2010/11)[73]
	Thrombocytopenia (Grade 4)	£58	
	Leukopenia (Grade 3)	£253	
	Neutropenia (Grade 3)	£253	
	Neutropenia (Grade 4)	£253	
	Hypertension	£441 (£273 to £486[a])	
	Anaemia (Grade 3)	£518	
	Platelet count decreased (Grade 4)	£58	
	White blood cell count decreased (Grade 3)	£253	

[a] Upper and lower quartiles

Abbreviations used in table: BSA, body surface area; CI, confidence intervals; ERG, Evidence Review Group; OS, overall survival; PFS, progression-free survival.

5.3.6 Perspective and time horizon

The economic evaluation was undertaken from the perspective of the NHS and Personal Social Services (PSS), and considered a 10-year time horizon in the base case.

The ERG considers that a 10-year time horizon is of sufficient duration to capture differences in costs and consequences associated with the addition of bevacizumab in the treatment pathway. Moreover, the ERG considers that a 10-year time horizon is likely to represent a lifetime time horizon for most patients in the model. The ERG notes that time horizon was varied in sensitivity analyses (Section 5.3.13).

5.3.7 Discounting and half-cycle correction

Discounting

The manufacturer stated that both costs and benefits were discounted at a rate of 3.5% per annum in the base case. The ERG agrees that this rate of discount is appropriate and in line with the NICE Guide to the Methods of Technology Appraisal.[70]

The ERG notes one minor error in the discounting of costs within the model; the manufacturer estimated the cost of palliative care as the difference between OS from one weekly cycle to the next (i.e., the number of deaths each week) multiplied by the cost of palliative care. The ERG agrees that this is reasonable; however, the manufacturer applied the discount rate to the number of patients with OS rather than to the cost of palliative care, which led to an incorrect estimate of total discounted cost.

In addition, the ERG identified two further issues with the manufacturer's use of discount rates in the model:

- the discount rate was not applied to the costs of post-progression treatments;
- in the model, the discount rate for benefits was set equal to the discount rate for costs. Although not an issue in the base case, for sensitivity analyses, it would have been preferable to maintain independence for these two rates (Section 6.1.4).

The ERG investigated the impact of amending the analysis to discount the costs of palliative care rather than the number of patients with OS. The impact on the deterministic ICER was small, with an estimated reduction in the ICER of £322 to £148,728 (Section 6.1.1; Analysis 1). The impact of discounting post-progression treatment costs was also small, with an increase in the deterministic ICER of £325 to £149,375 (Section 6.1.1; Analysis 2). The cumulative impact of Analyses 1 and 2 was minor, with an increase in the deterministic ICER of £2 to £149,052.

Half-cycle correction

The manufacturer applied a half-cycle correction to the model. The ERG notes that as a result of the short cycle length used within the model (1 week), the impact of the applied half-cycle correction on model results was minimal (a difference in the ICER of approximately £80). In addition, the ERG notes that half-cycle correction was not applied consistently throughout the model engine.

The manufacturer applied half-cycle correction to the number of patients with PFS, PD and OS in each week of the model. The half-cycle corrected numbers were used in the estimation of the cost of supportive care for PFS and PD, the cost of palliative care, and the QALYs. However, the half-cycle corrected PFS, PD and OS patient numbers were not applied to the drug costs of bevacizumab, carboplatin, and gemcitabine, or to the administration costs for these therapies.

The ERG corrected these inconsistencies; the effect was a decrease in the ICER of £1,935 to £147,115 (Section 6.1.1; Analysis 3). The magnitude of the effect was largely due to a fractional reduction in the number of bevacizumab patients each cycle, which resulted in a reduced drug cost of bevacizumab.

5.3.8 Treatment effectiveness and extrapolation

The manufacturer extrapolated Kaplan–Meier PFS and OS data from OCEANS for the bevacizumab group (bevacizumab in combination with gemcitabine and carboplatin) and the placebo group (placebo in combination with gemcitabine and carboplatin) using log-logistic parametric functions. The PFS and OS parametric models were estimated independently of one another, and were applied independently within the model. The manufacturer justified the use of the log-logistic extrapolation for PFS and OS, as this function was found to have the best statistical fit to the Kaplan–Meier PFS

and OS data. The extrapolated data were then used in the model engine to estimate, for each week, the proportion of patients who were in either:

- PFS health state; or
- PD health state (PD = OS – PFS); or
- death health state (1 – OS).

Rather than estimating the probability of transitioning between health states, the manufacturer estimated the proportion of patients within the PFS health state from the parametric function for PFS and applied within the model at each corresponding week. The proportion of patients within the PD health state was estimated by subtracting the proportion of patients with PFS from the proportion of patients with OS, and was applied within the model at the corresponding week. The following sections describe and critique the data used, the selection of the log-logistic parametric function, and the implementation of PFS and OS data within the economic model.

Progression-free survival

Within the manufacturer's model, the proportion of patients with PFS for the bevacizumab group and the placebo group was estimated from a log-logistic function applied to OCEANS Kaplan–Meier PFS data. The data used were taken from the final Kaplan–Meier PFS analysis carried out in September 2010, and were based on the investigator-assessed determination of PFS (Section 4.2.1). PFS was defined within OCEANS as the time from randomisation to PD or death due to any cause. The proportion of patients within the PFS health state in the model was estimated directly from the parametric function fitted for PFS, and applied within the model at each corresponding week.

The September 2010 dataset comprised the only analysis of PFS completed by the manufacturer and, within the model, resulted in 29.8 months of data for the bevacizumab group and 24.9 months of data for the placebo group. The bevacizumab group reached 0% PFS at month 29.8. In the placebo group, two patients remained at risk at month 24.9, after which no further data were available in the model; however, the Kaplan–Meier plot (Appendix 4) indicates that PFS for the placebo group was sustained until approximately month 29.

The manufacturer assessed the fit of the following parametric functions to OCEANS Kaplan–Meier PFS data: exponential; gamma; Gompertz; log-logistic; log normal; and Weibull. Each assessed distribution accounted for treatment group by using a covariate for the placebo group, thus the manufacturer assumed the treatment effect between the placebo and bevacizumab groups was proportional. The manufacturer did not provide a justification for this assumption (e.g., through presentation of log-cumulative hazard plots). The goodness-of-fit of each function to the OCEANS Kaplan–Meier PFS data were assessed visually (Figure 4), using the Akaike information criterion (AIC), and the Bayesian information criterion (BIC) (Table 30). The ERG notes that the methods used

to assess internal validity of each parametric distribution to the observed data are consistent with recommendations outlined by a Decision Support Unit (DSU) report published in 2011.[75]

Figure 4. Visual comparison of parametric functions describing progression-free survival of patients receiving bevacizumab (green line and purple dots) or placebo (blue line and light blue dots) (reproduced from MS; Figure 13, pg 116)

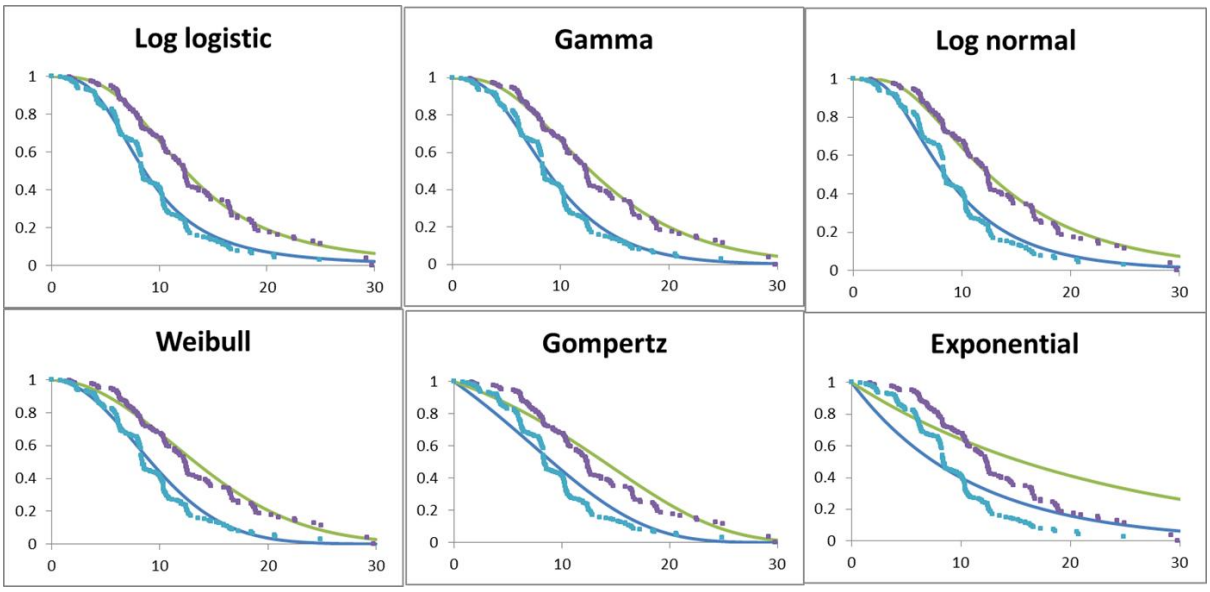


Table 30. Statistical fit of parametric distributions to progression-free survival (reproduced from MS; Table 28, pg 115)

Model	BIC	AIC
log-logistic	772.51	759.96
gamma	786.92	770.19
log normal	795.13	782.58
Weibull	805.91	789.18
exponential	1,001.22	992.86
Gompertz	1,173.25	1,160.71
Abbreviations used in table: AIC, Akaike information criterion; BIC, Bayesian information criterion.		

The manufacturer concluded that, of the parametric functions tested, the log-logistic, gamma, log normal and Weibull "appeared to provide close approximations to the observations from the study and are comparable with each other in terms of statistical and visual fit" (MS; pg 117). In the base case, the manufacturer selected the log-logistic distribution for the estimation and extrapolation of PFS data "since these were found to have the best statistical fit to the data" (MS; pg 122). The manufacturer's log-logistic survival analysis outputs are presented in Table 31.

From these results, the manufacturer estimated the log-logistic survival function to be:

$$\frac{1}{1+\varphi t^{\left(\frac{1}{\gamma}\right)}}$$

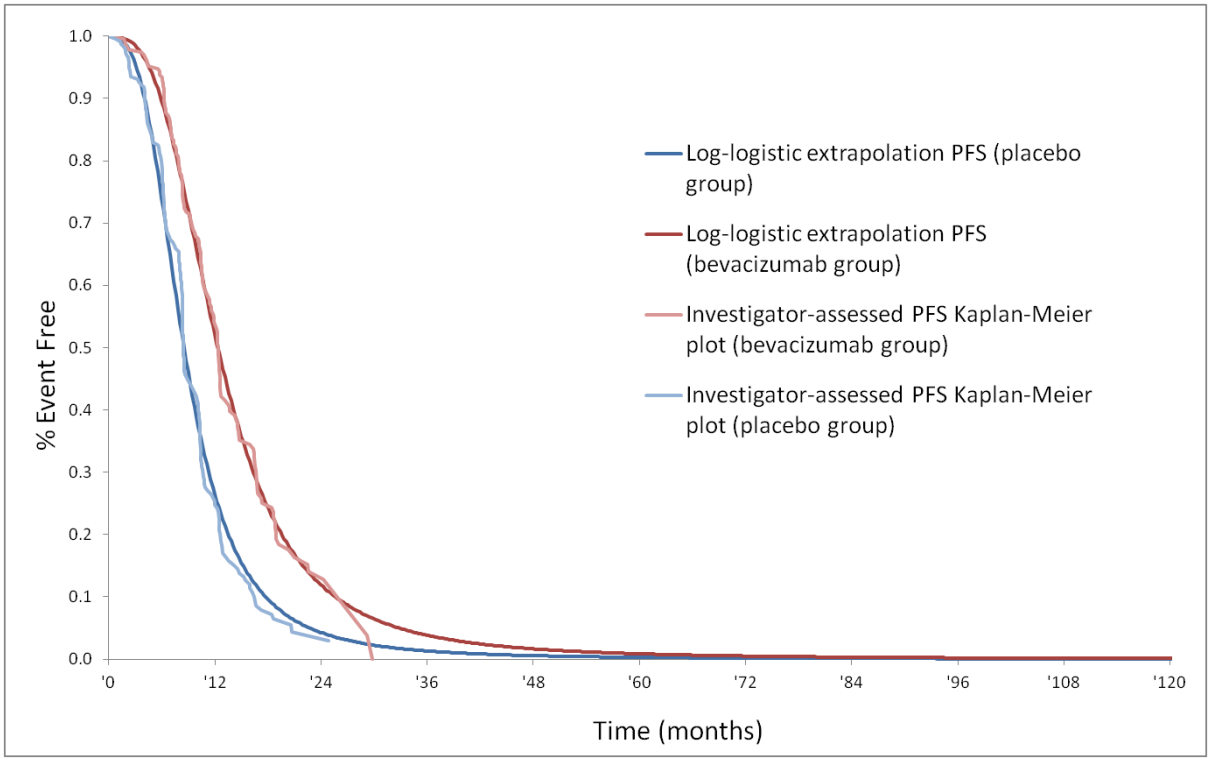
Where $\varphi = \exp\left(\frac{-(\beta_1+\beta_2)}{\gamma}\right)$ and t = time (months)

The manufacturer applied these equations within the model engine for both the bevacizumab and placebo groups to estimate PFS each week. Figure 5 presents the fitted log-logistic PFS distributions versus the Kaplan–Meier PFS plots for both arms.

Table 31. Results of the log-logistic survival analysis for progression-free survival using September 2010 data (reproduced from manufacturer's model)

	Estimate	Standard error
Intercept (β_1)	2.52	0.041
Covariate for placebo (β_2)	–0.37	0.056
Scaling factor (γ)	0.33	0.015

Figure 5. Kaplan–Meier and log-logistic progression-free survival curves (adapted from MS; Figure 16, pg 123)



The ERG notes that the manufacturer's model was set up to allow exploration of the impact of using alternative parametric functions, and Kaplan–Meier data alone to estimate the probability of PFS (Table 32). In addition, the manufacturer considered the impact on the base case cost-effectiveness

results of using Kaplan–Meier data with a parametric tail, and the Weibull parametric distribution in sensitivity analyses (Section 5.3.13).

Table 32. Mean progression-free survival estimated using alternative parametric forms and Kaplan–Meier data contained within the manufacturer's economic model

	Mean PFS (years)		
Selected PFS modelling methodology	**Bevacizumab**	**Placebo**	**Difference in means (bevacizumab minus placebo)**
Log-logistic (manufacturer base case)	*1.22*	*0.86*	*0.37*
Exponential	1.41	0.89	0.52
Gamma	1.18	0.81	0.37
Gompertz	1.16	0.80	0.36
Kaplan–Meier	1.16	1.00	0.17
Kaplan–Meier with parametric tail (log-logistic from month 24)	1.24	0.84	0.40
Log normal	1.23	0.84	0.39
Weibull	1.16	0.81	0.35
Abbreviation used in table: PFS, progression free survival.			

The ERG has three main concerns around the PFS data used within the manufacturer's model:

- use of parametric extrapolation rather than Kaplan–Meier data to estimate PFS;
- use of PFS data from a treatment regimen that may not reflect likely UK clinical practice;
- the impact of competing risks on estimates of PFS.

Use of parametric extrapolation

The ERG considers that the methods used to assess internal validity of each parametric distribution to the observed data are consistent with recommendations outlined in the DSU report[75]; however, the ERG considers that fitting a parametric distribution for PFS was unnecessary given the Kaplan–Meier PFS data available.

The dataset used to generate the Kaplan–Meier PFS plot represented the final PFS analysis, with a median follow-up time of 24 months. At this time point, 338 patients from a cohort of 484 (70%) had experienced either disease progression or death. In particular, at 29.8 months, all patients still at risk in the bevacizumab group had progressed or died (i.e., the probability of PFS at 29.8 months was 0% for patients in the bevacizumab group) and two patients remained at risk in the placebo group at month 29, according to the Kaplan–Meier plot.

To assess whether censoring might affect the estimates of PFS, the ERG asked the manufacturer to provide additional details around the number of patients censored at specific time points within the PFS analysis (approximately 30% patients). The manufacturer did not provide this information and stated "we do not have access to the exact number of such events at each month of follow-up". In the

absence of further information around censoring, the ERG assumes that the Kaplan–Meier data provides a reasonable estimate of PFS.

The ERG notes that the manufacturer's estimate of PFS (presented in Table 32; mean PFS difference between the placebo group and the bevacizumab group of 0.17 years) is likely to overestimate the benefit associated with the placebo group. This is because the estimate is based upon an assumption within the model whereby the two remaining placebo patients maintain PFS for the full duration of the model. The ERG considers that this would be unlikely to occur clinically. To provide a more reasonable estimate of PFS using the Kaplan-Meier data only, the ERG requested that the manufacturer present a scenario analysis in which PFS was modelled using Kaplan–Meier data and assuming 0% survival for the placebo group at the same time point as the bevacizumab group experienced 0% survival. The manufacturer did not provide this analysis, stating that "the requested scenarios represent a request for further analyses and data. They are not clarifications of the data presented in the submission". Therefore, the ERG conducted an exploratory analysis using Kaplan–Meier data and assuming that survival for the placebo group was 0% after month 29; that is, the remaining placebo patients were artificially censored at the last point for which information on PFS was available from the Kaplan–Meier plot. The ERG believes that assuming 0% survival for the placebo group was an appropriate simplifying assumption that would result in a bias towards the bevacizumab group; the PFS of placebo patients is likely to have been underestimated as the remaining placebo patients may have sustained PFS beyond this time point. The mean PFS for this scenario is presented in Table 33.

Table 33. Mean progression-free survival estimated using Kaplan–Meier data and assumptions on placebo group survival

	Mean PFS (years)		
Selected PFS modelling methodology	**Bevacizumab**	**Placebo**	**Difference in means**
Kaplan–Meier (ERG scenario)[a]	1.16	0.81	0.35
[a] Assuming 0% survival for the placebo group at month 29 Abbreviations used in table: PFS, progression-free survival.			

The ERG notes that the incremental mean PFS for bevacizumab for every considered parametric distribution (with the exception of the Weibull) (Table 32) exceeded the estimates of PFS from the ERG's Kaplan–Meier analysis (Table 33). Thus, the ERG considers that the use of parametric extrapolation may have overestimated the PFS benefit for the bevacizumab group compared with the placebo group. Using Kaplan–Meier data and assuming 0% placebo survival at month 29, the ERG estimated that the difference in mean PFS between the bevacizumab and placebo groups was 0.35 years, compared with 0.37 years difference for the log-logistic extrapolated PFS. This represents a small potential overestimate of PFS for the bevacizumab versus the placebo group. However, the

ERG notes that the overestimate is likely to be larger than this given that the estimate of 0.35 years additional PFS using the Kaplan–Meier data were based on an assumption of 0% survival for the placebo group at month 29, an assumption which is likely to favour bevacizumab for reasons discussed above.

The impact of using Kaplan–Meier data within the cost-effectiveness analysis (and assuming 0% survival for the placebo group at 29 months) was an increase in the ICER of £489 to £149,539 (Section 6.1.2; Analysis 10).

Use of data from a treatment regimen that may not reflect likely UK clinical practice

Within OCEANS, approximately 40% of patients received 7–10 cycles of gemcitabine plus carboplatin treatment. As outlined in Section 4.1.6, the consensus in the UK is that patients should receive a maximum of six cycles of gemcitabine plus carboplatin chemotherapy.[23] The ERG was unclear what the impact might be on PFS from OCEANS if usage of gemcitabine plus carboplatin was limited to six cycles in UK clinical practice. To investigate this, the ERG asked the manufacturer to provide PFS Kaplan–Meier data for those patients within OCEANS who received 1–6 cycles of gemcitabine plus carboplatin. The manufacturer was not able to access this information given the short time frames and due to the subgroup of patients not previously being defined (Box 1):

Box 1. Manufacturer response to the ERG request for additional Kaplan–Meier data

These analyses were not conducted at the time of the efficacy analyses, as this subgroup was neither a stratified group, nor a subgroup dictated by patient demographics. We are not able to access the database at short notice to conduct such additional analyses. The pattern of chemotherapy administration in the ITT population is reflected in the licence for this indication and so should reflect the chemotherapy usage and thus the cost-effectiveness for this combination therapy in the population of England and Wales.

The ERG is therefore unable to comment on whether the PFS data used within the model reflects the PFS that would be seen in UK clinical practice. The ERG notes that this is likely to create some uncertainty in the estimates of PFS; however, the ERG's clinical expert indicated that more than six cycles of chemotherapy is unlikely to be given in UK clinical practice as there is no evidence to indicate that a higher number of cycles is associated with an increase in clinical benefit.

The ERG considers it important to also note that, within the economic model, the manufacturer has limited gemcitabine and carboplatin chemotherapy to a maximum of six cycles in the estimation of costs, which, in contrast to the effectiveness data, is in line with UK clinical practice (Section 5.3.11).

Competing risks

The manufacturer used PFS data estimated with Kaplan-Meier methodology within the model. However, the ERG notes that death (from any cause) was a competing risk event; competing risks are encountered when patients under study are at risk of more than one mutually exclusive event. By using standard Kaplan-Meier methodology, the manufacturer has not explicitly accounted for competing risks, instead the manufacturer included death from any cause within the definition of PFS; the manufacturer defined PFS as the time from randomisation to disease progression or death due to any cause. However, the ERG believes that due to the low number of death events within the PFS dataset (five within the bevacizumab group and two within the placebo group), standard Kaplan-Meier techniques are likely to have been appropriate for the PFS analysis, and estimates of progression free survival are likely to be reasonable.

Overall survival

OS data were used within the manufacturer's economic model to estimate the proportion of people within the PD health state (PD = OS – PFS) and, implicitly, the death health state (death = 1 – OS) in each model cycle. Similar to the estimation of PFS above, the manufacturer estimated the duration of OS by applying a log-logistic distribution to the Kaplan–Meier OS data from OCEANS. At the time of submission, final OS data were not available (expected in 2013). Therefore, the manufacturer used interim survival analysis carried out in September 2010 to inform the log-logistic distribution. This dataset comprised 35.5 months of data for the bevacizumab group and 33.7 months of data for the placebo group. During these time periods, 29% of patients had died (Section 4.2.1). The probability of survival was then estimated through extrapolation of the chosen distribution and applied weekly for the full time horizon of the model.

The interim analysis of OS carried out in September 2010 was the first of three interim analyses conducted by the manufacturer. The manufacturer also analysed OS at August 2011 and March 2012. The results from these analyses were:

- in September 2010 approximately 29% patients had died; the median OS for bevacizumab was estimated to be 35.5 months compared with 29.9 months in the placebo group (hazard ratio versus placebo 0.751 [0.537 to 1.052])
- in August 2011 approximately 49% patients had died; the median OS for bevacizumab was estimated to be 33.3 months compared with 35.2 months in the placebo group (hazard ratio versus placebo 1.027 [0.792 to 1.331])
- in March 2012 approximately 59% patients had died; the median OS for bevacizumab was estimated to be 33.4 months compared with 33.7 months in the placebo group (hazard ratio versus bevacizumab 0.960 [0.760 to 1.214])

Within the MS, the manufacturer presented the Kaplan–Meier OS plots for the September 2010 and March 2012 interim analyses (Figure 6 and Figure 7, respectively). In Figure 6, the vertical lines indicate 95% CIs. In Figure 7, a line indicates censoring.

Figure 6. Overall survival of patients in the OCEANS study receiving bevacizumab (red) or placebo (blue) at the first interim analysis (September 2010; reproduced from MS; Figure 14, pg 117)

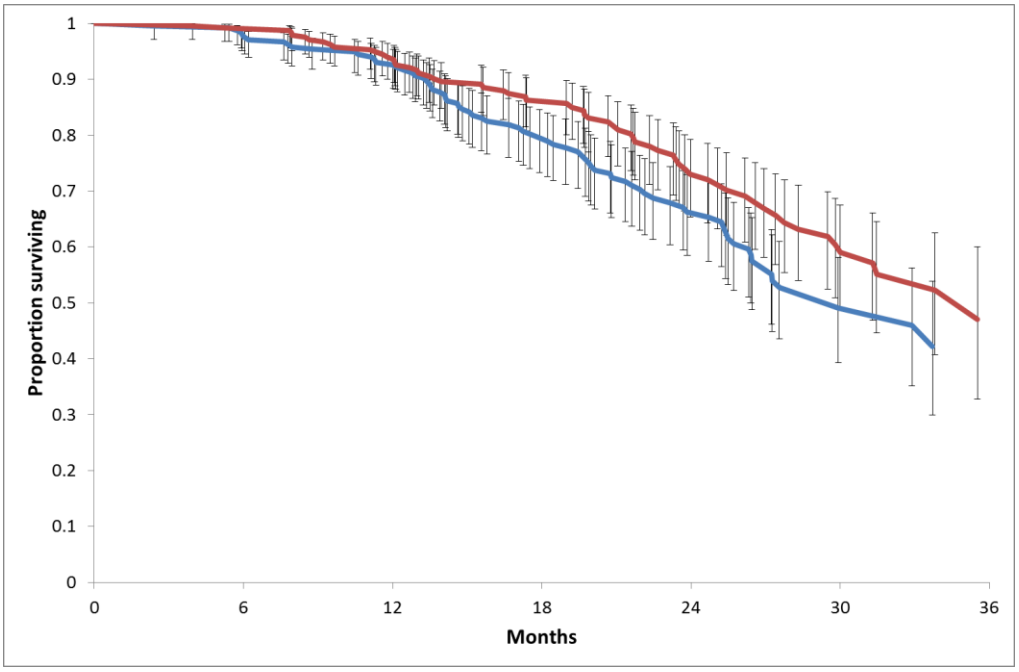
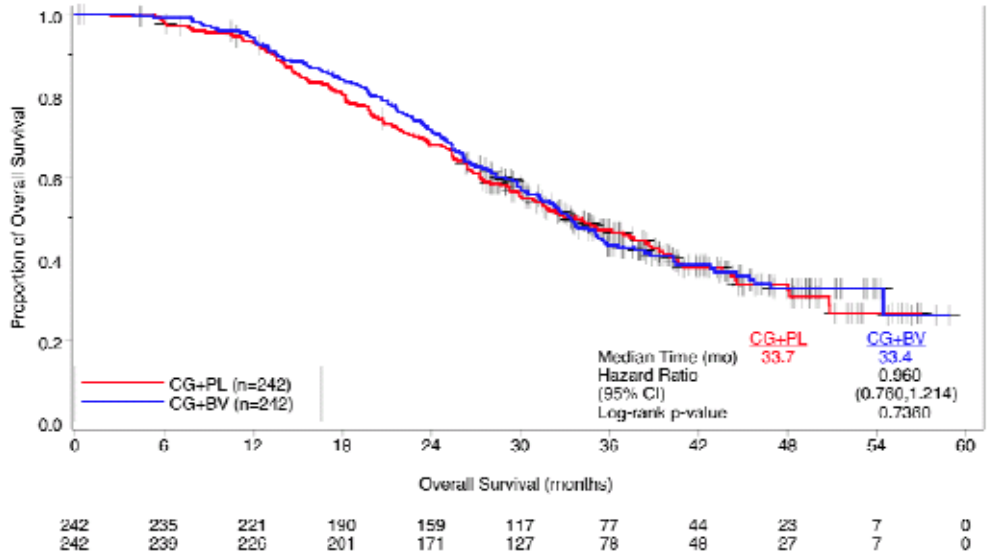


Figure 7. Overall survival of patients in the OCEANS study receiving bevacizumab (blue) or placebo (red) at the third interim analysis (March 2012; reproduced from MS; Figure 8, pg 70)



The manufacturer assessed the fit of the following parametric functions to OCEANS Kaplan–Meier OS data from September 2010: exponential; gamma; Gompertz; log-logistic; log normal; and Weibull. Each assessed distribution accounted for treatment group by using a covariate for the placebo group, and thus the manufacturer assumed the treatment effect between the placebo and bevacizumab groups was proportional. The manufacturer did not provide a justification for this assumption (e.g., through

presentation of log-cumulative hazard plots). The manufacturer assessed the goodness-of-fit of each of these functions using visual assessment (Figure 8), the AIC, and the BIC (Table 34).

Figure 8. Visual comparison of parametric functions describing overall survival of patients receiving bevacizumab (green line and purple dots) or placebo (blue line and light blue dots) (reproduced from MS; Figure 15, pg 119)

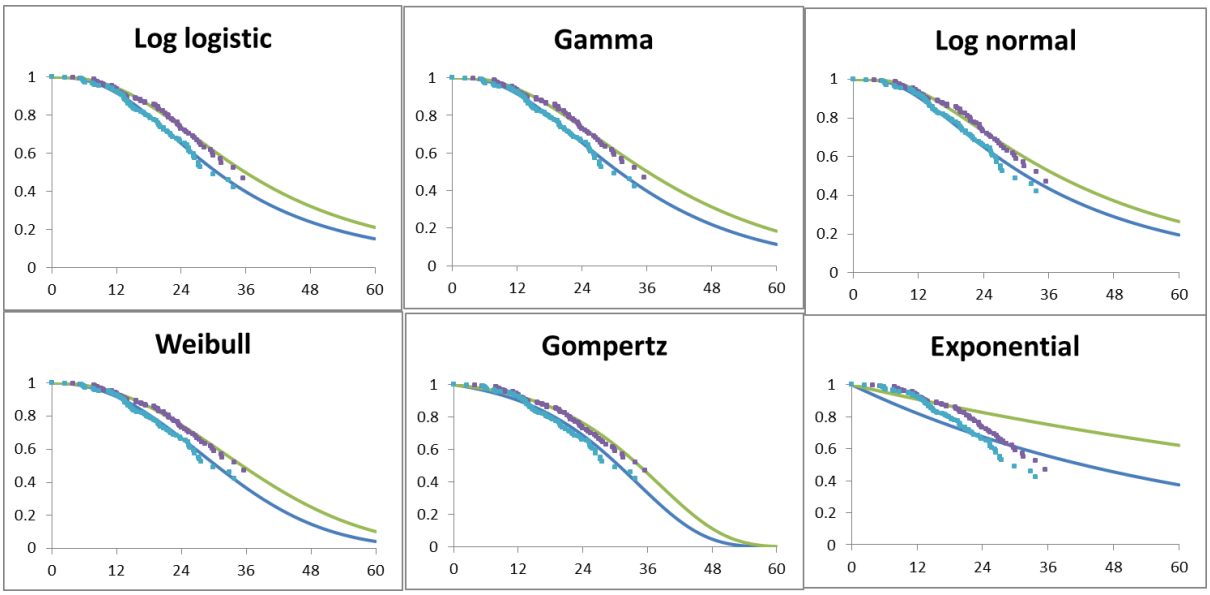


Table 34. Statistical fit of parametric curves to overall survival (reproduced from MS; Table 29, pg 118)

Model	BIC	AIC
log-logistic	608.93	596.38
gamma	615.06	598.33
log normal	611.49	598.94
Weibull	617.34	600.62
exponential	700.11	691.75
Gompertz	718.44	705.89
Abbreviations used in table: AIC, Akaike information criterion; BIC, Bayesian information criterion.		

The manufacturer concluded that statistical and visual comparison of the six parametric functions describing OS "reveals similar results to those for PFS, i.e. 4 functions are much better approximations for the data than the other 2" (MS; pg 118); the manufacturer was referring to the log-logistic, gamma, log-normal and Weibull functions. The manufacturer's log-logistic survival analysis outputs are presented in Table 35.

From these results, the manufacturer estimated the log-logistic survival function as:

$$\frac{1}{1+\varphi t^{\left(\frac{1}{\gamma}\right)}}$$

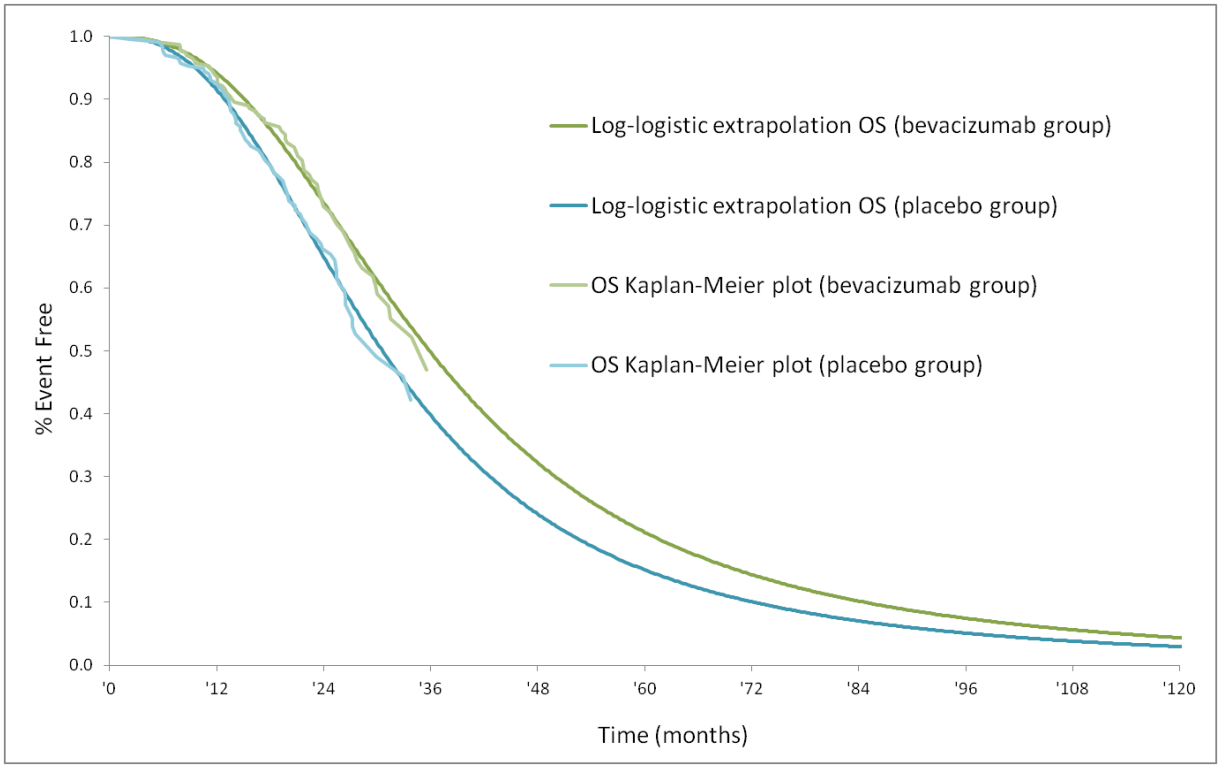
Where $\varphi = \exp\left(\frac{-(\beta_1+\beta_2)}{\gamma}\right)$ and t = time (months)

The manufacturer applied these equations within the model engine for both the bevacizumab and placebo groups to estimate OS each week. OS was then used to estimate the number of patients within the PD health state (OS – PFS). Figure 6 presents the log-logistic functions fitted to the OS data versus the Kaplan–Meier OS plots for both groups at the September 2010 time point.

Table 35. Results of the log-logistic survival analysis for overall survival using September 2010 data (reproduced from the manufacturer's model)

	Estimate	Standard error
Intercept (β_1)	3.58	0.066
Covariate for placebo (β_2)	–0.16	0.081
Scaling factor (γ)	0.39	0.027

Figure 9. Kaplan–Meier and log-logistic function overall survival curves (adapted from MS; Figure 16, pg 123)



The ERG notes that the manufacturer's model was constructed to allow exploration of the impact of using alternative parametric functions to estimate OS. The mean OS for each parametric function is presented in Table 36.

Table 36. Mean overall survival estimated using switches for alternative parametric forms contained within the manufacturer's model

	Mean OS (years)		
Selected OS parametric extrapolation	**Bevacizumab**	**Placebo**	**Difference in means**
Log-logistic (manufacturer base case)	*3.38*	*2.96*	*0.42*
Exponential	4.65	3.97	0.68
Gamma	3.20	2.77	0.43
Gompertz	2.67	2.39	0.28
Kaplan–Meier with parametric tail (log-logistic after month 36)	3.31	2.99	0.32
Log normal	3.60	3.14	0.46
Weibull	2.93	2.55	0.37
Abbreviation used in table: OS, overall survival.			

The ERG has four main concerns around the OS data used within the economic model:

- date of the OS analysis;
- confounding of OS estimates through bevacizumab use post-progression;
- method of extrapolation;
- use of data from a treatment regimen that may not reflect likely UK clinical practice.

Date of the analysis of overall survival

The manufacturer elected to use data from the first interim analysis of OS (September 2010) as the basis for extrapolation of OS within the economic model. The manufacturer acknowledged that use of data from this time point was a weakness within the economic evaluation, but claimed that it was necessary to use OS from this time point (Box 2).

Box 2. The manufacturer's rationale for selecting the first interim survival analysis for use within the economic model

"The main weakness of the economic evaluation is the use of a relatively early data-cut (September 2010) from the OCEANS study to inform the model. This was necessary because of the incompleteness of later data-cuts which, although containing more mature overall survival data, lack completeness of other outcomes important for a robust economic evaluation." (MS; pg 178)

To reduce uncertainty in the extrapolated estimates of OS, the ERG considers that the most mature OS data available should be used for extrapolation (i.e., March 2012 data). OS data from September 2010 were extrapolated by the manufacturer to estimate survival at later time points, up to and including March 2012. This generates uncertainty in estimates both up to March 2012 (where data are available) and beyond March 2012 because the dataset on which extrapolation is based is less mature; at the

September 2010 OS analysis 29% of patients had died compared with 59% patients at the March 2012 time point. Use of OS data from March 2012 would have generated more robust estimates of OS.

The ERG considers that as well as introducing additional and unnecessary uncertainty in the extrapolated estimates, the OS data included in the model is likely to overestimate the OS benefit for the bevacizumab group. This is because the data for OS in September 2010 showed a non-statistically significant OS benefit for the bevacizumab group which was not sustained in the two later interim analyses (Table 11).

For months 36–56, the ERG compared OS estimates from March 2012 Kaplan–Meier data (Figure 7) with OS estimates from the base case model (i.e., the log-logistic function fitted to the September 2010 Kaplan–Meier OS data) (Figure 9). During clarification, the ERG requested OS data from March 2012 from the manufacturer; however, the manufacturer did not supply these data. The ERG therefore approximated data from March 2012 from the Kaplan–Meier curve presented in Figure 7 using WebPlotDigitizer to estimate values on the Kaplan–Meier curve directly.[76] A summary of the ERG's findings is presented in Table 37.

The log-logistic extrapolation consistently underestimated OS for the placebo group by 7% to 10% at the time points included in Table 37. By contrast, the log-logistic extrapolation for the bevacizumab group both underestimated and overestimated OS at the same time points. This equates to an approximate overestimate of OS for the bevacizumab group compared with the placebo group by 2% to 8% at the time points considered in Table 37.

Table 37. Comparison of overall survival from Kaplan–Meier data from March 2012 versus extrapolated log-logistic overall survival estimates

	% OS						Potential overestimate of bevacizumab OS through use of log-logistic extrapolation (percentage points)
	Bevacizumab			Placebo			
Month	March 2012 Kaplan–Meier data[a]	Log-logistic extrapolation	Approximate difference (% points)	March 2012 Kaplan–Meier data[a]	Log-logistic extrapolation	Approximate difference (% points)	
36	45%	50%	+5%	47%	40%	–7%	8%
40	41%	43%	+2%	43%	33%	–10%	8%
44	39%	37%	–2%	38%	28%	–10%	8%
48	35%	32%	–3%	33%	24%	–9%	6%
52	35%	28%	–7%	29%	20%	–9%	2%
56	28%	24%	–4%	28%	18%	–10%	6%

[a] Estimated from visual appraisal of Figure 7 (MS; pg 70).
Abbreviations used in table: OS, overall survival.

During the clarification process, the ERG requested a scenario in which March 2012 data were modelled for OS. The manufacturer did not provide this analysis and stated: "the requested scenarios

represent a request for further analyses and data. They are not clarifications of the data presented in the submission". Furthermore, the manufacturer stated that "it is clear that if later data-cuts were more complete and were incorporated into the economic model, the ICER would be greater than the current estimate of £150,000 per QALY and therefore do not impact on the likelihood of meeting NICE's cost-effectiveness threshold".

The ERG was unable to model OS using March 2012 data because the manufacturer did not provide the necessary data. Instead, the ERG conducted a scenario analysis assuming that OS was the same for both the bevacizumab and placebo group (the ERG set the placebo group OS to equal bevacizumab group OS estimated from the log-logistic function). This scenario was based on the review of clinical data in which the hazard ratio for OS between the bevacizumab group and the placebo group was found at the March 2012 time point to be close to 1 (Section 4.2.1). The result of the analysis was an increase in the ICER of approximately £1.6 million to £1,749,614 (Section 6.1.2, Analysis 11).

Confounding of estimates of overall survival resulting from bevacizumab use post-progression

Throughout the MS, the manufacturer notes that OS may be confounded from the use of bevacizumab in the placebo group following progression. The manufacturer estimated that 18.1% of patients within the bevacizumab group received bevacizumab post-progression (37/204) compared with 34.7% (74/213) within the placebo group. These numbers were based on the second interim analysis of OS in August 2011. During clarification, the ERG requested the number of patients receiving bevacizumab post-progression in both treatment groups for the March 2012 analysis. The manufacturer did not provide this information and stated that "these data are not reported in the OCEANS CSR or elsewhere in the relevant publications".

The ERG recognises that treatment switching within randomised controlled trials (RCTs) can cause bias in OS estimates. When a patient switches during the study from the control therapy to the treatment being evaluated there is a risk that any clinical benefit associated with the experimental treatment will be underestimated.[77]

A number of approaches have been suggested that attempt to quantify the degree of confounding; these are discussed in detail in Morden *et al*.[77] During clarification, the ERG asked the manufacturer whether any of the approaches within this paper had been carried out to investigate the magnitude of any bias. The manufacturer stated that "no analyses have been conducted to correct for potential confounding of OS benefits in the OCEANS trial. The value of the information gained from such a correction (using whatever methods are deemed most appropriate) is likely to be small compared to the resources required and its impact on the decision at hand". The full extent of the potential bias of treatment switching on final data for OS is therefore unclear.

Method of extrapolation

As described above, the manufacturer applied the log-logistic extrapolation to the full data set from OCEANS, with treatment group included as a covariate. The manufacturer therefore assumed that the treatment effect between the placebo and bevacizumab groups was proportional. However, the manufacturer did not provide a justification for this assumption (e.g., through presentation of log-cumulative hazard plots). The manufacturer then selected the log-logistic parametric extrapolation based on visual assessment of the model and consideration of the AIC and BIC. The ERG notes that testing the fit of the parametric extrapolation to the observed data in this way is consistent with recommendations outlined in a DSU report,[75] and is satisfied that the manufacturer selected the parametric function that best fitted the September 2010 OS data.

However, the ERG notes that the AIC and BIC can only test how well a parametric function fits the observed data and cannot make a comment on the external validity of the extrapolation.[75] Given the concerns raised above around the use of less mature data for the purposes of extrapolation, the ERG cannot be confident that the selected extrapolation would be appropriate had the March 2012 dataset been used. The ERG also notes the DSU caution around use of the log-logistic function: "owing to their functional form, log-logistic models often result in long tails in the survivor function, and this must also be considered if they are to be used".[75]

Use of data from a treatment regimen that may not reflect likely UK clinical practice

Within OCEANS, approximately 40% patients received 7–10 cycles of gemcitabine plus carboplatin treatment. As outlined in Section 4.1.6, the consensus in the UK is that patients should receive a maximum of six cycles of gemcitabine plus carboplatin chemotherapy.[23] Similar to estimates of PFS, the ERG was unclear what the impact might be on OS data from OCEANS if usage of gemcitabine plus carboplatin was limited to six cycles in UK clinical practice. To investigate this, during clarification, the ERG asked the manufacturer to provide OS Kaplan–Meier data for those patients within OCEANS who received 1–6 cycles of gemcitabine plus carboplatin. The manufacturer was not able to access this information given the short time frames and due to the subgroup of patients not previously being defined.

The ERG is therefore unable to comment on whether the OS data used within the model reflect the OS that would be seen in UK clinical practice. The ERG notes that this is likely to create some uncertainty in the estimates of OS. However, the ERG also notes that it has been reported that the number of cycles of chemotherapy is not expected to influence median OS.[23]

5.3.9 Adverse event rates

The manufacturer incorporated adverse events of Grade 3 or more that occurred in greater than 2% of patients, regardless of study arm, within the economic model. Although not explicitly stated within

the MS, in the economic model, the adverse events were labelled as treatment-related. The data were taken from September 2010. The adverse events and associated rates included within the MS economic section are presented in Table 38.

Table 38. Treatment-related adverse event rates included within the economic model (adapted from MS; Table 44, pg 156)

Adverse event (Grade 3 where not stated)	Bevacizumab	Placebo
Epistaxis	6 (2.46%)	1 (0.4%)
Fatigue	5 (2.05%)	3 (1.2%)
Proteinuria	19 (7.79%)	0 (0%)
Thrombocytopenia	15 (6.15%)	14 (5.58%)
Thrombocytopenia (Grade 4)	15 (6.15%)	8 (3.19%)
Leukopenia	8 (3.28%)	7 (2.79%)
Neutropenia	40 (16.39%)	30 (11.95%)
Neutropenia (Grade 4)	14 (5.74%)	9 (3.59%)
Hypertension	33 (13.52%)	1 (0.4%)
Anaemia	14 (5.74%)	13 (5.18%)
Neutrophil count decreased	5 (2.05%)	8 (3.19%)
Neutrophil count decreased (Grade 4)	5 (2.05%)	3 (1.2%)
White blood cell count decreased	1 (0.41%)	6 (2.39%)

It is not clear from the MS whether the incident numbers relate to the number of patients experiencing an event or the number of patient events. However, review of the economic model indicates that the numbers in the table represent the number of patients experiencing each event.

The ERG noted two additional minor issues with the adverse event data included in the economic model. The percentage of patients within the bevacizumab group who experienced "neutrophil count decreased (Grade 4)" as presented in Table 38 was inconsistently reported between the MS and the submitted economic model; the economic model implied that three patients (1.23%) rather than five patients (2.05%), as reported in the MS, experienced "neutrophil count decreased (Grade 4)". Based on a number of typographical errors identified within the MS, the ERG considers that the economic model is more likely to be correct; therefore, the figure of 1.23% has been assumed to be correct.

Additionally, the percentage of patients within Table 38, and therefore the economic model, was estimated assuming a sample size for the "chemotherapy" group of 251, and a sample size for the "bevacizumab + chemotherapy" group of 244. These sample sizes do not match the intention-to-treat (ITT) population ("chemotherapy" = 242, "bevacizumab + chemotherapy" = 242) or the safety-evaluable population ("chemotherapy" = 233, "bevacizumab + chemotherapy" = 247). During clarification, the ERG asked the manufacturer to clarify the rationale for these sample sizes. The manufacturer stated that "these numbers are included in error. They ought to be 242 and 242

respectively". However, the ERG notes that the sample size for the safety-evaluable population was "chemotherapy" = 233 and "bevacizumab + chemotherapy" = 247.

The ERG updated the percentage of patients who experienced an adverse event based on the safety-evaluable population (placebo group = 233, bevacizumab group = 247). The impact of updating the sample size to reflect the safety-evaluable population was small, with a reduction in the ICER of £47 to £149,003 (Section 6.1.1; Analysis 4).

The manufacturer used the number of patient events to assign a cost associated with each adverse event (Section 5.3.11). The manufacturer did not apply a disutility associated with adverse events (Section 5.3.10).

5.3.10 Health-related quality of life

As health-related quality of life data (HRQoL) data were not collected as part of the OCEANS trial, the manufacturer carried out a systematic review to identify health state utility value (HSUV) studies relevant to the health states considered in the model. The following electronic databases were searched; ProQuest MEDLINE and MEDLINE in-process; ProQuest EMBASE; EconLit; and NHS EED. The search was carried out in August 2012 and was not restricted by date, publication type, or study design, but was restricted to English language publications. Details of the search strategy, and inclusion/exclusion criteria are provided in the MS (pg 253–257).

The review identified 35 publications, of which five were deemed relevant to the submission by the manufacturer (Brundage *et al.*[78], Krasner *et al.*[79], Pokrzywinski *et al.*[80], Havrilesky *et al.*[61], Vergote *et al.*[81]). The five studies are summarised in Table 39.

Table 39. Summary of health state utility value studies included by the manufacturer

Study	Population in which health effects were measured	Interventions assessed	Sample size	HRQoL collected	Relevance to reference case
Brundage *et al.*[78]	Patients in the CALYPSO trial; age >18; advanced ovarian, fallopian tube or extra-ovarian papillary serous cancer; 2nd or 3rd line platinum-sensitive patients; ECOG ≤2	PLDH; paclitaxel and carboplatin	976	EORTC-QLQ C30 OV28 Data collected at 3, 6, 9, and 12 months	Utility data not collected
Krasner *et al.*[79]	Patients in the OVA-301 trial; age >18; epithelial ovarian, epithelial fallopian tube or primary peritoneal cancer; 2nd line platinum-sensitive patients	Trabectedin and PLDH; PLDH	672	EORTC-QLQ C30 OV28 EQ-5D Data collected at screening and day 1 of every other cycle	Utility data collected from patients (EQ-5D)

Pokrzywinski *et al*.[80]	Recurrent platinum-sensitive ovarian, peritoneal or tubal cancer; 2nd line; ECOG ≤2	Docetaxel and carboplatin; docetaxel followed by carboplatin	148	FACT-O	Utility data not collected
Havrilesky *et al*.[61]	Recurrent platinum-sensitive ovarian cancer	Docetaxel and carboplatin; docetaxel followed by carboplatin	NR	NR	Utility data not collected
Vergote *et al*.[81]	Partially platinum-sensitive recurrent ovarian cancer	Trabectedin and PLDH; PLDH	214	EORTC-QLQ C30 OV28 Data collected at screening and day 1 of every other cycle	Utility data not collected
Abbreviations used in table: ECOG, Eastern Cooperative Oncology Group; EORTC-QLQ C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D, EuroQol 5 dimensions questionnaire; FACT-O, Functional Assessment of Cancer Therapy for ovarian cancer patients; HRQoL, health-related quality of life; HSUV, health state utility value; NR, not reported; OV28, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Ovarian Cancer Module; PLDH, pegylated liposomal doxorubicin hydrochloride.				

The manufacturer notes that Brundage *et al*.[78], Pokrzywinski *et al*.[80], Havrilesky *et al*.[61], and Vergote *et al*.[81] do not present EuroQol 5 dimensions questionnaire (EQ-5D) data and commented that mapping to EQ-5D would not be possible from the HRQoL measures collected in these papers. The manufacturer also noted that Krasner *et al*.[79] collected and reported EQ-5D. The manufacturer stated that "EQ-5D scores are available but are not converted into utilities in this paper" (MS; pg 131); however, EQ-5D scores represent a utility, and a utility for each treatment group at baseline and a utility change from baseline to end of treatment by therapy is reported (Table 40).[79] However, the paper does not report utilities associated with PFS or PD health states. The ERG reviewed the search terms used by the manufacturer to identify HSUV studies and is satisfied that there are unlikely to be any further relevant published HSUV papers.

Table 40. Summary of EQ-5D index values captured in Krasner *et al*.[79]

	PLDH		Trabectedin plus PLDH	
	N	**Mean score (SD)**	**N**	**Mean score (SD)**
EQ-5D index baseline	318	0.78 (0.163)	323	0.78 (0.171)
ED-5D index change from baseline to end of treatment	211	–0.05 (0.191)	233	–0.05 (0.201)
Abbreviations used in table: EQ-5D, EuroQol 5 dimensions questionnaire; PLDH, pegylated liposomal doxorubicin hydrochloride; SD, standard deviation.				

In the absence of relevant utility data identified from the HSUV study review, the manufacturer used HSUVs from TA222 to inform the economic model. Utility data in TA222 were taken from the OVA-301 study, in which HRQoL was captured using EQ-5D.[79] The OVA-301 study evaluated the

effectiveness of trabectedin plus PLDH versus PLDH in adult women with second-line treatment of platinum-sensitive ovarian cancer. The HSUVs utilised from TA222 are presented in Table 41.

Table 41. Summary of health state utility values used within the manufacturer's model (adapted from MS; Table B4; pg 136)

State	Utility value	95% CI	Manufacturer's justification
PFS	0.718	0.70 to 0.74	Used in TA222: Trabectedin in treatment of relapsed ovarian cancer
PD	0.649	0.61 to 0.69	Used in TA222: Trabectedin in treatment of relapsed ovarian cancer
Abbreviations used in table: CI, confidence interval; MS, manufacturer's submission; N/A, not applicable; PD, progressed disease; PFS, progression-free survival.			

The ERG notes that the manufacturer does not describe the methods used to identify and select TA222. However, TA222 is linked to the EQ-5D study identified from the literature search (Krasner *et al*.[79]) through the clinical trial OVA-301; OVA-301 was used within both Krasner *et al*.[79] and TA222. OVA-301 was an open label, RCT in women with ovarian cancer who had been treated previously with one platinum-based therapy. The manufacturer notes that the use of utility data from OVA-301 presented in TA222 should be interpreted with caution due to little overlap in the types of adverse event between OVA-301 and OCEANS. The ERG agrees that there were differences in the adverse effect profile of patients in OVA-301 compared with patients in OCEANS; for example, patients within OCEANS experienced hypertension and proteinuria, which were not reported within OVA-301, although patients within both OVA-301 and OCEANS experienced anaemia, fatigue, leukopenia, nausea, neutropenia, thrombocytopenia, and vomiting.

Despite these differences, the ERG considers the utilities selected to represent the most recent and relevant utility values in relapsed/recurrent ovarian cancer that are applicable to the health states considered in the economic model. The selected utilities (Table 41) were applied to the proportion of patients in each health state in each week of the model according to weekly PFS and OS (Section 5.3.8).

Although available in the ERG report for TA222,[9] the manufacturer elected not to use HRQoL data based on platinum sensitivity (i.e., partially platinum sensitive versus fully platinum sensitive). The manufacturer's rationale for this decision was based on arguments presented in the ERG report for TA222, in which the ERG highlighted a number of concerns about the validity of the data presented.[9] The ERG agrees that it was appropriate not to use HRQoL by platinum sensitivity.

The manufacturer noted that "serious adverse events are expected to result in either a short or long term detriment to health-related quality of life" (MS; pg 136). However, the ERG notes that the manufacturer did not apply disutilities to account for the increased incidence of adverse events in the bevacizumab group compared with the placebo group. During clarification, the ERG asked the manufacturer to provide a scenario analysis in which adverse event disutility was applied within the

model. The manufacturer did not provide this analysis and stated "the requested scenarios represent a request for further analyses and data. They are not clarifications of the data presented in the submission".

For completeness, the ERG investigated the impact of applying disutilities associated with adverse events in an exploratory analysis. To approximate the potential impact of adverse events on QALYs, the ERG applied adverse event disutilities used within TA250, a recent STA in breast cancer of which the ERG was aware.[22] Due to time constraints, the ERG used the disutilities presented within TA250 in an exploratory analysis and did not conduct a systematic review to identify more recent or more relevant disutility values (Table 42). The ERG acknowledges that this is a weakness of the exploratory analysis.

Table 42. Disutilities used by the ERG to estimate the impact of adverse events (taken from TA250)[22]

Adverse event	Estimate of disutility	95% CI
Anaemia	–0.12	–0.16 to –0.09
Diarrhoea	–0.10	–0.13 to –0.08
Dyspnoea	–0.12	–0.16 to –0.09
Fatigue	–0.12	–0.14 to –0.09
Febrile neutropenia	–0.15	–0.19 to –0.11
Hypertension	–0.12	–0.16 to –0.09
Neuropathy peripheral	–0.12	–0.16 to –0.09
Neutropenia	–0.12	–0.16 to –0.09
Thrombocytopenia	–0.12	–0.16 to –0.09
Abbreviation used in table: CI, confidence interval.		

The ERG conducted a set of exploratory analyses assessing the impact on the ICER of the application of disutilities in Table 42. The results of the exploratory analyses are presented in Section 6.1.2. For an assumed average adverse event duration of 1 week, the ICER increased by £341 to £149,391; for an average adverse event duration of 1 month, the ICER increased by £1,494 to £150,544.

5.3.11 Resources and costs

In the economic evaluation, the manufacturer identified six key types of cost: intervention and comparator drug costs; drug administration costs; supportive care costs; palliative care costs; post-progression treatment costs; and adverse event costs. The costs are summarised in Table 44 to Table 54.

The manufacturer conducted a systematic literature review to identify published sources of UK resource data for patients with recurrent or relapsed advanced or metastatic ovarian cancer. Four databases were searched (EMBASE, Medline, NHS EED and EconLit). The manufacturer deemed

two studies (Smith *et al*.[82] and Gore *et al*.[83]) to be relevant to the decision problem. Summaries of the characteristics of the studies are presented in Table 43.

Table 43. Summary of studies identified by the manufacturer as part of the literature search on resource use and costs

Study (Country)	Overview/patient population	Model type and time horizon	Costs and sources	ICER	Author conclusions
Smith *et al*.[82] (UK and USA)	A comparative economic analysis of PLDH versus topotecan in epithelial ovarian cancer in the USA and the UK from the perspective of the third party payer	A cost-minimisation analysis based on the trial data. The comparators were assumed to have the same efficacy	Costs of chemotherapy, drug administration and management of adverse events. Sources: BNF, National Blood Authority tariff, National Reference Costs, and published studies	ICER not reported. Total cost per person in the topotecan arm was $12,325 (95% CI: $9,445 to $15,415; p >0.05) higher in the USA-based analysis and $2,909 (95% CI: $779 to $3,415; p <0.05) higher in the UK-based analysis than for PLDH	PLDH was found to be cost saving. However, the authors focus was on transferability of cost-effectiveness results from one country to another. The authors concluded that cost assessments based on information obtained from one country may not be relevant for policy makers in a different country
Gore *et al*.[83] (poster) (UK)	Cost-effectiveness of trabectedin plus PLDH for the treatment of women with relapsed platinum-sensitive ovarian cancer in the UK, from the perspective of a third party payer	A decision analytic lifetime model was developed to estimate the cost per QALY	Drug, administration, medical management and adverse event costs Source: BNF, UK Healthcare Resource Group codes	Trabectedin plus PLDH increased mean PFS by 3.0 months, and OS by 9.7 months compared to PLDH. The total cost for trabectedin plus PLDH was £41,657 and for PLDH alone was £23,579. The incremental cost per QALY gained was calculated as £37,206	Analysis based on the final survival data showed a significant improvement in the mean OS and incremental cost per QALY

Abbreviations used in table: BNF, British National Formulary; CI, confidence interval; OS, overall survival; PFS, progression-free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; QALY, quality adjusted life year; UK, United Kingdom; USA, United States of America.

The ERG notes that the identified studies did not contain sufficient information for use within the economic model. Consequently, the manufacturer used unit cost data from four main data sources:

- NHS Reference Costs (2010–2011);[73]
- The Commercial Medicines Unit (CMU) 2012 electronic Market Information Tool (eMit);[84]
- British National Formulary (BNF) Volume 63;[71]
- Unit Costs of Health and Social Care 2011.[72]

In addition, the cost of palliative care was taken from a study by Guest *et al*.[74] The ERG notes that this study was not listed in the studies identified by the manufacturer's search of the literature on resource use. The MS does not report how this study was identified.

The CMU eMit is an online source of information on the historical average price paid for a product. The estimates provided are derived from data collected via a system covering approximately 95% of English NHS Trusts. The ERG notes that the manufacturer used public list prices from the BNF for bevacizumab and carboplatin, and a drug price obtained from the CMU eMit for the cost of gemcitabine. The ERG considers that the public list price should be used in the base case, rather than the CMU eMit price, as per the NICE Guide to the Methods of Technology Appraisal.[70] This is discussed further below.

With the exception of the CMU eMit, the ERG is satisfied that relevant sources of resource use and cost data were used within the economic model, and that the unit costs were correctly adjusted to account for the weekly cycle length.

Intervention and comparator drug costs

Bevacizumab, gemcitabine and carboplatin are all administered through intravenous infusion in the secondary care setting. The required dose for each therapy is determined by patient body weight (bevacizumab), BSA (gemcitabine) or creatinine clearance rates (which are in turn dependent on patient age and weight; carboplatin: target area under curve [AUC] of 4 mg/ml/min).

To calculate the cost per visit for each drug, the manufacturer first calculated the quantity of drug needed based on individual patient age, weight, and/or BSA. To capture the quantity of drug used in the UK, the manufacturer used baseline characteristics from a UK cohort (Sacco *et al.*[69]) rather than the OCEANS study (see Section 5.3.3). Sacco *et al.*[69] reported BSA and age for each individual within the study, but did not report individual weight. To estimate individual weight, the manufacturer used a mathematical formula reported by Du Bois and Du Bois[85]:

$$bw = a \cdot \left(\frac{\alpha bsa}{\mu bsa}\right)^{\frac{1}{0.425}}$$

Where:

- bw = calculated individual body weight;
- a = overall mean weight (68.15 kg);
- αbsa = individual BSA available from Sacco *et al.*;
- μbsa = calculated mean BSA.

A summary of the dosages for bevacizumab, gemcitabine and carboplatin used within the economic model are presented in Table 44.

Table 44. Summary of the intervention and comparator drug dosages used in the model

	Bevacizumab	Gemcitabine	Carboplatin
Information required to estimate dose	Individual patient weight	Individual patient BSA	Creatinine clearance (target AUC of 4 mg/ml/min) based on individual patient weight and age
Dosage used within the economic model	Dosage = 15 mg per kg	Dosage = 1,000 mg per m^2	Dosage = β* ((0.85*(((140-a)*w)/(72*f)))+ 25) Where: β = target AUC of 4 mg/ml/min a = age w = weight f = serum creatinine (mg/dL) (Calvert *et al.*[86]; Cockcroft and Gault[87])
Abbreviations used in table: AUC, area under the curve; BSA, body surface area.			

The ERG notes that appropriate methodology and formulae were used to calculate the quantity of drug needed per patient. Furthermore, the ERG considers the use of UK population BSA from Sacco *et al.*[69] to be appropriate. As the ERG was unable to locate the reference for overall population body weight (68.15 kg), the impact of varying this parameter was investigated in sensitivity analysis (Section 6.1.4).

A summary of the intervention and comparator drug costs used within the model base case are presented in Table 45. The ERG notes that the cost for carboplatin included in the MS (pg 149;

£21.84 per 600 mg) does not reflect the cost used within the economic model, or within the BNF (£260 per 600 mg). The ERG assumes that the cost reported in the MS is a typographical error. In the base case, the manufacturer assumed that there would be no vial sharing for bevacizumab; however, the impact of bevacizumab vial sharing was explored by the manufacturer in sensitivity analysis (Section 5.3.13). By contrast, carboplatin and gemcitabine are routinely used in the NHS, and thus, in the base case, the manufacturer assumed that there would be vial sharing of these drugs.

Table 45. Costs of intervention and comparator drugs used in the model

Intervention	Vial size (mg)	Cost per vial	Cost per mg	Average dose per administration (mg)	Average total cost per administration
Bevacizumab	100	£242.66	£2.43	260	£2,556
	400	£924.40	£2.31	832	
Carboplatin	600	£260.00	£0.43	359	£155
Gemcitabine	1,000	£12.57	£0.01	1,713	£21
Abbreviation used in table: mg, milligram.					

The ERG notes that the cost of gemcitabine in the BNF for a 1,000 mg vial is £162.00.[73] The NICE Guide to the Methods of Technology Appraisal states that the public list price should be used in the base case analysis.[70] Therefore, the ERG conducted an analysis using the BNF public list price of gemcitabine 1,000 mg (£162.00). Additionally, the ERG sought clinical advice on the extent of vial sharing. The ERG was advised that whilst vial sharing occurs for some drugs, it is not appropriate to assume vial sharing for all drugs. The ERG therefore conducted a sensitivity analysis excluding the assumption of vial sharing for gemcitabine and carboplatin in the model.

The impact of using the list price of gemcitabine was small, with an increase in the ICER of £74 to £149,124 (Section 6.1.2; Analysis 12). To assess the impact of no vial sharing, the ERG used prices available in the BNF for alternative vial sizes (Table 46).[71] The impact of no vial sharing for gemcitabine and carboplatin was also small, with an increase in the ICER of £58 to £149,108 (Section 6.1.2; Analysis 13).

Table 46. Cost per vial for carboplatin and gemcitabine as reported in the BNF[73]

Intervention	Vial size (mg)	Cost per vial
Carboplatin	50	£22.04
	150	£56.92
	450	£168.85
	600	£260.00
Gemcitabine	200	£32.00
	1,000	£162.00
	1,500	£213.93
	2,000	£324.00
Abbreviations used in table: BNF, British National Formulary; mg, milligram.		

Cost of drug administration

Bevacizumab, gemcitabine and carboplatin are all administered in secondary care through intravenous infusion, and as such are associated with an administration cost. Within the economic model, the manufacturer accounted for administration costs associated with the drugs and the cost of pharmacy preparation of the infusions. The manufacturer assumed that each drug would require 6 minutes of pharmacy time to prepare. Thus, as the bevacizumab group received three drugs, it was assumed that 18 minutes of pharmacy time would be required.

The cost associated with preparation of infusions was taken from the Unit Costs of Health and Social Care (hospital pharmacist, including qualifications).[72] The cost of administration was sourced from NHS reference cost data[73] and differed between first and subsequent visits. Administration costs within the model are summarised in Table 47.

Table 47. Costs of drug administration and infusion preparation used in the model

Cost component	Unit cost	Cost per minute	Cost per visit	HRG code	Source
First cycle administration	£265.37	–	£265.37	(SB13Z): Deliver more complex parenteral chemotherapy at first attendance (day case)	National reference costs [73]
Subsequent cycles administration	£85.07	–	£85.07	(SB97Z): Same day chemotherapy admission/attendance (day case and regular day/night)	National reference costs [73]
Preparation of infusion	£46 per hour	£0.77	£4.60	N/A	Unit costs of health and social care [72]
Abbreviations used in table: HRG, Healthcare Resource Group; N/A, not applicable.					

The ERG notes that, in contrast to the economic model, the MS states that an additional 12 minutes (rather than 6 minutes) of pharmacy time were required for the preparation of each bevacizumab infusion (MS; pg 151). In addition, the ERG was unable to verify the citation of 12 minutes for infusion preparation time from the source referenced by the manufacturer. Furthermore, clinical advice received by the ERG suggests that it is likely that between 25 and 30 minutes of pharmacy time would be required to prepare one infusion. Consequently, during the clarification process, the ERG requested:

- clarification that the reference cited for 12 minutes pharmacy time was correct;
- a scenario analysis in which the 12 minutes additional pharmacy preparation time for bevacizumab (as stated in the MS) was implemented in the economic model;
- details of the manufacturer's rationale for assuming that the same amount of pharmacy time was required for all chemotherapy drugs.

The manufacturer did not present an updated scenario in which the preparation time was updated to 12 minutes. The ERG conducted this analysis and the ICER increased by £341 to £149,391 (Section 6.1.1; Analysis 5). In addition, the manufacturer was not able to provide an alternative reference for the 12 minutes pharmacy time, and responded that "the reference has been used extensively in previous assessments of bevacizumab in other indications and it is clear that uncertainty around the true pharmacy preparation time required has a very small impact on the total administration costs". As the ERG was unable to validate the reference, the ERG conducted an analysis reflecting clinical advice and modelled 25 minutes of infusion preparation time for each chemotherapy drug. The analysis generated an increase in the ICER of £818 to £149,868 (Section 6.1.2; Analysis 14).

Total intervention cost (drug costs plus administration costs)

The total cost of an intervention per visit was calculated as the sum of the individual costs of the drug, administration, and infusion preparation. The cost per visit for bevacizumab, gemcitabine, and carboplatin are presented in Table 48.

Table 48. Total costs of an intervention (drug and administration costs)

	Drug cost per visit	Administration cost per visit	Pharmacy cost per visit	Total cost per visit
Bevacizumab				
Cost of bevacizumab, carboplatin and gemcitabine (cycle one, first administration)	Bevacizumab: £2,556.65 Carboplatin: £155.43 Gemcitabine: £21.53	£265.37	£4.60 * 3 = £13.80	£3,012
Cost of gemcitabine (cycles one to six, day eight)	Gemcitabine: £21.53	£85.07	£4.60	£111
Cost of bevacizumab, carboplatin and gemcitabine (cycle two to six)	Bevacizumab: £2,556.65 Carboplatin: £155.43 Gemcitabine: £21.53	£85.07	£4.60 * 3 = £13.80	£2,832
Cost of bevacizumab (cycle seven onwards)	Bevacizumab: £2,556.65	£85.07	£4.60	£2,645
Placebo				
Cost of carboplatin + gemcitabine (cycle one, first administration)	Carboplatin: £155.43 Gemcitabine: £21.53	£265.37	£4.60 * 3 = £13.80	£456
Cost of gemcitabine (cycles one to six, day 8)	Gemcitabine: £21.53	£85.07	£4.60	£111
Cost of carboplatin + gemcitabine (cycle two to six)	Carboplatin: £155.43 Gemcitabine: £21.53	£85.07	£4.60 * 2 = £9.20	£271

Within the model, the manufacturer applied intervention costs (drug, administration and pharmacy infusion costs) to the number of patients who remained on therapy (bevacizumab and/or gemcitabine and carboplatin) in OCEANS, rather than the number of patients remaining in the PFS health state. In addition, the manufacturer restricted gemcitabine and carboplatin therapy to a maximum of 6 cycles. The model did not restrict the possible number of cycles of bevacizumab. The ERG was unclear

whether this reflected the likely use of bevacizumab in UK clinical practice. During the clarification process, the ERG asked the manufacturer to confirm how long after completion of the gemcitabine plus carboplatin regimen bevacizumab should be administered. The manufacturer confirmed that bevacizumab should be used in clinical practice up until disease progression, which is in contrast to the licensed indication for front-line treatment whereby bevacizumab is administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use as single agent until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier.

The ERG notes that the number of patients remaining on bevacizumab, gemcitabine and carboplatin therapy in OCEANS is fewer than the number of patients estimated to be within the PFS health state. This is because patients discontinued therapy in OCEANS after disease progression and for other reasons (e.g., unacceptable toxicity). A comparison of the average number of patients on treatment in the first 6 cycles (18 weeks) for each therapy versus the average PFS for the same time period is presented in Table 49 for information.

Table 49. Comparison of the proportion of patients remaining on treatment in OCEANS versus progression-free survival for bevacizumab, carboplatin and gemcitabine

Treatment group	Mean proportion of PFS for the first six cycles (18 weeks) of therapy	Mean proportion of patients remaining on therapy within six cycles (18 weeks)		
		Bevacizumab	Carboplatin	Gemcitabine
Bevacizumab	0.99	0.95	0.85	0.93
Placebo	0.97	N/A	0.87	0.93
Abbreviations used in table: N/A, not applicable; PFS, progression-free survival.				

The ERG considers that the number of patients remaining on therapy within OCEANS may more accurately reflect intervention usage in clinical practice than the number of patients with PFS because patients may discontinue therapy due to adverse events. The ERG also notes that the restriction of gemcitabine and carboplatin therapy to a maximum 6 cycles is reflective of UK clinical practice (Section 4.1.6). Therefore, the ERG accepted the manufacturer's base case assumption that the cost of therapy would reflect usage observed in OCEANS. However, the ERG notes that, although costs incorporated in the economic model reflected clinical practice (i.e. a maximum of six cycles of gemcitabine and carboplatin), the treatment effectiveness data used did not, and included data from patients who received up to 10 cycles of therapy. As discussed in Section 5.3.8, it is unclear what impact this would have on effectiveness results; however, the ERG notes that it has been reported that the number of cycles of chemotherapy is not expected to influence median OS.[23]

The ERG notes that the administration cost associated with gemcitabine was applied to the number of patients who received carboplatin. The ERG considers this to be a minor issue. The ERG conducted an analysis in which administration costs associated with gemcitabine were applied to gemcitabine

patients remaining on treatment. The impact on the ICER was small, with a £54 increase to £149,104 (Section 6.1.1; Analysis 6).

Supportive care cost

Patients within the PFS and PD health states were assumed to receive different levels of supportive care. The cost of supportive care was calculated from unit cost data reported in NHS reference costs.[73] Resource use was based on assumptions used in TA222 and expert opinion for PFS and PD, respectively. The resource use assumptions, Healthcare Resource Group (HRG) codes and resultant supportive care costs used in the manufacturer's model are summarised in Table 50. The ERG is satisfied that the HRG codes and resource use assumptions used by the manufacturer in the calculation of supportive care costs are appropriate.

Table 50. Cost of supportive care for progression-free survival and progressed disease health states used in the economic model (reproduced from MS; Table 43, pg 154)

Health states	Items	Frequency	Unit cost	HRG code	Average weekly cost
PFS	Outpatient visit to consultant oncologist	Once per month	£134	Outpatient attendance data (503; Gynaecological Oncology)	£30.92
	CT scan	Once every two months	£114	Weighted average of Outpatient CT scans (RA08Z-14Z)	£13.15
Total cost per weekly cycle					**£44.08**
PD	Outpatient visit to consultant oncologist	Once every three months	£134	Outpatient attendance data (503; Gynaecological Oncology)	£10.31
Total cost per weekly cycle					**£10.31**
Abbreviations used in table: CT, computerised tomography; HRG, Healthcare Resource Group; NHS, National Health Service; PFS, progression-free survival; PD, progressive disease.					

Cost of palliative care

The manufacturer captured the cost of palliative care within the model through application of costs from Guest *et al*.[74] Guest *et al*.[74] examined the treatment patterns and corresponding costs of healthcare resource use associated with palliative care for patients with different types of advanced cancer; from initiation of strong opioid treatment until death. Resource utilisation data associated with palliative care were obtained from the DIN-LINK database; DIN-LINK is an anonymised database of individual primary care records in the UK, from general practices that use a health information systems software program (iSOFT, formerly Torex; iSOFT Group, plc, Manchester, UK). Palliative care costs for ovarian cancer were estimated to be £4,789 per patient using costs from 2000–2001. The manufacturer inflated this cost to current prices (£6,727) using the Hospital and Community Health Services Pay and Pricing index.[72;74] The inflated cost was applied to all patients entering the death state. The ERG is satisfied that relevant palliative care costs were used and were correctly uplifted to current prices.

Cost of post-progression interventions

The manufacturer also captured the cost associated with treatments after disease progression. Patients could receive the following treatments as recommended by their physician:

- other chemotherapy drugs;
- radiotherapy;
- surgery.

Post-progression chemotherapy

Post-progression drugs were excluded from further costing in the model if they met any of the following criteria:

- equivalent duration and numbers of patients in both arms (costs and benefits likely to balance out);
- drugs received as part of a clinical trial (impossible to cost when price is unknown);
- only received by a single patient in one group (negligible impact on survival or cost);
- interventions not expected to impact survival (e.g., haemostasis drugs).

The total cost of chemotherapy drugs per patient was applied in the model engine as a one-off cost and was not subject to discounting. The total cost was estimated as follows:

$$\text{Total cost} = \frac{\left((ac \cdot na_{IV}) + (Cmg \cdot na_{D} \cdot Dpt)\right) \cdot n}{N}$$

Where:

- ac = cost of intravenous administration;
- na_{IV} = average number of intravenous administrations per patient;
- Cmg = average cost of drug per mg;
- na_{D} = average number of drug administration's per patient;
- Dpt = average dosage per patient (based on baseline characteristics such as age, weight and BSA);
- n = number of patients who had the drug post-progression;
- N = number of patients randomised to each group of OCEANS (N = 242).

Post-progression chemotherapy costs used in the model are summarised in Table 51.

Table 51. Post-progression chemotherapy costs included within the model

	Bevacizumab		Placebo	
Treatment	**Number of patients**	**Total cost (drug plus administration cost)**	**Number of patients**	**Total cost (drug plus administration cost)**
Anastrozole	3	£9	2	£9
Bevacizumab	27	£141,847	67	£418,076
Caelyx	14	£31,122	15	£29,393
Carboplatin	60	£15,278	44	£12,913
Cisplatin	16	£627	12	£439
Cyclophosphamide	6	£1,086	15	£2,308
Docetaxel	2	£1,430	4	£1,430
Doxorubicin	112	£20,687	121	£23,153
Etoposide	6	£2,588	11	£5,608
Gemcitabine	35	£13,143	38	£16,219
Irinotecan	2	£1,089	5	£1,307
Paclitaxel	53	£11,438	71	£16,166
Pemetrexed	4	£8,246	2	£4,123
Sorafenib	0	N/A	2	£9,580
Tamoxifen	9	£13	12	£13
Trabectedin	2	£251	1	£125
Temozolomide	1	£211	1	£105
Thalidomide	0	N/A	2	£2,558
Topotecan	58	£72,339	68	£90,162
Vinorelbine	1	£764	6	£4,584
Total patients receiving any subsequent anti-cancer therapy	**204**		**213**	
Total cost		**£322,167**		**£638,271**
Cost per patient in OCEANS (N = 242)		**£1,331**		**£2,637**
Abbreviation used in table: N/A, not applicable.				

During the clarification process, the ERG asked the manufacturer to verify the source of average BSA used in the calculation of dose for the relevant therapies listed in Table 51. The manufacturer confirmed that the number used within the model was incorrect and should link to the average BSA reported in Sacco *et al.*[69] (1.71 m^2). The ERG updated the analysis to reflect this; the impact of this correction was miniscule, and the estimated ICER reduced by £1 to £149,049 (Section 6.1.1; Analysis 7).

Post-progression radiotherapy

Post-progression radiotherapy was grouped into five categories; palliative; undefined; radiotherapy to the brain; radiotherapy to the pelvis; and radiotherapy to the spine. Each category was associated with a specific number of radiotherapy fractions. Calculation of the cost of delivering radiotherapy fractions was simplified by the manufacturer, with a single HRG code used regardless of the type of

radiotherapy delivered. The manufacturer's rationale for this was simplification of an otherwise complex distribution of cost calculations. The HRG code used was SC23Z "Deliver a fraction of complex treatment on a megavoltage machine", reported to cost £117.85. The total cost of radiotherapy was calculated as follows:

$$\text{Radiotherapy cost} = \frac{(nT_i \cdot nF_i \cdot HRc)}{N}$$

Where:

- nT_i = number of patients requiring radiotherapy for each radiotherapy type, i;
- nF_i = number of radiotherapy fractions delivered for each radiotherapy type, i;
- i = radiotherapy type (palliative, undefined, or radiotherapy to the brain, pelvis or spine);
- HRc = cost of radiotherapy defined by the HRG code (£117.85);
- N = number of patients randomised to each group (N= 242).

The total cost per patient of radiotherapy was estimated to be £63 and £66 per patient in the placebo and bevacizumab groups, respectively (Table 52).

Table 52. Post-progression radiotherapy costs included in the model

	Bevacizumab			Placebo		
Treatment	**Number of patients**	**Number of fractions per patient**	**Total cost (total fractions x £117.85)**	**Number of patients**	**Number of fractions per patient**	**Total cost (total fractions x £117.85)**
Palliative radiotherapy	3	1	£354	2	1	£236
Radiotherapy to brain	3	9	£3,182	2	9	£2,121
Radiotherapy to spine	5	10	£6,482[a]	0	10	£0
Radiotherapy to pelvis	2	15	£3,535	4	15	£7,071
Undefined radiotherapy	2	10	£2,357	5	10	£5,892
Total cost	£15,909			£15,320		
Average cost per patient (N = 242)	£65.74			£63.31		
[a] Note, one patient in the bevacizumab group had 15 fractions for spinal radiotherapy						

Post-progression surgery

The manufacturer reported that 14 patients in the bevacizumab group and 11 patients in the placebo group underwent surgical procedures in the OCEANS trial. Although there were 24 different surgical procedures carried out in total, the manufacturer used one HRG code for all the procedures (MB05A: gynaecological malignancy with length of stay of 1 day or more; £2,793). The total cost per patient of post-progression surgery was estimated as follows:

$$\text{Surgery cost} = \frac{nS \cdot HRc}{N}$$

Where:

- nS = number of patients requiring surgery in each arm;
- HRc = cost of surgery defined by the HRG code;
- N = number of patients randomised to each group (N = 242).

The cost of post-progression surgery used in the manufacturer's model was £162 (14 surgeries at £2,793 each, divided by 242) for patients in the bevacizumab group and £127 (11 surgeries at £2,793 each, divided by 242) for patients in the placebo group.

Total post-progression costs

All post-progression treatment costs were summed and applied as a one-off cost in the model. The estimated average cost per patient applied to each treatment group is summarised in Table 53.

Table 53. Total estimated costs of post-progression treatments for patients in the OCEANS study (reproduced from manufacturer's model)

Post-progression cost	Bevacizumab	Placebo
Subsequent lines of chemotherapy	£1,331	£2,639
Radiotherapy	£66	£63
Surgical procedures	£162	£127
Total	£1,559	£2,828

The ERG has two key concerns with the mean estimates of post-progression cost:

- date of the analysis;
- lack of discounting of post-progression costs within the model.

The ERG notes that the use of a less mature dataset (September 2010 rather than March 2012) to inform post-progression treatment costs may have led to inaccurate estimation of costs; post-progression therapies used after September 2010 would not be captured in this data set. During clarification, the ERG asked the manufacturer to provide a scenario analysis using the latest available

data (March 2012) for estimates of post-progression chemotherapy, surgery, and radiotherapy cost. The manufacturer did not provide this analysis stating that "the requested scenarios represent a request for further analyses and data. They are not clarifications of the data presented in the submission". The ERG is therefore unable to estimate an updated ICER; however, the ERG notes that the estimates of post-progression costs are likely to be underestimated, because the ERG considers it likely that patients would have received additional post-progression treatment after September 2010.

The ERG also notes that the costs of post-progression treatment were implemented as a one-off cost in the model. Therefore, these costs were not subjected to discounting. The ERG is concerned that this may result in a bias toward bevacizumab because the post-progression cost for the placebo group is greater than the bevacizumab group. During the clarification process, the ERG requested a scenario analysis in which post-progression treatment costs were applied at the point at which patients progressed, and were therefore subject to a discount rate. The manufacturer did not provide this analysis. For completeness, the ERG conducted this analysis. The result of this analysis was an increase in the ICER of £325 to £149,375 (Section 6.1.1; Analysis 2).

The ERG notes that the manufacturer's assumption that each individual intravenous drug was associated with an administration cost may have overestimated the cost of post-progression chemotherapy. The ERG considers that some therapies may have been administered concomitantly. To assess the impact of this assumption on post-progression chemotherapy costs, the ERG asked the manufacturer to indicate which treatments were taken concomitantly. The manufacturer stated that this information was contained within the model. However, the ERG considers that this information was not clear from the model, and that it is unclear what impact this would have on model results.

The ERG notes that the manufacturer simplified the estimation of costs of radiotherapy and surgery by assuming one HRG code for a radiotherapy fraction (SC23Z "Deliver a fraction of complex treatment on a megavoltage machine"; £117.85) and one HRG for a cost of surgery (MB05A: gynaecological malignancy with length of stay of 1 day or more; £2,793). The ERG considers that these assumptions are appropriate for simplicity; however, the ERG notes that the impact of varying these costs was not tested in one way sensitivity analysis. The ERG considered the impact of the cost of post-progression in deterministic and probabilistic sensitivity analysis (PSA; Section 6.1.4).

In addition, the ERG notes that, in contrast to the costs of post-progression treatments reported in the MS (£1,326 and £2,726 for bevacizumab and placebo, respectively: MS; pg 157), the costs used in the model were £1,331 and £2,637 for the bevacizumab group and placebo group, respectively. Due to a number of typographical errors found within the MS, the ERG considers that the model results are likely to be correct.

Cost of adverse events

The manufacturer's model accounted for the cost of Grade 3 and 4 adverse events occurring in greater than 2% of patients (regardless of treatment arm). However, Grade 3 and 4 adverse events that did not confer "significant additional cost for the health system, i.e. use of low cost generic medication" or that "clinical advice indicated that the usual treatment pathway for the adverse event was discontinuation of treatment" were excluded from the cost calculation.

Episodes of decreased neutrophil/white blood cell counts as a result of cytotoxic chemotherapy were assumed to be treated with a course of filgrastim (14 daily subcutaneous injections). The cost of and proportion of patients per treatment group who experienced each included adverse effect is presented in Table 54. Total cost of adverse events per intervention was the sum of each adverse event multiplied by the cost of each adverse event.

The total cost associated with adverse events was estimated at £224 and £146 for the bevacizumab and placebo groups, respectively. Costs were applied as a one-off cost and were not discounted. The costs of adverse events included in the model as described in the MS are presented in Table 54.

Table 54. List of adverse events and summary of costs included in the economic model (>2% incidence in either arm; adapted from MS; Table 44, pg 156)

Adverse event (Grade 3 unless otherwise stated)	**Bevacizumab**	**Placebo**	**Cost per episode**	**NHS Reference Costs 2010–2011[73]**
Epistaxis	6 (2.46%)	1 (0.4%)	£0	N/A
Fatigue	5 (2.05%)	3 (1.2%)	£0	N/A
Proteinuria	19 (7.79%)	0 (0%)	£0	N/A
Thrombocytopenia	15 (6.15%)	14 (5.58%)	£58	821 – blood transfusion
Thrombocytopenia (Grade 4)	15 (6.15%)	8 (3.19%)		
Leukopenia	8 (3.28%)	7 (2.79%)	£253	XD25Z – neutropenia drugs band 1
Neutropenia	40 (16.39%)	30 (11.95%)		
Neutropenia (Grade 4)	14 (5.74%)	9 (3.59%)		
Hypertension	33 (13.52%)	1 (0.4%)	£441	EB04I – hypertension without complications
Anaemia	14 (5.74%)	13 (5.18%)	£518	SA04F – iron deficiency anaemia without CC
Neutrophil count decreased	5 (2.05%)	8 (3.19%)	£738	Course of G-CSF (14 days subcutaneous injection with 30M units of Neupogen)
Neutrophil count decreased (Grade 4)	5 (2.05%)	3 (1.2%)		
White blood cell count decreased	1 (0.41%)	6 (2.39%)		
Total cost used in the model	**£224.11**	**£145.61**	–	–
Abbreviations used in table: CC, complications; G-CSF, granulocyte colony-stimulating factor; N/A, not applicable.				

The ERG notes that the manufacturer included a cost for "platelet count decreased" of £57.72 in the economic model (HRG 821 – blood transfusion[73]) but does not describe this cost within the MS. The ERG considers that it was appropriate to include this cost because the incidence was greater than 2% in the bevacizumab group; therefore, the ERG assumes that the omission of these costs from the MS was a typographical error.

The ERG also notes that the cost of "Neutrophil count decreased" (£738) was not applied in the model; the ERG considers this omission to be an error in the model. Additionally, the cost applied in the model for "White blood cell count decreased" was £253, not £738 as stated in the MS; the ERG also considers this omission to be an error in the model. The ERG updated the model to include both of these costs (Section 6.1.1; Analysis 8). The impact of this analysis was small; the ICER reduced by £84 to £148,966.

The total costs of adverse events per patient presented by the manufacturer for the bevacizumab and placebo group of £224.11 and £145.61, respectively, are based on the inclusion of "platelet count decreased" cost, "white blood cell count decreased" (at £253 rather than £738), and the exclusion of "Neutrophil count decreased" cost. The updated total costs of adverse events per patient as estimated by the ERG including the updates described above was £265.41 (bevacizumab group) and £211.98 (placebo group).

The ERG agrees with the manufacturer that inclusion of lower cost generic drugs would not affect overall costs in a meaningful way and agrees that it is appropriate to exclude these costs from the model. Furthermore, the ERG notes that in the base case model the manufacturer used the lowest cost (£52.71) associated with granulocyte colony-stimulating factor (G-CSF) and did not vary these costs in sensitivity analysis. Additionally, the manufacturer did not include a cost associated with administering the injection. The ERG notes that use of the lowest drug cost and excluding administration costs is likely to be a conservative assumption that biases against bevacizumab because the incidence of adverse events in which the G-CSF cost was used was greater in the placebo group compared with the bevacizumab group. The ERG considered the impact of varying the cost of a course of G-CSF in sensitivity analysis (Section 6.1.4).

Clinical opinion considered the HRG codes used by the manufacturer to be appropriate for the adverse events presented. As a sensitivity analysis, the ERG compared the cost of adverse events used in the model with the cost of adverse events used in TA222. TA222 reported estimates of costs for: thrombocytopenia (Grade 3 and 4), which was estimated to be £464 (SA13Z: Single Plasma Exchange, Leucophoresis or Red Cell Exchange); neutropenia Grade 3, which was estimated to be £137 (Gynaecological Oncology outpatient – Consultant Led: Follow Up attendance Non-Admitted Face to Face plus drugs); neutropenia Grade 4, which was estimated to be £2,149; and anaemia

(Grade 3 and 4), which was estimated to be £464. The ERG carried out a sensitivity analysis implementing these costs. The effect on the ICER was small, with an increase of £110 to £149,160 (Section 6.1.2; Analysis 15).

The ERG noted that all costs of adverse events used by the manufacturer, with the exception of hypertension, were estimated from the average cost for all activity, regardless of activity type (e.g., inpatient, outpatient, elective, or non-elective) within NHS reference costs. The cost of hypertension was taken from "non-elective, short stay data" as opposed to the average cost for all activity (£1,225). The ERG was unclear why the cost associated with hypertension was not taken from the average cost for all activity to be consistent; therefore, the ERG conducted a scenario analysis on this variable, setting the cost of hypertension to £1,225. The effect on the ICER was an increase of £432 to £149,482 (Section 6.1.2; Analysis 16).

In addition, the estimated adverse event costs were assigned to the first cycle of treatment in the submitted model and therefore were not subject to discounting. The ERG notes that this assumption is likely to bias against bevacizumab because the cost of adverse events is higher in the bevacizumab group compared with the placebo group.

Summary of resources and costs included in the model

- The manufacturer included the following costs in the economic model: drug; administration; supportive care; palliative care; post-progression treatments; adverse events;
- The total drug cost for bevacizumab, gemcitabine and carboplatin were calculated by multiplying the average quantity of drug required (based on estimates of age, weight, and BSA from a UK cohort) by the cost of the drug. The costs of bevacizumab and carboplatin were taken from the BNF; however, the cost of gemcitabine was taken from CMU EMit. A scenario analysis using the BNF cost of gemcitabine is presented in Section 6.1.2;
- The cost of gemcitabine and carboplatin estimated by the manufacturer assumed that vial sharing occurred in clinical practice. Clinical advice indicated that vial sharing could not be assumed; therefore, the ERG carried out a scenario analysis relaxing the assumption of vial sharing (Section 6.1.2);
- The cost of drug administration was taken from National Reference Costs.[73] The ERG noted a small error in the application of drug administration costs for gemcitabine, where drug administration costs were applied to the number of patients remaining on carboplatin (Section 6.1.1);
- The time associated with preparation of the infusion in the pharmacy was estimated by the manufacturer to be 6 minutes per infusion. The ERG was unable to verify the reference that the manufacturer used to support this assumption. Following clinical advice, the ERG carried out a scenario analysis assuming that pharmacy preparation time per infusion was 25 minutes (Section 6.1.2);
- The cost of drug and administration was applied to the number of patients on treatment in OCEANS rather than the number of patients with PFS. The ERG agrees that this was appropriate;

- Costs of supportive care were based upon assumptions around the number of outpatient visits and CT scans required (£44.08 per week in the PFS health state, £10.31 per week in the PD health state). The ERG agrees that these were reasonable;
- Cost of palliative care was taken from Guest *et al.*[74] The ERG agrees that the cost used was reasonable and was appropriately uplifted to current prices (£6,727 per patient);
- Cost of post-progression interventions included the cost of subsequent drug, radiotherapy, and surgery. The cost of post-progression treatment was estimated by the manufacturer to be £2,828 per patient in the placebo group and £1,559 per patient in the bevacizumab group. Post-progression treatment data was taken from the first analysis (September 2010); therefore, the ERG considers that the costs of post-progression therapies are likely to be underestimated. Moreover, post-progression costs were not subject to discounting which is likely to bias in favour of bevacizumab. The ERG carried out a scenario analysis applying a discount rate to these costs (Section 6.1.1);
- Adverse event costs were included as a one-off cost in the model for treatment-related adverse events with a 2% or higher incidence, excluding adverse events where treatment was likely to be given with lower cost generic drugs. Adverse event incidence was taken from the first data analysis in September 2010. The ERG also noted a number of inconsistencies between the costs applied in the model and the costs reported in the MS. The ERG carried out an analysis amending these figures (Section 6.1.1).

5.3.12 Cost effectiveness results

The manufacturer presented the base case results, calculated deterministically (using mean parameter values only) as well as probabilistically (assessing the simultaneous effect of parameter uncertainty). The ERG notes that an incremental analysis was performed; results from the manufacturer's deterministic and probabilistic incremental analyses are presented in Table 55.

Table 55. Base case incremental deterministic and probabilistic results (adapted from MS; Tables B11 and 50, pgs 168 and 171, respectively)

Intervention	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER (inc. cost per inc. LYG	ICER (inc. cost per inc. QALY)
Deterministic results								
Placebo	£14,912	2.96	1.98	–	–	–	–	–
Bevacizumab	£59,340	3.38	2.28	£44,428	0.42	0.298	£105,707	£149,050
Probabilistic results								
Placebo	£14,937	2.96	1.98	–	–	–	–	–
2.5% and 97.5% percentiles	£14,302 to £15,646	2.63 to 3.31	1.75 to 2.21	–	–	–	–	–
Bevacizumab	£59,368	3.38	2.28	£44,431	0.42	0.30	£140,124	£221,750
2.5% and 97.5% percentiles	£58,305 to £60,669	2.97 to 3.78	2.01 to 2.55	£43,882 to £45,105	–0.01 to 0.84	0.02, 0.57	–£163,277 to £725,369	£69,979 to £857,367
Abbreviations used in table: ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life years gained; QALYs, quality adjusted life years.								

The results of the deterministic and probabilistic analyses suggested that the estimated ICER for the bevacizumab group compared with the placebo group was £149,050/QALY (deterministic estimate) and £221,750/QALY (probabilistic estimate). The ERG notes that NICE advises that where models consist of non-linear combinations of parameters, probabilistic results are preferred because setting parameters to their mean values will not provide the correct estimates of mean costs and QALYs.[70] The ERG believes that the difference between the manufacturer's estimate of the deterministic and probabilistic ICER indicates non-linearity, and asserts that the probabilistic ICER is likely to provide a more reliable estimate of cost-effectiveness.

The manufacturer also presented detailed deterministic estimates of disaggregated costs and benefits for the bevacizumab and placebo groups (Table 56 and Table 57, respectively), and compared the modelled outcomes with the OCEANS trial outcomes at the September 2010 time point (Table 58).

Table 56. Summary of costs for each treatment by health state (adapted from MS; Table B9, pg 166)

Health state	Bevacizumab	Placebo	Increment
PFS	£50,118	£4,380	£45,738
PD	£2,712	£3,952	–£1,241
Total	£59,340	£14,912	£44,428
Abbreviations used in table: PD, progressed disease; PFS, progression-free survival.			

Table 57. Summary of QALYs gained for each treatment by health state (adapted from MS; Table B8, pg 166)

Health state	Bevacizumab	Placebo	Increment
PFS	0.879	0.616	0.263
PD	1.397	1.362	0.035
Total	2.276	1.978	0.298
Abbreviations used in table: PD, progressed disease; PFS, progression free survival; QALYs, quality adjusted life years.			

Table 58. Model outcomes compared with the clinical results of OCEANS (adapted from MS; Table B6, pg 165)

Outcome	Clinical trial result (median, months)	Model result (months)	Difference[a] (months)	% error in predictions
Placebo				
PFS	8.40	8.77	0.37	+4.4%
Post-progression survival	21.53	21.92	0.39	+1.8%
OS	29.93	30.69	0.76	+2.5%
Bevacizumab				
PFS	12.40	12.46	0.06	+0.5%
Post-progression survival	23.12	23.54	0.42	+1.8%
OS	35.52	36.00	0.48	+1.4%

[a] Difference = model – trial results

Abbreviations used in table: OS, overall survival; PFS, progression-free survival.

The model appears to over-predict the duration of PFS, PD, and OS relative to observed data in the OCEANS trial at the September 2010 clinical data cut-off, with overestimations of between 1.8% and 4.4% in the chemotherapy group and 0.5% to 1.8% in the bevacizumab group. The ERG notes that this results in an under-predicted relative difference in events between the bevacizumab group and the placebo group; for example, PFS was overestimated in the placebo group by 4.4% compared with the 0.5% overestimate observed in the bevacizumab group. The ERG notes that these results are based on modelling of data from September 2010. Thus, whereas the results of Table 58 imply that the estimated ICERs in the base case may be biased against bevacizumab, it was unclear whether this bias persisted if data from March 2012 were analysed. The ERG therefore requested an analogous analysis using data from the most recently available data set (March 2012). The manufacturer responded that "this scenario analysis is a request for further data and analysis rather than a request for clarification of the submission and is not supplied." The ERG is therefore unable to validate model outcomes compared with clinical outcomes from the latest available time point.

5.3.13 Sensitivity analyses

The manufacturer carried out deterministic and probabilistic sensitivity analyses to assess the impact of changes in the base case assumptions on the ICER. The following sections summarise the methods and results of each analysis.

Deterministic sensitivity analysis

The manufacturer presented results of one-way sensitivity analysis (OWSA) and results from a number of scenario analyses.

One-way sensitivity analysis

The manufacturer varied a selection of inputs in OWSA in relation to the deterministic ICER. The inputs varied, the upper and lower values used, and the resultant deterministic ICERs are summarised in Table 59. From the inputs varied by the manufacturer, the ICER ranged from between £126,671 (high value for PFS utility) and £202,027 (5-year time horizon).

Table 59. Results of one-way sensitivity analysis (adapted from MS; Table 49, pg 168)

		Estimates using lower input value				Estimates using upper input value			
Input	**Mean input value**	**Lower input value**	**Inc. QALYs**	**Inc. costs**	**ICER**	**Upper input value**	**Inc. QALYs**	**Inc. costs**	**ICER**
Base case			**0.298**	**£44,428**	**£149,050**		**0.298**	**£44,428**	**£149,050**
PFS utility[a]	0.718	0.574	0.245	£44,428	£181,035	0.862	0.351	£44,428	£126,671
PD utility[a]	0.649	0.519	0.291	£44,428	£152,610	0.779	0.305	£44,428	£145,653
Drug administration cost (first visit plus subsequent visits)[b]	£265 + £85	£172 + £0	0.298	£43,469	£145,832	£298 + £96	0.298	£44,546	£149,445
Cost of supportive care (PFS)[a]	£44	£35	0.298	£44,260	£148,486	£53	0.298	£44,596	£149,614
Cost of supportive care (PD)[a]	£10	£8	0.298	£44,422	£149,031	£12	0.298	£44,434	£149,070
Time horizon[c]	10 years	5 years	0.218	£44,064	£202,027	15 years	0.317	£44,494	£140,305
Costs and benefits discount rate[d]	3.5%	0%	0.336	£44,874	£133,671	6%	0.275	£44,129	£160,239

[a] Varying through upper and lower 20% of the mean estimate.

[b] Varying through upper and lower quartiles.

[c] Varying through upper and lower 50% of the mean estimate.

[d] Varying using NICE reference case guidance.

Abbreviations used in table: ICER, incremental cost-effectiveness ratio; Inc., incremental; NICE, National Institute for Health and Clinical Excellence; PD, progressed disease; PFS, progression-free survival; QALY, quality adjusted life year.

The manufacturer did not vary the following parameters in OWSA:

- average weight of the UK population (68.15 kg) used in the estimation of individual weight;
- cost of pharmacy infusion preparation;
- cost of palliative care;
- cost of adverse events;
- cost of post-progression therapy.

Scenario analyses

The manufacturer investigated the impact on the ICER of the following scenario analyses:

- vial sharing of bevacizumab permitted;
- using patient baseline characteristics of age, weight and BSA from OCEANS (with and without bevacizumab vial sharing);
- alternative forms of parametric extrapolation for PFS (Kaplan–Meier plus a log-logistic tail, Weibull);
- alternative forms of parametric extrapolation for OS (Kaplan–Meier plus a log-logistic tail, Weibull);
- time on therapy using PFS data, rather than OCEANS data;
- assuming no progressive disease treatment costs;
- assuming no palliative care costs;
- assuming no costs of adverse events.

The ICER for these scenarios ranged between £141,722 (vial sharing of bevacizumab permitted) and £191,842 (alternative parametric form for OS). The results of each of the scenario analyses are summarised in Table 60. The ICER for these scenarios ranged between £141,722 (vial sharing of bevacizumab permitted) and £191,842 (alternative parametric form for OS).

Table 60. Results of the scenario analyses (adapted from MS; Tables 49, 51, and 52)

Scenario	Inc. QALYs	Inc. costs	ICER
Base case (deterministic estimate)	**0.298**	**£44,428**	**£149,050**
Vial sharing of bevacizumab permitted	0.298	£42,244	£141,722
Using patient baseline characteristics of age, weight and BSA from OCEANS (no bevacizumab vial sharing)	0.298	£47,859	£160,561
Using patient baseline characteristics of age, weight and BSA from OCEANS (bevacizumab vial sharing permitted)	0.298	£45,785	£153,603
Alternative forms of parametric extrapolation for PFS (Kaplan–Meier plus a log logistic tail from month 24)	0.300	£44,488	£148,074
Alternative forms of parametric extrapolation for PFS (Weibull)	0.297	£44,403	£149,461
Alternative forms of parametric extrapolation for OS (Kaplan–Meier plus a log logistic tail from month 35)	0.231	£44,394	£191,842
Alternative forms of parametric extrapolation for OS (Weibull)	0.268	£44,470	£165,683
Time on therapy using PFS data rather than OCEANS data	0.298	£56,596	£189,873
Assuming no progressive disease treatment costs	0.298	£45,697	£153,308
Assuming no palliative care costs	0.298	£44,498	£149,285
Assuming no costs of adverse events	0.298	£44,349	£148,787
Abbreviations used in table: BSA, body surface area; ICER, incremental cost-effectiveness ratio; Inc., incremental; OS, overall survival; PFS, progression-free survival; QALYs, quality adjusted life years.			

The manufacturer concluded within the submission that "the results of the deterministic sensitivity analysis demonstrated the insensitivity of the model to estimates of disease management costs for PFS and PD health states, inclusion of costs associated with management of adverse events and palliative

care or post-progression treatments"; "The model was most sensitive to assumptions around the modelling of OS, the duration of treatment and the utility of patients in PFS" (MS; p174).

The ERG notes that no scenario analysis investigated within the deterministic sensitivity analysis resulted in an ICER of less than £126,000. However, the ERG notes that a number of inputs were not varied in OWSA (e.g., costs of pharmacy infusion preparation, palliative care, adverse events, or post-progression therapy). For completeness, the ERG conducted an OWSA including these variables (Section 6.1.4).

Probabilistic sensitivity analysis

Model parameter uncertainty was explored using PSA. Individual parameters within the model were assigned a probability distribution from which estimates were simultaneously sampled for 5,000 iterations. The inputs varied in PSA and the assigned distributions are outlined in Table 61. In PSA, for scenarios where PFS was estimated to be greater than OS, the manufacturer assumed that OS was equal to PFS (i.e. the proportion of patients in PD was 0%).

Table 61. Inputs and probability distributions used in probabilistic sensitivity analysis

Input	Mean estimate	Probability distribution
PFS log-logistic survival function	β_1: 2.52 (SE 0.04) β_2: –0.37 (SE 0.05) γ: 0.33 (SE 0.01)	Parameters varied using the covariance matrix estimated from log-logistic survival analysis
OS log-logistic survival function	β_1: 3.58 (SE 0.07) β_2: -0.16 (SE 0.08) γ: 0.39 (SE 0.03)	Parameters varied using the covariance matrix estimated from log-logistic survival analysis
PFS utility	0.72 (95% CI: 0.70 to 0.74)	Beta distribution
PD utility	0.65 (95% CI: 0.61 to 0.69)	Beta distribution
Weekly cost of supportive care (PFS)	£44.08	Gamma distribution
Weekly cost of supportive care (PD)	£10.31	Gamma distribution
Adverse event rates	Event rates for adverse events included in the model	Beta distribution
β_1, Intercept, β_2, covariate for placebo, γ, scaling factor. Abbreviations used in table: CI, confidence interval; OS, overall survival; PD, progressed disease; PFS, progression-free survival; SE, standard error.		

The following inputs were not varied in PSA:

- average dose of bevacizumab, gemcitabine and carboplatin required;
- pharmacy infusion preparation costs;
- cost of adverse events included in the model;
- duration or costs of treatments received following progression (i.e., post-progression treatments and palliative care costs).

The ERG notes that the MS states that costs and frequency of adverse events were included in PSA using a gamma distribution. From review of the economic model, the ERG believes that the frequency of adverse events was varied in PSA using a beta distribution and adverse event cost was not varied. The ERG notes that the manufacturer did not provide a rationale for excluding the above inputs from the PSA. As part of the clarification process, the ERG requested an updated sensitivity analysis. The manufacturer responded that "The request for an update of the PSA parameters to include costs of post-progression therapies and palliative care however, is outside the scope of the clarification letter as it represents a request for further analyses and data".

Figure 10 and Figure 11 present the cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC) for the addition of bevacizumab to gemcitabine and carboplatin compared with gemcitabine and carboplatin alone, in the treatment of recurrent ovarian cancer. In Figure 10, the line on the graph indicates an ICER of £30,000.

Figure 10. Cost-effectiveness plane for addition of bevacizumab to carboplatin/gemcitabine combination therapy (white triangle; deterministic estimate) (reproduced from MS; Figure 22, pg 170)

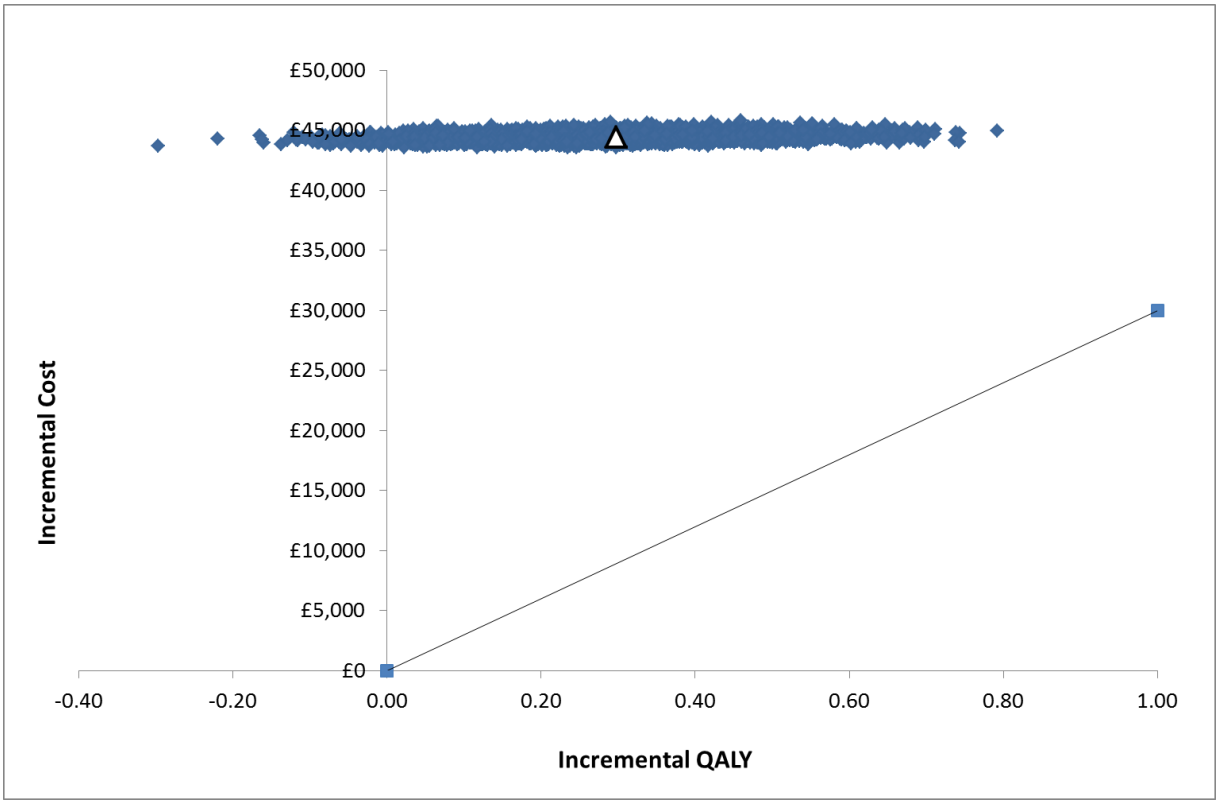
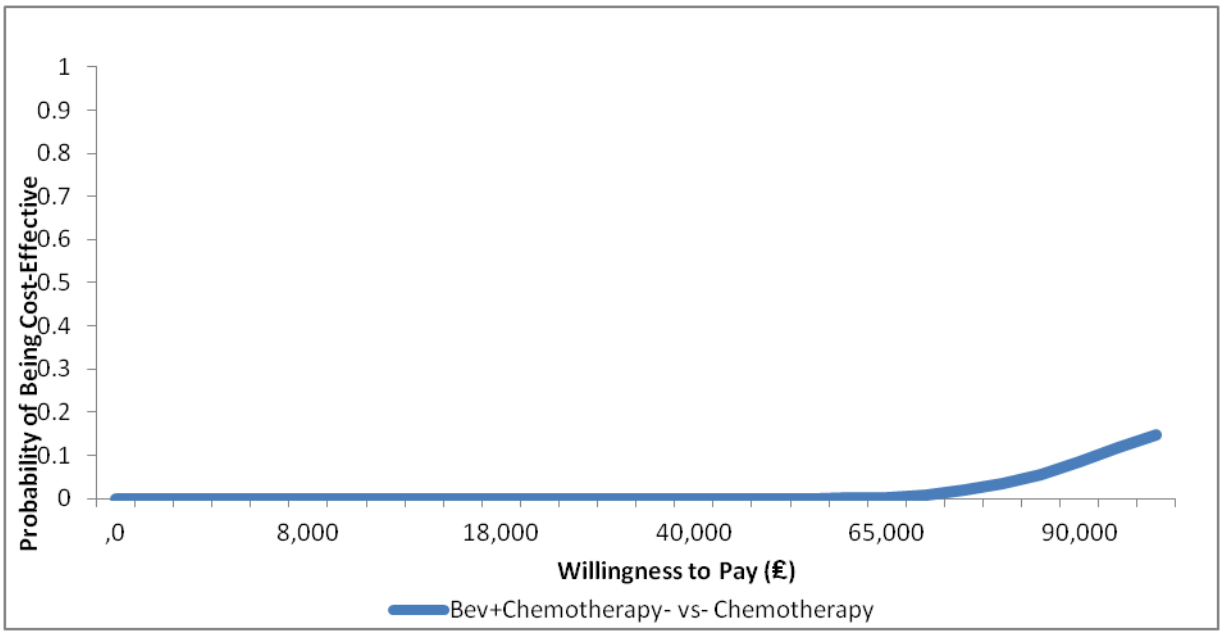


Figure 11. Cost-effectiveness acceptability curve (reproduced from manufacturer's model)



The manufacturer summarised the results of the PSA as follows (MS; pg 170): "There is a 0.0% chance of the addition of 15mg/kg bevacizumab to carboplatin/gemcitabine combination therapy being considered cost-effective at a willingness to pay threshold of £30,000 per QALY. At a willingness to pay threshold of £100,000 per QALY, this rises to 14.7%".

For completeness, the ERG conducted PSA including the variables excluded from the manufacturer's PSA (Section 6.1.4).

5.3.14 Model validation and face validity check

The manufacturer stated that internal validation and debugging was undertaken by an external agency: Outcomes International (MS; pg 175). The following measures were taken to check and validate the integrity of the model:

- checked for completeness of the results by comparing with relevant publications in ovarian cancer;
- extreme value testing of model parameters to ensure that the results were logical and made intuitive sense.

The ERG notes that details of model validation reported within the MS were limited and that there was no mention of clinical expert involvement for the validation of model structure or inputs. Overall, the ERG considers it important to note there were no major errors identified in the operation of the model; however, a number of minor errors and inconsistency of reporting between the MS and the economic model were identified.

The ERG notes that the modelled results for bevacizumab and its comparators were higher than the trial results at the September 2010 time point. For example, compared with September 2010 OCEANS trial results, the duration of PFS, PD and OS were higher for the bevacizumab group by 0.12, 0.42 and 0.48 months, respectively. The ERG notes that it is expected that there would be some discrepancy between observed trial events and those predicted from a model as model results are constrained by the assumptions used. However, the ERG notes that the model under-predicts the relative difference between the bevacizumab and placebo group. Therefore, for the initial 30 months of modelled time horizon, the model may be considered conservative; however, the ERG was unable to establish the impact of using March 2012 data on model predictions because the manufacturer did not provide these data.

6 ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 Additional economic analyses

The Evidence Review Group (ERG) identified several adjustments and some alternative model inputs for the manufacturer's base case evaluation of the addition of bevacizumab to gemcitabine and carboplatin combination therapy. Section 6.1.1 presents the results of a number of model corrections, Section 6.1.2 presents the results of a number of scenario analyses, and Section 6.1.3 presents the ERG's revised base case ICER. The sensitivity of the base case ICER to changes in model inputs are explored in Section 6.1.4.

Section 6.1.5 presents the results of exploratory analyses estimating an incremental cost-effectiveness ratio (ICER) for the comparison of bevacizumab in combination with gemcitabine and carboplatin versus: paclitaxel in combination with carboplatin; PLDH in combination with carboplatin; carboplatin as monotherapy.

6.1.1 Model corrections

The ERG the following corrections to the manufacturer's base case ICER:

- updating the estimation of palliative care cost discounting;
- applying post-progression treatment costs (chemotherapy, radiotherapy and surgery) at the point of progression, with these costs subject to discounting;
- correcting the application of half-cycle correction within the model;
- correcting the body surface area (BSA) used for calculation of post-progression treatment costs to the average BSA found in Sacco *et al*.[69] (1.71 m^2);
- amending the sample size applied to adverse event rates in the model to those of the safety-evaluable population (placebo group = 233, bevacizumab group = 247);
- applying the cost outlined in the manufacturer's submission (MS; £738) for the "neutrophil count decreased" and "white blood cell count decreased" adverse events instead of the £0 and £253 applied in the model, respectively;
- applying the cost of gemcitabine administration to the number of patients on gemcitabine treatment, rather than the number of patients on carboplatin;
- applying an additional 12 minutes of pharmacy infusion preparation time for bevacizumab as outlined in the MS, rather than the additional 6 minutes of pharmacy infusion preparation time included in the economic model.

Results of the model corrections are presented in Table 62. The ICER including model corrections was estimated to be £147,368. This represents a reduction in the manufacturer's deterministic base case ICER of £1,682.

Table 62. Additional economic analyses conducted by the ERG: model corrections

Analysis		Intervention	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER for individual scenario	ICER including previous scenario
Manufacturer's base case (deterministic)		**Placebo**	**£14,912**	**1.98**	**–**	**–**	–	–
		Bevacizumab	**£59,340**	**2.28**	**£44,428**	**0.30**	**£149,050**	–
1	Discounting final costs and QALYs	Placebo	£14,350	1.98	£44,332	0.30	£148,728	*N/A*
		Bevacizumab	£58,681	2.28				
2	Applying post-progression treatment costs at the point of progression	Placebo	£14,612	1.98	£44,525	0.30	£149,375	*£149,052*
		Bevacizumab	£59,136	2.28				
3	Correcting the application of half-cycle correction within the model	Placebo	£14,887	1.98	£43,851	0.30	£147,115	*£147,117*
		Bevacizumab	£58,738	2.28				
4	Correcting the sample size applied to AE rates in the model to those of the safety-evaluable population	Placebo	£14,924	1.98	£44,414	0.30	£149,003	*£147,070*
		Bevacizumab	£59,338	2.28				
5	Applying 12 minutes of pharmacy infusion preparation time for bevacizumab as outlined in the MS, rather than 6 minutes of pharmacy infusion preparation time included in the model	Placebo	£14,912	1.98	£44,529	0.30	£149,391	*£147,404*
		Bevacizumab	£59,442	2.28				
6	Applying cost of gemcitabine administration to the number gemcitabine patients	Placebo	£14,958	1.98	£44,444	0.30	£149,104	*£147,472*
		Bevacizumab	£59,402	2.28				
7	Correcting BSA used for calculation of post-progression treatment costs (to 1.71 m^2)	Placebo	£14,916	1.98	£44,427	0.30	£149,049	*£147,471*
		Bevacizumab	£59,344	2.28				
8	Applying the cost outlined in the MS (£738) for the "neutrophil count decreased" and "white blood cell count decreased" AEs instead of the £0 and £253 applied in the model, respectively	Placebo	£14,979	1.98	£44,403	0.30	£148,966	*£147,368*
		Bevacizumab	£59,382	2.28				
9	All model corrections	Placebo	£14,156	1.98	£43,926	0.30	**£147,368**	
		Bevacizumab	£58,083	2.28				

Abbreviations used in table: AE, adverse event; BSA, body surface area; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; MS, manufacturer's submission; N/A, not applicable; QALYs, quality adjusted life years.

6.1.2 Scenario analyses

The ERG modelled the following scenarios:

- modelling progression-free survival (PFS) using Kaplan–Meier data only (assuming 0% survival for the placebo group at month 29);
- assuming overall survival (OS) was the same for the placebo group as the bevacizumab group;
- assuming no vial sharing of gemcitabine and carboplatin;
- applying 25 minutes pharmacy preparation time per infusion for bevacizumab, carboplatin and gemcitabine;
- updating the cost of gemcitabine to £162 for 1,000 mg (source: British National Formulary [BNF]);
- applying costs of adverse events from TA222;
- applying the cost of hypertension adverse event using overall average activity cost from National Health Service (NHS) reference costs (£1,225).

Results of the above scenario analyses are presented in Table 64. The estimated ICERs ranged between £149,108 (assuming no vial sharing of carboplatin and gemcitabine) and £1,749,614 (assuming OS was the same in the placebo group as the bevacizumab group).

The ERG also investigated the effect of applying disutilities associated with adverse events. The ERG conducted an analysis assessing a range of average duration of adverse event disutilities. The results of this analysis are presented in Table 63. For an average adverse event duration of 1 week, the deterministic ICER increased by £341 to £149,391, for an average adverse event duration of 1 month, the ICER increased by £1,494 to £150,544.

Table 63. Effect of adverse event disutility duration on the manufacturer's base case ICER

	Average duration of disutility (all adverse events)					
	0 weeks	**1 week**	**2 weeks**	**1 month**	**2 months**	**3 months**
Incremental cost[a]	£44,428	£44,428	£44,428	£44,428	£44,428	£44,428
Incremental QALYs[a]	0.298	0.297	0.297	0.295	0.292	0.289
ICER	£149,050	£149,391	£149,734	£150,544	£152,068	£153,623

[a] bevacizumab group minus placebo group

Abbreviations used in table: ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years.

Table 64. Additional economic analyses conducted by the ERG: scenario analyses

Analysis		Intervention	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER for individual scenario	ICER including model corrections
Manufacturer's base case (deterministic)		**Placebo**	**£14,912**	**1.98**	**£44,428**	**0.30**	**£149,050**	*N/A*
		Bevacizumab	**£59,340**	**2.28**				
10	Modelling PFS using only Kaplan–Meier data	Placebo	£14,834	1.98	£44,398	0.30	£149,539	*£147,851*
		Bevacizumab	£59,232	2.27				
11	Assuming OS was the same for the placebo group as the bevacizumab group	Placebo	£15,068	2.25	£44,272	0.03	£1,749,614	*£1,736,361*
		Bevacizumab	£59,340	2.28				
12	Cost of gemcitabine 1,000 mg at £162 (source: BNF)	Placebo	£17,839	1.98	£44,450	0.30	£149,124	*£147,411*
		Bevacizumab	£62,289	2.28				
13	Assuming no vial sharing of gemcitabine and carboplatin	Placebo	£17,181	1.98	£44,445	0.30	£149,108	*£147,402*
		Bevacizumab	£61,626	2.28				
14	Including 25 minutes pharmacy preparation time per infusion	Placebo	£15,149	1.98	£44,672	0.30	£149,868	*£147,841 (excluding analysis 5 Table 62)*
		Bevacizumab	£59,821	2.28				
15	Applying costs of adverse events from TA222	Placebo	£15,010	1.98	£44,460	0.30	£149,160	*£147,447*
		Bevacizumab	£59,471	2.28				
16	Applying the cost of hypertension using overall average activity cost from NHS reference costs (£1,225)	Placebo	£14,916	1.98	£44,557	0.30	£149,482	*£147,793*
		Bevacizumab	£50,472	2.28				

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

6.1.3 ERG base case ICER

The ERG deterministic and probabilistic revised base case ICERs were estimated to be £148,360 and £212,079 respectively (Table 65). The ERG's revised deterministic and probabilistic base case ICERs were comparable to the manufacturer's estimates (£149,050 and £221,750, respectively). The revised base case ICERs incorporated model corrections (Table 62) and the following scenarios:

- PFS estimated using Kaplan–Meier data (Analysis 10, Table 64);
- Cost of gemcitabine taken from the BNF, £162 for 1,000 mg (Analysis 12, Table 64);
- Assuming no vial sharing of gemcitabine and carboplatin (Analysis 13, Table 64);
- Including 25 minutes pharmacy preparation time per infusion (Analysis 14, Table 64).

The parameters used for the probabilistic ICER are described in Section 6.1.4. The base case ICER did not incorporate an assumption that OS was the same for both the bevacizumab and the placebo groups (Analysis 11, Table 64) or an estimate of adverse event disutility (Table 63). Although the ERG believes that the OS benefit associated with bevacizumab is overestimated in the manufacturer's base case, without data from March 2012, the ERG is unable to comment with confidence on the degree of the overestimate. Similar for adverse event disutility, although the ERG believes that the QALY gain for the bevacizumab group was overestimated in the base case because the manufacturer did not account for adverse event disutilities, the degree of the overestimate is unclear. The ERG therefore considers it likely that the true ICER is higher than the ERG's revised base case estimate. Incorporation of the assumption of equivalent OS to the ERG's revised base case resulted in a deterministic ICER of £1,826,779 (£44,059 incremental cost and 0.02 additional QALYs per patient for the bevacizumab group compared with the placebo group).

Table 65. ERG base case ICER

Intervention	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	Inc. cost per inc LYG	Inc. cost per inc. QALY
Deterministic results								
Placebo	£16,571	3.14	1.98	–	–	–	–	–
Bevacizumab	£60,618	3.62	2.27	£44,048	0.48	0.30	£92,362	£148,360
Probabilistic results								
Placebo	£16,593	3.14	1.77	–	–	–	–	–
2.5% and 97.5% percentiles	£15,031, £18,172	2.75, 3.54	0.85, 2.62	–	–	–	–	–
Bevacizumab	£60,518	3.62	2.04	£43,925	0.47	0.27	£193,951	£212,079
2.5% and 97.5% percentiles	£51,980, £68,774	3.16, 4.09	1.06, 2.96	£35,690, £51,915	0.01, 0.95	–0.01, 0.57	£34,290, £643,795	–£314,539, £982,628
Abbreviations used in table: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life years gained; QALY, quality-adjusted life year.								

6.1.4 Additional sensitivity analyses

One-way sensitivity analysis (OWSA) was carried out on the manufacturer's base case deterministic estimate, and the ERG deterministic base case (Table 66). Inputs were varied between their upper and lower 95% Confidence Intervals (95% CIs) or upper and lower quartiles where available, and an upper and lower 20% value if this information was not available. The discount rates were varied between 0% and 6% and the time horizon between 5 years and 15 years, as per the manufacturer's sensitivity analysis. The most sensitive variables from OWSA are presented in Table 66. For the manufacturer's base case, results showed that the model was sensitive to the time horizon and the average body weight of the UK cohort from Sacco *et al*.[69]. The ICER did not fall below £120,000 for any parameter. The results of the OWSA for the ERG base case were similar and no scenario resulted in an ICER below £120,000.

Table 66. One-way sensitivity analysis results

Input	Model base case value	Lower estimate	Upper estimate	ICER with lower estimate	ICER with upper estimate
Manufacturer's base case deterministic ICER	**£149,050**				
Time horizon	10	5	15	£202,028	£140,305
Assumed average body weight of UK cohort	68.15	54.52	81.78	£120,630	£176,252
Benefit discount rate	3.5%	0%	6%	£132,267	£161,375
PFS utility	0.72	0.70[a]	0.74[a]	£152,618	£145,646
Subsequent cycle administration cost	£85.07	£0[b]	£96[b]	£145,832	£149,446
Post-progression treatment cost per patient (placebo)	£2,828	£2,262	£3,393	£150,948	£147,153
Cost discount rate	3.5%	0%	6%	£150,632	£148,002
Post-progression treatment cost per patient (bevacizumab)	£1,559	£1,247	£1,870	£148,005	£150,096
ERG's base case deterministic ICER	**£148,360**				
Time horizon	10	5	15	£201,370	£139,610
Assumed average body weight of UK cohort	68.15	54.52	81.78	£120,186	£175,325
Benefit discount rate	3.5%	0%	6%	£131,794	£160,520
PFS utility	0.72	0.70[a]	0.74[a]	£151,755	£145,114
Post-progression treatment cost per patient (placebo)	£2,831	£2,265	£3,398	£150,064	£146,656
Subsequent cycle administration cost	£85	£0[b]	£96[b]	£145,151	£148,754
Cost discount rate	3.5%	0%	6%	£149,851	£147,384
PD utility	0.65	0.61[a]	0.69[a]	£149,716	£147,063

[a] 95% Confidence intervals.

[b] Upper and lower quartiles

Abbreviations used in table: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; mg, milligram; PD, progressed disease; PFS, progression-free survival.

The ERG conducted probabilistic sensitivity analysis (PSA) on the ERG's revised base case. The distributions selected for each variable are presented in Appendix 14. In addition to including additional variables in the sensitivity analysis, the ERG also amended the manufacturer's analysis to use the standard error around the utility values to inform the beta distribution parameters. The average probabilistic ICER was estimated to be £212,079 per QALY. This was similar to the manufacturer's estimated probabilistic ICER of £221,750. Figure 12 and Figure 13 present the cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC) for the addition of bevacizumab to gemcitabine and carboplatin compared with gemcitabine and carboplatin alone, in the treatment of recurrent ovarian cancer. In Figure 12, the line on the graph indicates an ICER of £30,000.

The inclusion of additional parameters within the PSA resulted in a wider distribution of incremental cost estimates when compared with the manufacturer's original PSA; however, the overall conclusions of the PSA were similar to the manufacturer's results. At a willingness to pay (WTP) threshold of £30,000 per QALY, the ERG estimated that there was a 0% chance that the addition of 15 mg/kg bevacizumab to carboplatin/gemcitabine combination therapy would be considered cost-effective. At a WTP threshold of £100,000 per QALY, the probability increased to 11.5%.

Figure 12. Cost-effectiveness plane for the ERG base case probabilistic sensitivity analysis (line represents ICER of £30,000)

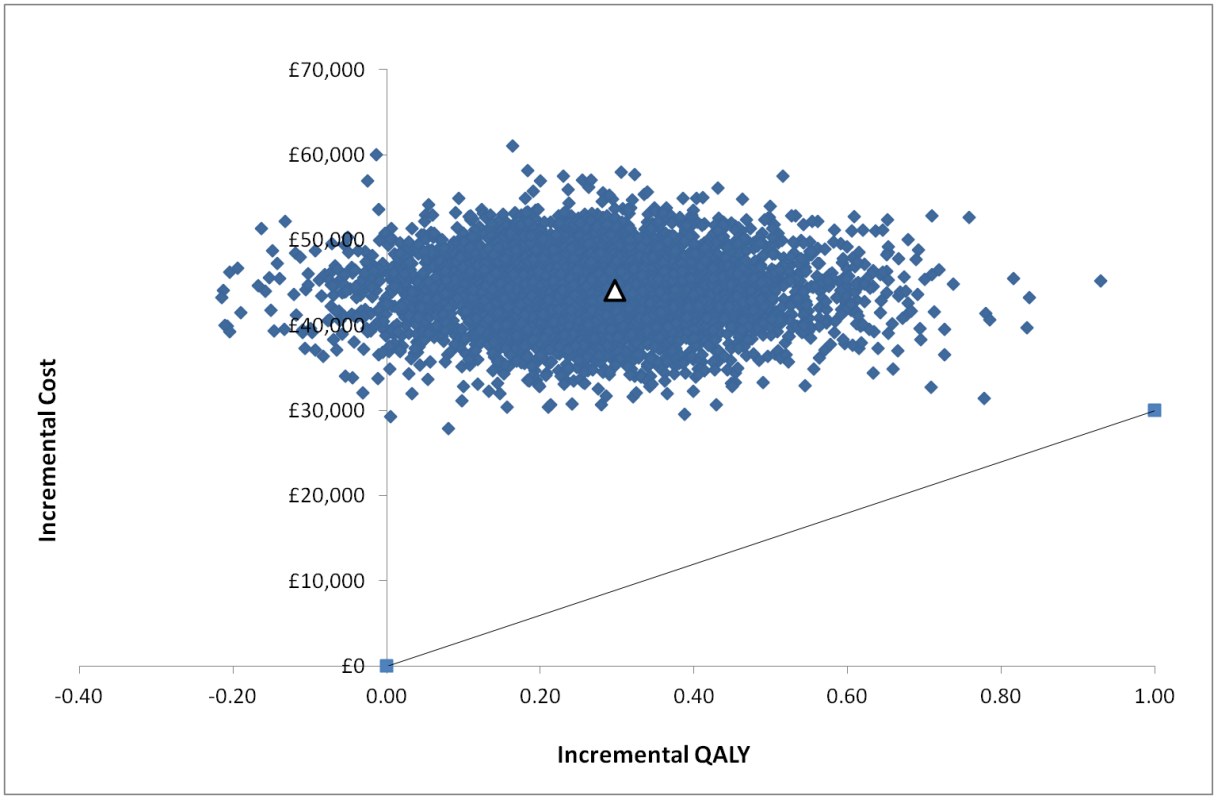
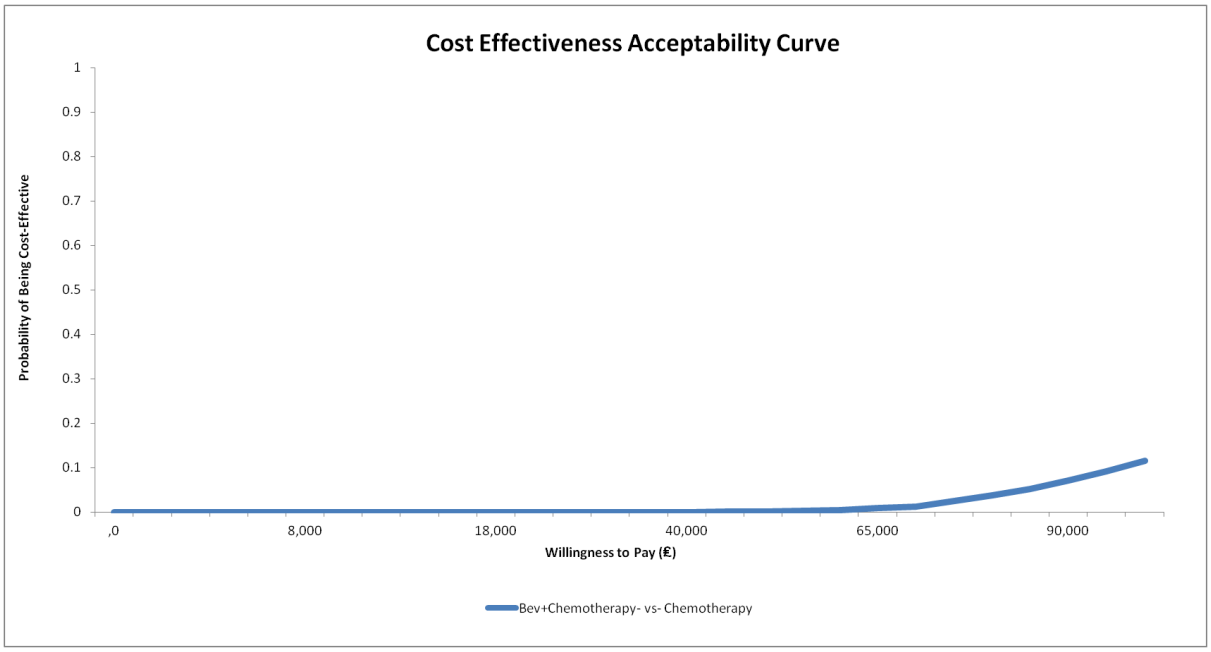


Figure 13. Cost-effectiveness acceptability curve for the ERG base case probabilistic sensitivity analysis



6.1.5 Exploratory analysis of bevacizumab cost-effectiveness versus alternative comparators

The manufacturer did not compare the clinical and cost-effectiveness of bevacizumab in combination with gemcitabine and carboplatin against three of the four comparators outlined in the NICE scope:[26]

- paclitaxel in combination with a platinum compound;
- pegylated liposomal doxorubicin hydrochloride (PLDH) in combination with a platinum compound;
- platinum-based chemotherapy as monotherapy.

As noted in Section 2.2, clinical opinion stated that around 50% of women with recurrent advanced ovarian cancer would be treated with paclitaxel in combination with a platinum compound. The ERG considers, therefore, that omission of a comparison with paclitaxel in combination with a platinum compound represents an important limitation when considering the cost-effectiveness of bevacizumab in UK clinical practice. In addition, clinical advice has indicated that PLDH in combination with a platinum compound is likely to be increasingly used in clinical practice and is therefore an important comparator.

The ERG conducted an NMA to investigate the comparative effectiveness of bevacizumab in combination with gemcitabine and carboplatin versus the comparators listed in the final scope issued by NICE. The ERG conducted the analysis around the PFS outcome measure. The results of the analysis implied that bevacizumab in combination with gemcitabine and carboplatin was associated

with a statistically significant increase in PFS when compared with each of the comparators outlined in the NICE scope (Section 4.3). The results of this analysis additionally implied that:

- there was no statistically significant difference in PFS between paclitaxel in combination with carboplatin versus gemcitabine in combination with carboplatin; the hazard ratio (HR) was estimated to be 0.978 (paclitaxel plus carboplatin versus gemcitabine plus carboplatin) with 95% Credible Interval (CrI) 0.753 to 1.263;
- there was no statistically significant difference in PFS between PLDH in combination with carboplatin versus gemcitabine in combination with carboplatin; the HR was estimated to be 1.198 (PLDH plus carboplatin versus gemcitabine plus carboplatin) with 95% CrI 0.893 to 1.580;
- there was a statistically significant difference in PFS between platinum therapy alone and gemcitabine plus carboplatin; the HR was estimated to be 0.723 (carboplatin versus gemcitabine plus carboplatin) with 95% CrI 0.580 to 0.89.

In the following sections the ERG explores the comparison of bevacizumab with the remaining comparators within the NICE scope. The ERG notes that the analysis is limited to observations around PFS, because an NMA was not conducted to explore OS. The results of the cost-effectiveness analyses should therefore be interpreted with caution.

Paclitaxel and carboplatin

The NMA results indicated a lack of statistical significance between paclitaxel in combination with carboplatin versus gemcitabine in combination with carboplatin, in terms of PFS. Therefore, the ERG conducted an exploratory analysis of bevacizumab in combination with gemcitabine and carboplatin versus paclitaxel in combination with carboplatin and made the following assumptions:

- OS and PFS estimates for paclitaxel plus carboplatin were assumed to be the same as OS and PFS estimates for the placebo group (gemcitabine plus carboplatin) used within the manufacturer's model;
- the cost of paclitaxel was taken from the BNF and assumed to be £601.03 for a 50 mL (300 mg) vial;[71]
- the dose of paclitaxel was assumed to be 175mg/m^2 every three weeks for a maximum of six cycles;
- the number of patients remaining on paclitaxel therapy was assumed to be the same as the number of patients remaining on carboplatin therapy in the manufacturer's model;
- all other inputs and assumptions were kept the same as in the ERG's revised base case model.

The deterministic results of this analysis are presented in Table 67. The ICER was estimated to be £148,014.

Table 67. Exploratory analysis of bevacizumab in combination with carboplatin and gemcitabine versus paclitaxel in combination with carboplatin

Intervention	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER (inc. cost per inc. LYG)	ICER (inc. cost per inc. QALY)
Deterministic results								
Paclitaxel plus carboplatin	£16,672	3.14	1.98	–	–	–	–	–
Bevacizumab, gemcitabine and carboplatin	£60,616	3.62	2.27	£43,945	0.48	0.30	£92,146	£148,014
Abbreviations used in table: ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life years gained; mg, milligram; PD, progressed disease; PFS, progression-free survival; QALY, quality adjusted life year.								

PLDH and carboplatin

The NMA results indicated a lack of statistical significance between PLDH in combination with carboplatin versus gemcitabine in combination with carboplatin, in terms of PFS. Therefore, the ERG conducted an exploratory analysis of bevacizumab in combination with gemcitabine and carboplatin versus PLDH in combination with carboplatin and made the following assumptions:

- OS and PFS estimates for PLDH plus carboplatin were assumed to be the same as OS and PFS estimates for the placebo group (gemcitabine plus carboplatin) used within the manufacturer's model;
- the cost of PLDH was taken from the BNF and assumed to be £712.49 for a 25mL vial (50mg) vial;[71]
- the dose of PLDH was assumed to be 30mg/m^2 every three weeks for a maximum of six cycles;
- the number of patients remaining on PLDH therapy was assumed to be the same as the number of patients remaining on carboplatin therapy in the manufacturer's model;
- all other inputs and assumptions were kept the same as in the ERG's revised base case model.

The results of this deterministic analysis are presented in Table 68. The ICER was estimated to be £145,621.

Table 68. Exploratory analysis of bevacizumab in combination with carboplatin and gemcitabine versus PLDH in combination with carboplatin

Intervention	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER (inc. cost per inc. LYG)	ICER (inc. cost per inc. QALY)
Deterministic results								
PLDH plus carboplatin	£17,382	3.14	1.98	–	–	–	–	–
Bevacizumab, gemcitabine and carboplatin	£60,617	3.62	2.27	£43,234	0.48	0.30	£90,656	£145,621
Abbreviations used in table: ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life years gained; mg, milligram; PD, progressed disease; PFS, progression-free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; QALY, quality adjusted life year.								

Carboplatin

For simplicity, the ERG conducted an exploratory analysis of bevacizumab in combination with gemcitabine and carboplatin versus carboplatin alone and made the following assumptions:

- OS and PFS estimates for carboplatin were assumed to be the same as OS and PFS estimates for the placebo group (gemcitabine plus carboplatin) used within the manufacturer's model;
- pharmacy preparation time was reduced to 25 minutes for the carboplatin group;
- all other inputs and assumptions were kept the same as in the ERG's revised base case model.

The results of this deterministic analysis are presented in Table 69. The ICER was estimated to be £159,273. The ERG notes that the "true" ICER is likely to be lower than this figure, because gemcitabine plus carboplatin is associated with a statistically significant increase in PFS compared with carboplatin alone, and therefore the number of additional QALYs associated with bevacizumab is likely to be underestimated in the current scenario.

Table 69. Exploratory analysis of bevacizumab in combination with carboplatin and gemcitabine versus carboplatin

Intervention	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER (inc. cost per inc. LYG)	ICER (inc. cost per inc. QALY)
Deterministic results								
Carboplatin	£13,329	3.14	1.98	–	–	–	–	–
Bevacizumab, gemcitabine and carboplatin	£60,617	3.62	2.27	£47,288	0.48	0.30	£99,156	£159,273
Abbreviations used in table: ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life years gained; mg, milligram; PD, progressed disease; PFS, progression-free survival; QALY, quality adjusted life year.								

7 OVERALL CONCLUSIONS

7.1 Summary of clinical effectiveness issues

The manufacturer presents the case for the addition of bevacizumab compared with addition of placebo to gemcitabine and carboplatin for the treatment of first recurrence of platinum-sensitive ovarian cancer based on data derived from the OCEANS randomised controlled trial (RCT).[28] OCEANS provides the only direct evidence presented within the manufacturer's submission (MS).

Addition of bevacizumab to gemcitabine and carboplatin was associated with a statistically significant improvement in the primary outcome of progression-free survival (PFS) (Hazard ratio [HR] 0.48; 95% Confidence Interval [CI]: 0.39 to 0.61; p <0.0001). Median duration of PFS was 12.4 months in the bevacizumab group compared with 8.4 months in the placebo group. However, the Evidence Review Group (ERG) considers it important to note that, as data are derived from a single RCT, the evidence on clinical effectiveness of addition of bevacizumab to gemcitabine and carboplatin in the population of interest to the decision problem is limited. As a sensitivity analyses, PFS was also determined by an Independent Review Committee (IRC). The results of the IRC-determined analysis support the findings from the investigator-assessed analysis.

The manufacturer reported results from three interim analyses of OS data. None of the interim analysis found a statistically significant difference between the addition of bevacizumab and the addition of placebo in duration of OS. The direction of effect in the first interim analysis favoured bevacizumab but the difference did not reach statistical significance (25% reduction in risk of mortality; HR 0.75; 95% CI: 0.53 to 1.05). The effect size generated from the second and third interim analyses approaches 1, that is, there is no difference between bevacizumab and placebo in duration of OS.

In the submitted evidence, a larger proportion of patients in the bevacizumab group experienced an adverse event compared with the placebo group, and more patients in the bevacizumab group discontinued treatment as the result of an adverse event.

At the time of writing of the ERG's report, bevacizumab does not have a licence for use in the treatment of recurrent ovarian cancer. However, the Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion on the use of bevacizumab in combination with gemcitabine plus carboplatin for the treatment of patients with first-recurrence of platinum-sensitive ovarian cancer (comprises epithelial ovarian cancer [EOC], fallopian tube cancer [FTC], and primary peritoneal cancer [PPC]) who have not received prior therapy with a vascular endothelial growth factor (VEGF) inhibitor or VEGF receptor-targeted agent. The ERG considers that the population

outlined in the positive opinion, and which it is anticipated that the licence will stipulate, is relevant to the scope issued by NICE.

The submitted direct evidence addresses only one comparison of interest outlined in the NICE scope. In terms of indirect evidence, the manufacturer identified three large trials that could potentially be used to construct a network meta-analysis (NMA). The manufacturer decided against carrying out an NMA. After independently evaluating the RCTs identified by the manufacturer, and obtaining clinical advice, the ERG considers that the identified trials were sufficiently comparable to inform an NMA. The ERG undertook an exploratory analysis, the results of which suggest that addition of bevacizumab to gemcitabine and carboplatin prolongs duration of PFS compared with all chemotherapeutic regimens listed as comparators of interest in the final scope. For example, bevacizumab added to gemcitabine and carboplatin was associated with a reduction in risk of progression or death from any cause of 53% compared with paclitaxel plus carboplatin (HR 0.47; 95% Credible Interval [CrI]: 0.33 to 0.66) and of 42% compared with PLDH plus carboplatin (HR 0.58; 95% CrI: 0.39 to 0.82). The ERG stresses that its analyses are speculative and, as such, should be interpreted with caution.

With regards to the manufacturer's systematic reviews, the ERG has some reservations around the methods implemented. Abstracts were appraised by only one reviewer and the manufacturer specified an inclusion criterion that trials should include a minimum of 200 patients. The ERG suggests that these restrictions limit the robustness of the manufacturer's systematic reviews. However, the ERG acknowledges that the manufacturer has likely identified all studies evaluating bevacizumab in the treatment of first recurrence of platinum-sensitive ovarian cancer. By contrast, the ERG notes that RCTs that could potentially inform an NMA were excluded at appraisal stage. Due to time constraints, the ERG was unable to replicate the manufacturer's review of the literature to inform an NMA, and considers that there may be additional relevant studies not reported in the manufacturer's submission (MS).

Within the MS, several inconsistencies and omissions were noted in the reporting of various analyses and number of events. Inconsistent reporting of data was also prominent in the manufacturer's response to the ERG's requests for clarification. In particular, the number of patients discontinuing due to an adverse effect remains unclear. Importantly, during clarification, the manufacturer was unable to confirm the number of patients lost to follow-up at the time of final PFS analysis, or to provide a mean PFS. In addition, the numbers of patients censored at the time of final PFS analysis and at the time of the three interim OS analyses are unclear. Although reasons for censoring of patients are described in full in the MS, no details on the number of patients censored in each analysis are reported in either the MS or the full publication of OCEANS. The ERG also has concerns around the transparency and consistency in the reporting of the results from the sensitivity analysis based on

IRC-determined outcomes, and, in particular, the considerable discrepancy between the investigator-assessed and IRC-determined proportion of patients having a complete response.

Taken together, the direct and indirect evidence on clinical effectiveness suggest that addition of bevacizumab to gemcitabine and carboplatin is effective in prolonging PFS in first-recurrence of platinum-sensitive ovarian cancer. However, data on OS suggest that there is no benefit from adding bevacizumab to gemcitabine and carboplatin for this outcome. The ERG notes that data on OS are immature and results should be interpreted with caution.

7.2 Summary of cost-effectiveness issues

The manufacturer estimated that the incremental cost-effectiveness ratio (ICER) for the addition of bevacizumab to gemcitabine and carboplatin was £149,050/quality adjusted life year (QALY; deterministic) and £221,750/QALY (probabilistic). The manufacturer found that this estimate was robust to changes in model inputs, and concluded that key drivers of the cost-effectiveness results were the cost and duration of treatment with bevacizumab and the time horizon of the analysis (MS; pg 174). In addition, the manufacturer noted that "the model was most sensitive to assumptions around the modelling of OS, the duration of treatment and the utility of patients in PFS" (MS; pg 174).

The ERG's revised base case ICER for the addition of bevacizumab to gemcitabine and carboplatin was comparable to the manufacturer's estimate, and was calculated to be £148,360/QALY (deterministic) and £212,079/QALY (probabilistic). The ERG agrees with the manufacturer that the model was robust to changes in many of the model inputs; however, the ERG considers that the key driver of the cost-effectiveness results was the estimate of OS gain associated with bevacizumab. The manufacturer elected to use data from September 2010, rather than March 2012, in the economic analysis. In September 2010, 29% of patients had died compared with 60% at the March 2012 time point. Because the September 2010 data are immature and subject to substantial censoring, the ERG has concerns that the OS gain estimated for the bevacizumab group is associated with a large degree of uncertainty. Moreover, at the September 2010 time point, an OS benefit was found for the bevacizumab group that was not sustained at the March 2012 analysis; therefore, the ERG believes that the OS benefit associated with bevacizumab is likely to be overestimated. The ERG was not able to estimate the impact of this uncertainty within the ERG's revised base case ICER as the necessary OS data from March 2012 were not provided, and the degree of confounding in estimates of OS as a result of bevacizumab use in the placebo group post-progression was unclear. The ERG undertook a scenario analysis on the manufacturer's base case deterministic ICER (£149,050/QALY) in which OS was assumed to be the same for both the bevacizumab and the placebo group; the estimated ICER with this assumption was approximately £1.75 million. Including the assumption of equivalent OS within the ERG's revised base case, the deterministic ICER increased to approximately £1.8 million.

The ERG therefore considers that the ERG's revised base case ICER is likely to be a underestimate of the "true" ICER, but notes that the degree of the bias from use of September 2010 data for OS is uncertain.

7.3 Implications for research

The only direct evidence presented within the MS was derived from comparison of addition of bevacizumab versus addition of placebo to gemcitabine plus carboplatin. At this time, gemcitabine plus carboplatin is not recommended by NICE for the treatment of first recurrence of platinum-sensitive ovarian cancer. The ERG carried out an exploratory network-meta analysis that suggested that adding bevacizumab to gemcitabine and carboplatin is associated with a statistically significant improvement in PFS compared with doublet chemotherapy regimens typically used in UK clinical practice to treat recurrent platinum-sensitive ovarian cancer. Direct evidence comparing addition of bevacizumab to other platinum-based chemotherapies versus platinum-based chemotherapy regimens (single agent or in combination) would provide a broader evidence base on the effectiveness of bevacizumab in the treatment of platinum-sensitive ovarian cancer. The ERG considers that studies investigating the clinical effectiveness of bevacizumab when added to other chemotherapies typically used in UK clinical practice could be informative for service provision within the NHS. In addition, the ERG suggests that there is a need for further research into the clinical benefit of adding bevacizumab to gemcitabine and carboplatin for the outcome of OS in recurrent platinum-sensitive ovarian cancer. The ERG notes that, at the time of writing, OS data from OCEANS are immature and that planned analysis when data are more complete may shed light on this issue.

The exploratory NMA carried out by the ERG was based on data presented in the MS and supplementary data provided by the manufacturer on request. Following on from the ERG's concerns around the robustness of the manufacturer's systematic reviews of the literature, the ERG suggests that it may be informative to repeat the NMA after development of a review protocol that follows recommended review practices.

8 REFERENCES

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9 APPENDICES

Appendix 1. Full details of trials identified by manufacturer for network meta-analysis

Characteristic	CALYPSO[35]	ICON4[36]	AGO-OVAR-2.5[37]
Population	Platinum-sensitive relapsed/recurrent ovarian	Platinum-sensitive relapsed/recurrent ovarian	Platinum-sensitive relapsed/recurrent ovarian
Number of patients	976	802	356
Inclusion criteria	• ≥18 years old with a histologically confirmed diagnosis of cancer of the ovary, fallopian tube, or extraovarian papillary serous tumour; • Disease progression longer than 6 months after first- or second-line platinum-based chemotherapy regimen; • Previous taxane therapy required; • Measurable disease according to RECIST or CA-125 assessable disease according to Gynecologic Cancer InterGroup criteria or histologic proven diagnosis of relapse; • Eastern Cooperative Oncology Group performance status of ≤2; • Life expectancy of at least 12 weeks; • Adequate bone marrow, renal, and hepatic function.	• Relapsed epithelial ovarian cancer requiring chemotherapy; • Previously received platinum-based chemotherapy; • Treatment-free for more than 6 months (>12 months in the Italian ICON4 group); • No concomitant or previous malignant disease likely to interfere with treatment or outcomes; • Provided informed written consent to enter the trial. **Note: there were three protocols for this trial and there were slight differences in eligibility criteria among the three protocols.** • Patients in the MRC CTU protocol trial were permitted to have had more than one line of previous chemotherapy, whereas those randomised in the Italian and AGO protocols must have had only one previous line. • Measurable disease was required for patients randomised in the Italian protocols, but not in the MRC CTU or AGO protocol. • The diagnosis of relapsed disease at entry into the trial in 18 patients in the MRC CTU protocol was based on raised CA125 concentrations. • Patients randomised into the AGO protocol must	• ≥18 years old; • Recurrent ovarian cancer at least 6 months after completion of first-line, platinum-based therapy; • Measurable or assessable lesions per Southwest Oncology Group criteria; • Eastern Cooperative Oncology Group performance status of 0 to 2; • Adequate bone marrow reserve; • Estimated glomerular filtration rate greater than 50 mL/min; • No serious concomitant systemic disorders incompatible with the study; • An estimated life expectancy 12 weeks or longer.

		have previously received cisplatin plus paclitaxel or carboplatin plus paclitaxel; all patients in ICON4 were simply required to have had previous platinum-based chemotherapy, with or without paclitaxel.	
Age (years)	***Median age***: *PLDH plus carboplatin*: 60.5 *Paclitaxel plus carboplatin*: 61	***Median age***: *Paclitaxel plus platinum-based chemotherapy*: 61 *Platinum-based chemotherapy*: 59.2	***Median age***: 58 *Gemcitabine plus carboplatin*: 59 *Carboplatin alone*: 58
Intervention	PLDH (30 mg/m^2 intravenously on day 1) and carboplatin (AUC 5 intravenously on day 1)[a]	Paclitaxel plus platinum-based chemotherapy. • Patients following the MRC CTU and IRFMN protocols and assigned paclitaxel plus platinum chemotherapy were to receive 175 mg/m^2 paclitaxel given in a 3 hour infusion, followed by carboplatin or cisplatin at the same dose as in the comparator group. Patients following the AGO protocol and assigned paclitaxel plus carboplatin were to receive 185 mg/m^2 paclitaxel given in a 3 hour infusion, followed by carboplatin at the same dose as in the comparator group.	Gemcitabine 1,000 mg/m^2 on days 1 and 8 plus carboplatin (AUC 4 on day 1).
Comparator	Paclitaxel (175 mg/m^2 intravenously on day 1) and carboplatin (AUC 5 intravenously on day 1)[a]	Conventional platinum-based chemotherapy. • Patients could receive a platinum agent as a monotherapy, or platinum agent in combination with another drug. • The dose of carboplatin was determined by the AUC method of Calvert and colleagues, and was a minimum of 5 mg (GFR+25), where GFR is the GFR determined by a radioisotope method or 24 h urine collection. If the GFR was assessed by the Cockcroft formula, the carboplatin dose was a minimum of 6 mg (GFR+25). • The planned minimum dose of cisplatin, in ICON4 patients only, was 75 mg/m^2 if given as one agent and 50 mg/m^2 if given in combination	Carboplatin at an AUC 5 on day 1, based on the Calvert formula.

		with other drugs.	
Number of cycles	Median of 6 in both arms	Not reported	Median of 6 in both arms
Interval since last chemotherapy	***6–12 months***: *PLDH plus carboplatin*: 35% *Paclitaxel plus carboplatin*: 36.1% ***>12 months***: *PLDH plus carboplatin*: 65% *Paclitaxel plus carboplatin*: 63.9%	***≤12 months***: *Paclitaxel plus platinum-based chemotherapy*: 23% *Platinum-based chemotherapy*: 27% ***>12 months***: *Paclitaxel plus platinum-based chemotherapy*: 77% *Platinum-based chemotherapy*: 73%	***6–12 months***: *Gemcitabine plus carboplatin*: 39.9% *Carboplatin alone*: 39.9% ***>12 months***: *Gemcitabine plus carboplatin*: 59.6% *Carboplatin alone*: 60.1%
Key outcomes recorded	***PFS*** Disease progression was defined according to RECIST and GCIG modifications and may have included any of the following: • occurrence (clinically or imaging signs) of any new lesion; • increase in measurable and/or non-measurable tumour defined by RECIST; • CA125 elevation defined by GCIG criteria; health status deterioration attributable to disease; • death of any cause before progression is diagnosed. Evaluation assessments were independently reviewed.	• ***OS*** (primary outcome) • ***PFS*** Defined as time from randomisation to first appearance of progressive disease or death from any cause • ***Quality of life***	• ***PFS*** Defined as the time from the date of random assignment to the date of disease progression or death from any cause. Progressive disease was based on clinical and/or radiologic evaluation. Progressive disease was not based on CA125 elevation without other clinical or radiologic evidence of disease progression. • ***Duration of response*** Measured from the date of first response to the date of disease progression or death due to any cause. • ***OS*** Measured from the date of random assignment to the date of death from any cause
Notes	• Included women who had received two previous lines of chemotherapy (~15% of women); • Open-label design; • ~60% of women had measurable disease based on RECIST; • All patients received antiemetics, including a serotonin antagonist and corticosteroid;	• Patients followed one of three protocols: one coordinated by the MRC CTU for hospitals in the UK, Norway, and Switzerland, one by the IRFMN in Italy; and one by AGO; • Included women who had received two previous lines of chemotherapy (~9% of women); • 71% of patients in the conventional platinum-based chemotherapy group received carboplatin	• Open-label design; • Study not powered to detect differences in OS. • Cycles were repeated every 21 days for six cycles in the absence of progressive disease or unacceptable toxicity. At the investigator's discretion, benefiting patients could receive a maximum of 10 cycles of

	• In the absence of unacceptable toxicity or disease progression, patients were treated for a total of 6 courses of therapy. If disease stabilised or partial response was achieved after 6 courses of therapy, patients were allowed to remain on therapy until progression.	alone; • 80% of patients in the paclitaxel plus platinum-based chemotherapy group received paclitaxel plus carboplatin. • Patients following the MRC CTU protocol were assigned at least six cycles. Patients following the IRFMN protocol were assigned at least three cycles and a further three cycles administered according to the results of response assessment. Patients following the AGO protocol were assigned a minimum of six and a maximum of eight cycles.	therapy.
[a] Based on the Calvert formula using glomerular filtration rate calculated from serum creatinine values according to the method of Cockroft and Gault. Abbreviations used in table: AGO, Arbeitsgemeinschaft Gynaekologische Onkologie; AUC, area under the curve; GCIG, Gynecologic Cancer InterGroup; IRFMN, Istituto Mario Negri; MRC CTU, Medical Research Council's Clinical Trials Unit; OS, overall survival; PFS, progression-free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; RECIST, Response Evaluation Criteria in Solid Tumors; vs, versus.			

Appendix 2. Quality assessment of OCEANS[28]

Question	How is the question addressed in the study? (description in MS[a])	Manufacturer's assessment (yes/no/not clear/NA)	ERG's comment
Was randomisation carried out appropriately?	Patients were randomised in a 1:1 ratio into one of two treatment arms: placebo or bevacizumab. The randomisation was performed using an interactive voice response system. Two randomisation audits were performed by an external DCC to ensure that the randomisation had been carried out correctly: one after approximately 30 patients and one after approximately 200 patients were enrolled in the study	Yes	Agree
Was the concealment of treatment allocation adequate?	The Sponsor's personnel, the CRO, investigators, and patients were blinded to treatment assignment of bevacizumab or placebo. The Sponsor's personnel remained blinded until the database lock for the final PFS analysis. Subsequent to this database lock, patient treatment assignments were unblinded and provided to the treating investigator. The protocol offered the option of unblinding at progression; therefore, investigators and patients may have been unblinded to treatment assignment of bevacizumab or placebo at the time of investigator-determined disease progression	Yes	Unclear The ERG considers that the manufacturer's text describes the level of blinding rather than how treatment allocation was concealed
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Prognostic factors, such as age, performance status, histology subtype and platinum-free interval, were all similar between groups	Yes	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	The Sponsor's personnel, the CRO, investigators, and patients were blinded to treatment assignment of bevacizumab or placebo	Yes	Agree (based on the response to the question concerning concealment of treatment allocation)
Were there any unexpected imbalances in drop-	No unexpected imbalances in drop-outs occurred between the study groups	No	The ERG notes that discontinuation

outs between groups? If so, were they explained or adjusted for?			due to adverse effects was considerably higher in the bevacizumab group than in the placebo group
Is there any evidence to suggest that the authors measured more outcomes than they reported?	There is no evidence to suggest this	No	Agree
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Efficacy analyses were based on the ITT population. Safety analysis was based on the primary safety population (all patients receiving any partial or full dose of protocol treatment)	Yes	Agree

Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

[a] Reproduced from Table 62 (pg 200) of the MS.

Abbreviations used in table: CRO, contract research organisation; DCC, data co-ordinating centre; ERG, Evidence Review Group; ITT, intention-to-treat; MS, manufacturer's submission; PFS, progression-free survival.

Appendix 3. Quality assessment of CALYPSO, ICON4, and AGO-OVAR-2.5

Quality assessment of CALYPSO (reproduced from MS; Table 67, pg 215)

Question	How is the question addressed in the study? (description in MS[a])	Manufacturer's assessment (yes/no/not clear/NA)	ERG's comment
Was randomisation carried out appropriately?	Patients were centrally randomised to treatment. Randomisation was conducted in permuted blocks with stratification.	Yes	Agrees
Was the concealment of treatment allocation adequate?	This was an open-label study	No	Agrees
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Baseline prognostic factors were comparable between groups, although 5% more patients in the carboplatin + paclitaxel arm had received two prior lines of therapy	Yes	Agrees
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	This was open-label study and was not blinded. The primary efficacy outcome (PFS) was evaluated by independent review of progression as well as symmetry of tumour assessments. Secondary and safety outcomes have a low risk of bias as they are all relatively objective measures.	No	Agrees
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No unexpected imbalances in drop-outs occurred between the study groups.	No	The ERG notes that the proportion of patients discontinuing treatment early for toxicity was significantly smaller in the carboplatin plus PLDH group compared with the carboplatin plus paclitaxel group
Is there any evidence to suggest that the authors measured more outcomes than they reported?	There is no evidence to suggest this	No	Agrees

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The primary outcome evaluated PFS using the ITT population; it also included exploratory subgroup analyses.	Yes	Agrees
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination. Abbreviations used in table: ERG, Evidence Review Group; ITT, intention-to-treat; MS, manufacturer's submission; PFS, progression-free survival; PLDH, pegylated liposomal doxorubicin hydrochloride.			

Quality assessment of ICON4 (reproduced from MS; Table 65, pg 212)

Question	**How is the question addressed in the study? (description in MS[a])**	**Manufacturer's assessment (yes/no/not clear/NA)**	**ERG's comment**
Was randomisation carried out appropriately?	Randomisation was done independently in the three protocols, although similar information was collected for all patients. 1:1 randomisation was conducted by telephone/fax using a method of computerised minimisation.	Yes	Agrees
Was the concealment of treatment allocation adequate?	This was an open-label study.	No	Agrees
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	All of the prognostic factors were comparable at baseline.	Yes	Agrees
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	This was an open-label study. There is a low risk of bias for the relatively objective efficacy outcomes. ICON4, which recruited two thirds of the patient population, established an independent data monitoring and ethics committee.	No	Agrees
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	10% more patients in the standard chemotherapy group didn't complete six cycles of therapy. This was explained due to a higher proportion of disease progression (56%) or death within six cycles for this group, alongside toxic effects (39%) and patient's preference (5%).	Yes	Agrees

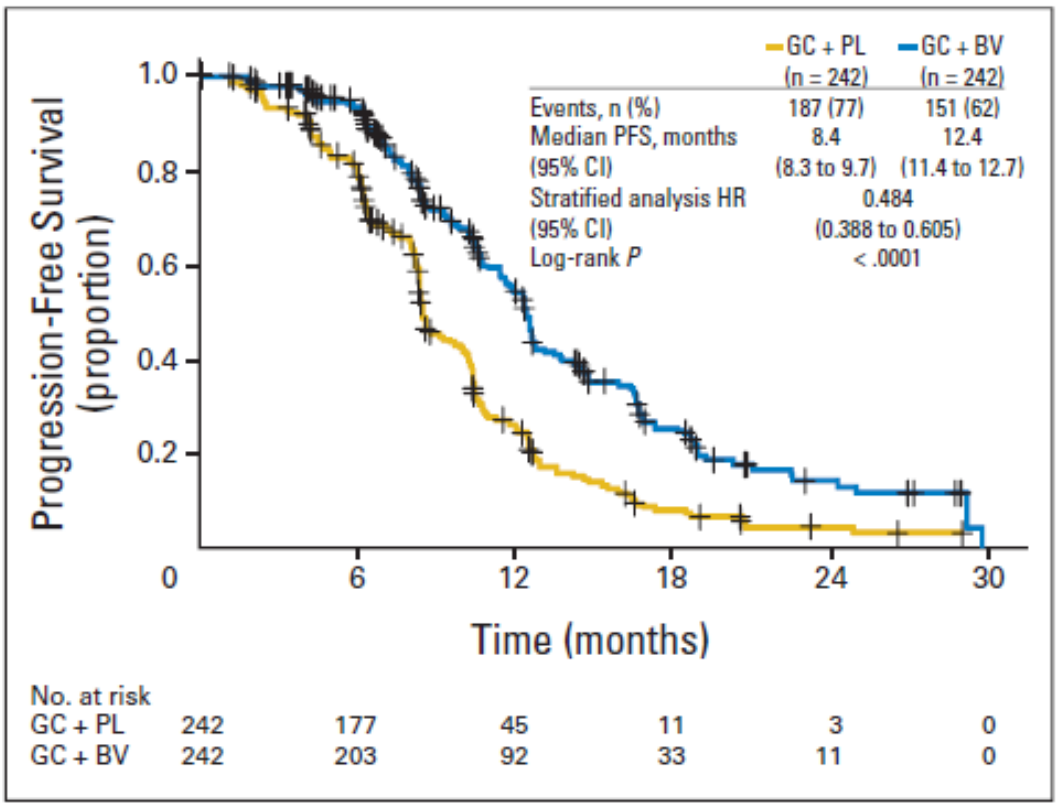
Is there any evidence to suggest that the authors measured more outcomes than they reported?	There is no evidence to suggest this.	No	Agrees
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The efficacy outcomes of the ITT population were assessed, alongside several subgroup analyses.	Yes	Agrees
NB: ICON4 and AGO-OVAR-2.2 were conducted in parallel. There were three protocols for three different coordinating centres Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination. Abbreviations used in table: ERG, Evidence Review Group; ITT, intention-to-treat; MS, manufacturer's submission; PFS, progression-free survival.			

Quality assessment of AGO-OVAR-2.5 (reproduced from MS; Table 66, pg 213)

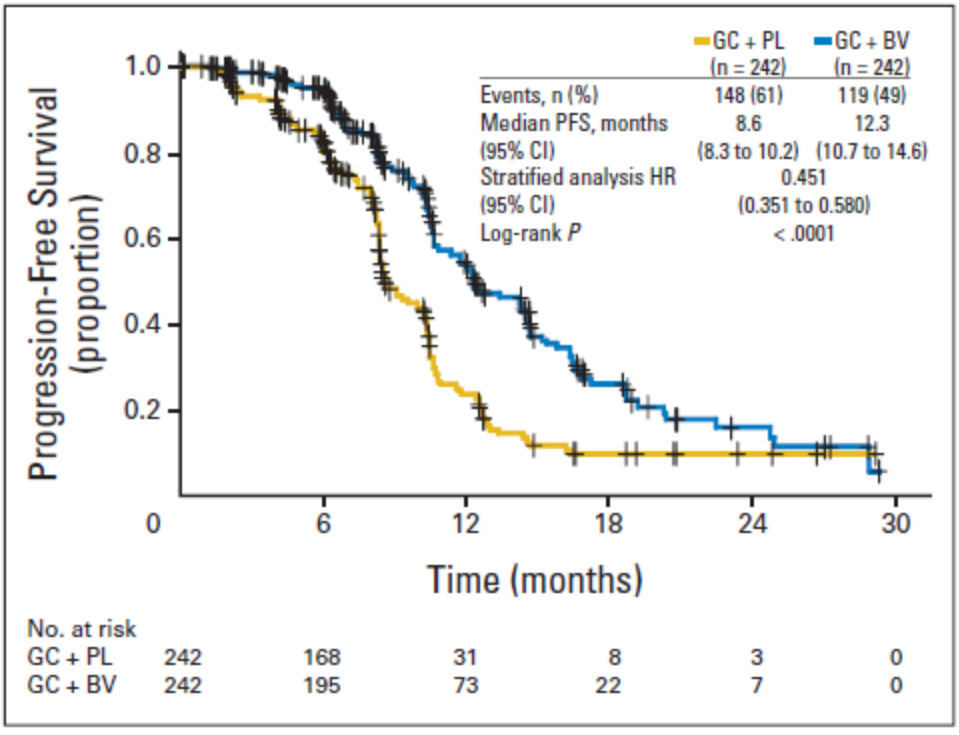
Question	**How is the question addressed in the study? (description in MS[a])**	**Manufacturer's assessment (yes/no/not clear/NA)**	**ERG's comment**
Was randomisation carried out appropriately?	Random assignment was conducted through the central AGO-OVAR office after stratification. A 1:1 random assignment was used within each stratum with a block size of ten; each patient had a 50% chance of random assignment to either treatment arm.	Yes	Agrees
Was the concealment of treatment allocation adequate?	This was an open-label study.	No	Agrees
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Baseline prognostic factors were comparable between groups	Yes	Agrees
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	This was an open-label study.	No	Agrees

Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Drop-outs are not sufficiently reported	Not clear	Agrees
Is there any evidence to suggest that the authors measured more outcomes than they reported?	There is no evidence to suggest this was the case.	No	Agrees
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The efficacy analyses were conducted on the ITT population. Safety analysis was conducted on the safety population, which included all patients who received at least one dose of the study drug.	Yes	Agrees
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination. Abbreviations used in table: CRO, contract research organisation; DCC, data co-ordinating centre; ERG, Evidence Review Group; ITT, intention-to-treat; MS, manufacturer's submission; PFS, progression-free survival.			

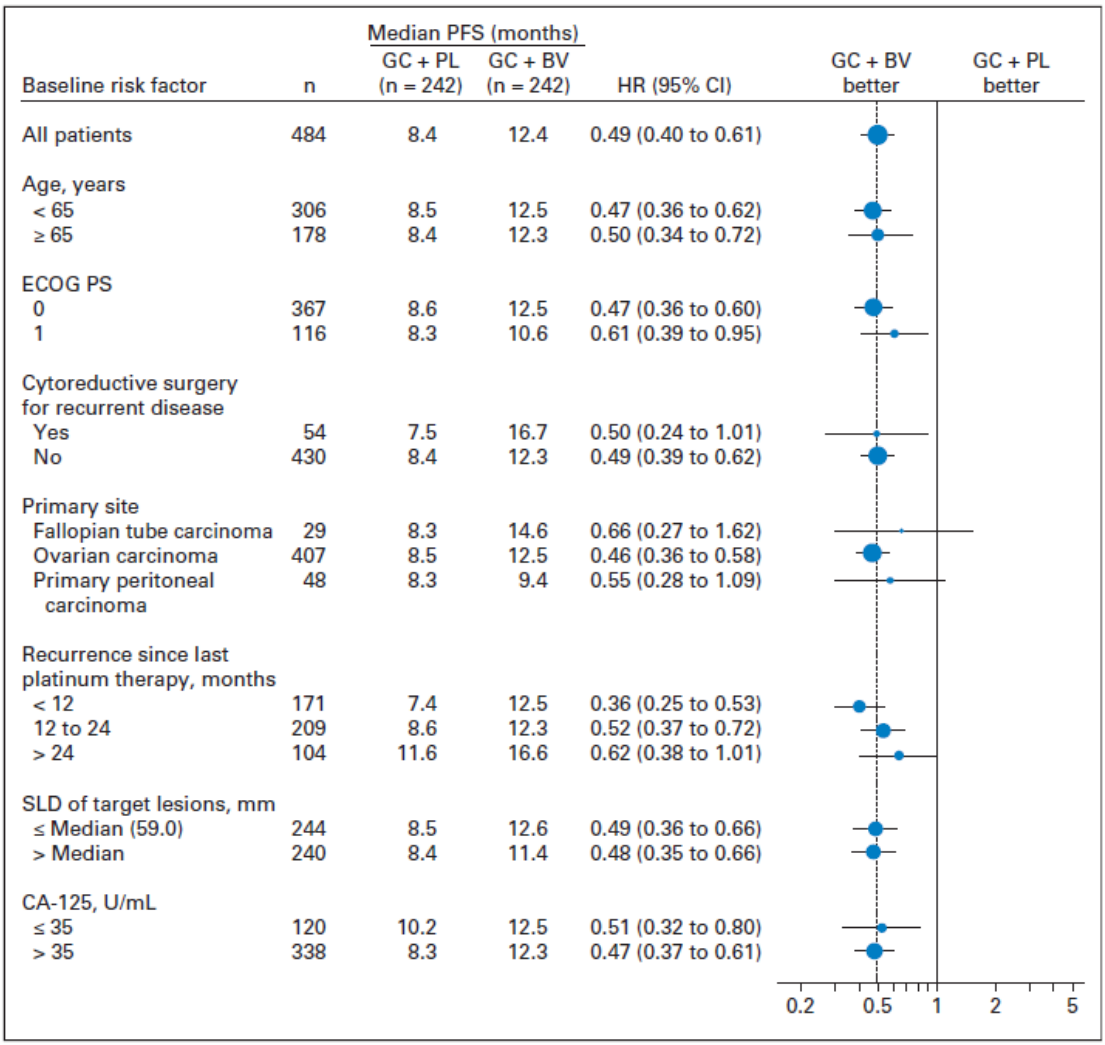
Appendix 4. Kaplan–Meier estimates of investigator-assessed progression-free survival (censored for non-protocol specified therapy) (reproduced from MS; Figure 4, pg 62)



Appendix 5. Kaplan–Meier estimates of independent review committee-assessed progression-free survival (censored for non-protocol specified therapy) (reproduced from MS; Figure 6, pg 65)



Appendix 6. Pre-specified subgroup analyses of progression-free survival (reproduced from MS; Figure 5, pg 64)



Appendix 7. Absolute event rates for subgroup analyses of progression-free survival (data provided by manufacturer during clarification)

Characteristic	Bevacizumab		Placebo	
	n	N	n	N
Age				
<65 years	102	157	117	149
≥65 years	49	85	70	93
ECOG				
0	113	182	145	185
1	38	59	42	57
Cytoreductive surgery for recurrent disease				
Yes	15	30	16	24
No	136	212	171	218
Primary site of disease				
Fallopian tube carcinoma	9	14	11	15
Ovarian carcinoma	126	200	158	207
Primary peritoneal carcinoma	16	28	18	20
Recurrence since last platinum therapy (months)[a]				
6–12	63	100	83	102
>12	88	142	104	140
SLD of target lesions (mm)				
≤Median (59.0 mm)	69	118	99	126
>Median	82	124	88	116
CA125 (U/mL)				
≤35 U/mL	33	57	45	63
>35 U/mL	108	171	135	167

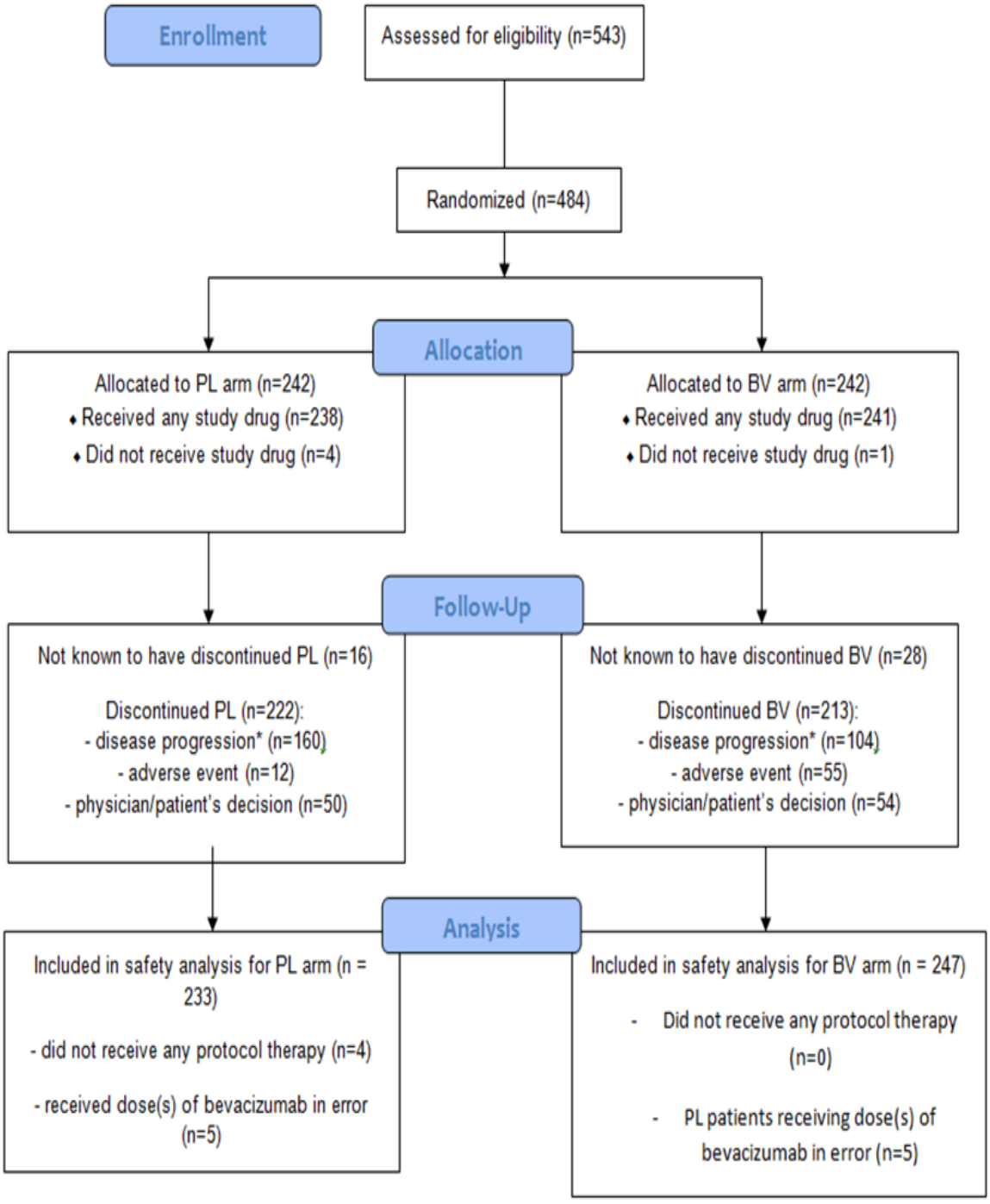
[a] Data presented in table were supplied by manufacturer on request. For the subgroup analysis based on interval since last platinum therapy, the OCEANS Clinical Study Report provides a breakdown of time to recurrence based on stratified categories of 6–12 and >12 months, which does include the number of events. These are the data supplied by the manufacturer on request. However, the schematic provided in the manufacturer's submission, which was published in the full publication of OCEANS,[28] reports subgroups since last platinum therapy based on categories of <12, 12–24, and >24 months. The manufacturer was unable to provide the absolute events for these subgroups during clarification.

HR for subgroup 6–12 months since last platinum therapy: 0.41; 95% CI: 0.29 to 0.58.

HR for subgroup >12 months since last platinum therapy: 0.55; 95% CI: 0.41 to 0.73.

Abbreviations used in table: ECOG, Eastern Cooperative Oncology Group; mm, millimetre; SLD, sum of longest diameters.

Appendix 8. Corrected patient flow diagram provided by manufacturer during clarification



Appendix 9. Treatment-emergent adverse events leading to study drug discontinuation (safety-evaluable patients; reproduced from manufacturer's response to clarification)

MedDRA System Organ Class MedDRA Preferred Term	Bevacizumab (N = 247)	Placebo (N = 233)
Any adverse events	49 (19.8)	11 (4.7)
Blood and lymphatic system disorders		
Anaemia	2 (0.8)	—
Neutropenia	4 (1.6)	1 (0.4)
Thrombocytopenia	4 (1.6)	2 (0.9)
Cardiac disorders		
Acute myocardial infarction	—	1 (0.4)
Cardiomyopathy	1 (0.4)	—
Myocardial infarction	1 (0.4)	—
Ear and labyrinth disorders		
Vertigo	1 (0.4)	—
Gastrointestinal disorders		
Abdominal pain	1 (0.4)	—
Gingival recession	1 (0.4)	—
Intestinal obstruction	1 (0.4)	1 (0.4)
Nausea	1 (0.4)	—
Oral pain	1 (0.4)	—
Small intestinal obstruction	1 (0.4)	1 (0.4)
Vomiting	2 (0.8)	—
General disorders/administration site conditions		
Chest discomfort	1 (0.4)	—
Chest pain	1 (0.4)	—
Pyrexia	1 (0.4)	—
Hepatobiliary disorders		
Cholecystitis	—	2 (0.9)
Injury, poisoning, and procedural complications		
Humerus fracture	—	1 (0.4)
Wound complication	1 (0.4)	—
Wound dehiscence	1 (0.4)	—
Investigations		
Blood creatinine increased	1 (0.4)	—
Haemoglobin decreased Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (0.4)	—
Glioblastoma	1 (0.4)	—
Tumour compression	—	1 (0.4)
Nervous system disorders		
Cerebral ischaemia	—	1 (0.4)
Cerebrovascular accident	—	1 (0.4)
Convulsion	1 (0.4)	—

Encephalopathy	1 (0.4)[a]	—
Hemorrhage intracranial	1 (0.4)	—
Hemorrhagic stroke	1 (0.4)	—
Headache	2 (0.8)	—
Leukoencephalopathy	1 (0.4)	—
RPLS	3 (1.2)[b]	—
Transient ischaemic attack	2 (0.8)	—
Renal and urinary disorders		
Hydronephrosis	1 (0.4)	—
Pollakiuria	1 (0.4)	—
Proteinuria	6 (2.4)	—
Reproductive system and breast disorders		
Female genital tract fistula	1 (0.4)	—
Respiratory, thoracic, and mediastinal disorders		
Dyspnoea	1 (0.4)	—
Epistaxis	3 (1.2)	—
Pulmonary embolism	2 (0.8)	—
Skin and subcutaneous tissue disorders		
Rash	1 (0.4)	—
Skin disorder	1 (0.4)	—
Skin ulcer	1 (0.4)	—
Vascular disorders		
Arterial thrombosis	1 (0.4)	—
Embolism arterial	1 (0.4)	—
Hypertension	9 (3.6)	—
Phlebitis	—	1 (0.4)
Thrombophlebitis superficial	2 (0.8)	—
Vena cava thrombosis	1 (0.4)	—

All reported events were included regardless of relationship to study drug.

Maximum severity was selected for each event for each patient. Only those adverse events that occurred within 30 days after last administration of study drug and on or before the cut-off date (17th September 2010) were included in this analysis.

[a] One patient had encephalopathy of unknown aetiology.

[b] Two were MRI-confirmed RPLS cases.

Abbreviations used in table: MRI, magnetic resonance imaging; RLPS, reversible posterior leukoencephalopathy syndrome.

Appendix 10. Key baseline characteristics of patients in CALYPSO, ICON4, and AGO-OVAR-2.5 (adapted from MS; Table 14, pg 80)

Trial name	Age (years)	Performance score	Proportion of patients with two or more lines of previous chemotherapy	Platinum sensitivity (interval since last chemotherapy)
CALYPSO				
PLDH plus platinum	Median: 60.5 (24–82)	ECOG 0: 286/466 (61.4%) ECOG 1: 158/466 (33.9%) ECOG 2: 13/466 (2.8)	58/466 (12.4%)	6–12 months: 161/466 (35.0%) >12 months: 305/466 (65.0%)
Paclitaxel plus platinum	Median: 61 (27–82)	ECOG 0: 317/466 (62.5%) ECOG 1: 164/466 (32.3%) ECOG 2: 15/466 (3.0)	88/466 (17.3%)	6–12 months: 183/466 (36.1%) >12 months: 324/466 (63.9%)
ICON4				
Paclitaxel plus platinum	Median: 60.0	WHO 0: 246/392 (62.8%) WHO 1: 121/392 (30.9%) WHO 2–3: 25/392 (6.4%)	37/392 (9.4%)	6–12 months: 92/392 (35.0%) >12 months: 300/392 (65.0%)
Platinum monotherapy	Median: 59.2	WHO 0: 262/410 (63.9%) WHO 1: 122/410 (29.7%) WHO 2–3: 26/410 (6.3%)	30/410 (7.3%)	6–12 months: 111/410 (27.1%) >12 months: 299/410 (72.9%)
AGO-OVAR-2.5				
Gemcitabine plus carboplatin	Median: 59 (36–78)	ECOG 0: 83/178 (46.6%) ECOG 1: 79/178 (44.3%) ECOG 2: 11/178 (6.2%)	0/178 (0%)	6–12 months: 71/178 (39.9%) >12 months: 106/178 (59.6%)
Platinum monotherapy	Median: 58 (21–81)	ECOG 0: 93/178 (52.2%) ECOG 1: 72/178 (40.4%) ECOG 2: 9/178 (5.1%)	0/178 (0%)	6–12 months: 71/178 (39.9%) >12 months: 107/178 (60.1%)

***Alberts* et al.**				
PLDH plus carboplatin	Median: 66.9 (range 43–87)	Zubrod 0: 20/31 (65%) Zubrod 1: 11/31 (35%)	0/31 (0%)	Not reported
Carboplatin alone	Median: 62.5 (range 31–80)	Zubrod 0: 16/30 (53%) Zubrod 1: 14/30 (47%)	0/30 (0%)	Not reported
***Gonzalez-Martın* et al.**				
Paclitaxel plus carboplatin	Median: 59 (40–77)	ECOG 0: 17/38 (47.2%) ECOG 1: 17/38 (47.2%) ECOG 2: 2/38 (5.6%)	7/38 (18.4%)	6–12 months: 17/38 (44.7%) >12 months: 21/38 (55.3%)
Carboplatin alone	Median: 61 (35–77)	ECOG 0: 14/40 (35.9%) ECOG 1: 18/40 (46.2%) ECOG 2: 7/40 (17.9%)	5/40 (12.5%)	6–12 months: 16/40 (40.0%) >12 months: 24/40 (60.0%)
Abbreviations used in table: ECOG, Eastern Cooperative Oncology Group; PLDH, pegylated liposomal doxorubicin hydrochloride; WHO, World Health Organization.				

Appendix 11. Details of references excluded from the manufacturer's review based on trial size

Publication author (as listed in the MS; reasons for exclusion)	Full reference details provided by the manufacturer on request	ERG's assessment of the full publication and reason for exclusion, where applicable
2010		
Bafaloukos, D	Bafaloukos D, Linardou H, Aravantinos G, *et al*. *BMC Med* 2010 Jan 7;8:3	Excluded Does not report HR for difference between groups in TTP; unable to incorporate result into NMA
Gonzalez-Martin, A	Gonzalez-Martin A, Casado A, Arranz J, *et al*. Annals of Oncology, suppl. SUPPL. 8 21 (Oct 2010): viii307	Excluded Not comparison of interest: compares paclitaxel plus carboplatin versus gemcitabine plus carboplatin followed by paclitaxel plus carboplatin
Markman, M	Markman M, Moon J, Wilczynski S, *et al*. *Gynecol Oncol* 116. 3 (Mar 2010): 323-325	Included Long-term follow-up of Alberts (2008) but does not report additional data on PFS
Nam, E	Nam E, Kim J, Kim J, *et al*. *Am J Clin Oncol* 33; 3 (Jun 2010): 233-7	Excluded Not RCT; retrospective study Not intervention of interest: belotecan with and without cisplatin
2008		
Alberts, D	Alberts D, Liu P, Wilczynski S, *et al*. *Gynecol Oncol* 108; 1 (Jan 2008): 90-4	Included Study stopped early due to poor accrual rate (61 patients enrolled out of a planned 900)
2005		
Gonzalez-Martin, A	Gonzalez-Martin A, Calvo E, Bover I, *et al*. *Ann Oncol* 2005;16:749-55	Included
2002		
de Jongh, F	de Jongh F, de Wit R, Verweij J, *et al*. *Eur J Cancer* 2002;38:2005-13	Excluded Not comparison of interest: different dosing regimen of paclitaxel versus each other. Not relevant to the decision problem
Abbreviations used in table: MS, manufacturer's submission.		

Appendix 12. Full details of additional trials included in the network meta-analysis

Characteristic	Alberts *et al*.[55]	Gonzalez-Martın *et al*.[56]
Population	Platinum-sensitive relapsed/recurrent ovarian	Platinum-sensitive relapsed/recurrent ovarian
Number of patients	61	81
Inclusion criteria	Patients had to meet the following eligibility criteria: • histologically diagnosed stage III or IV disease consistent with epithelial carcinoma of the ovary, peritoneal carcinoma or mixed mullerian tumors; • relapse or progression of disease within 6–24 months of completing front-line platinum-based chemotherapy (either single agent or combination therapy); • progressive disease according to RECIST criteria or GCIG CA-125 progression criteria; • performance status of 0–1 by Zubrod; • consolidation therapy (i.e., up to 12 courses of non-platinum containing continuing chemotherapy or biological therapy following first-line platinum-based chemotherapy) during the 6–24 months progression-free and platinum-free interval was allowed, provided it was completed at least 28 days prior to registration; • surgical debulking for recurrent/progressive disease is allowed with recovery from side effects prior to registration; • no prior cumulative anthracycline (e.g., doxorubicin, daunorubicin, epirubicin) dose in excess of 240 mg/m^2 and no prior therapy with PLDH; • no prior abdominopelvic irradiation; • free from class 2 or greater cardiac problems as defined by New York Heart Association Criteria; • no evidence of active or uncontrolled infection; • no known brain metastases, severe gastrointestinal symptoms or grade 2 or greater sensory neuropathy per CTC 2.0 criteria at the time of registration.	Patients had to meet the following eligibility criteria: • recurrent, histologically confirmed epithelial ovarian cancer; • platinum-sensitive disease, defined as tumour progression >6 months after the completion of platinum-based chemotherapy; • no more than two previous chemotherapy lines; • the last regimen administered must have included a platinum-derived compound; • bi-dimensionally measurable disease as measured by computed tomography (CT) scan, or clinically evident but non-measurable disease that was evaluable by CA-125 Rustin's criteria; • ECOG performance status <2 • life expectancy of at least 12 weeks; • adequate bone marrow (granulocytes >2,000/mm^3, platelets >100,000/mm^3), renal (creatinine clearance >40 ml/min) and liver (serum bilirubin and transaminases <1.5x upper normal limit) function; • age >18 years; • written informed consent provided.
Age (years)	***Median age***: *PLDH plus carboplatin*: 66.9 *Carboplatin alone*: 62.5	***Median age***: *Paclitaxel plus carboplatin*: 59 *Carboplatin alone*: 61
Intervention	Intravenous carboplatin (AUC = 5 mg/mL/min) every 4weeks administered over a minimum of 15 min plus intravenous PLDH (30 mg/m^2) every 4 weeks administered over 1 h	Paclitaxel 175 mg/m^2 over 3 h plus carboplatin (AUC 5)

Comparator	Intravenous carboplatin (AUC = 5 mg/mL/min) every 4 weeks administered over a minimum of 15 min.	Carboplatin alone (AUC 5)[a]
Number of cycles	Median number of cycles was 7 in the PLDH plus carboplatin group and 6 in the carboplatin alone group.	Median number of cycles was 6 in each group
Interval since last chemotherapy	Not reported	***6–12 months***: *Paclitaxel plus carboplatin*: 44.7% *Carboplatin alone*: 40.0% ***>12 months***: *Paclitaxel plus carboplatin*: 55.3% *Carboplatin alone*: 60.0%
Key outcomes recorded	• ***Objective response (primary outcome)*** • ***Disease progression*** Objective response and disease progression were defined according to standard RECIST criteria. The GCIG CA-125 progression criteria were included in defining disease progression • ***OS*** • ***PFS***	• ***OS*** • ***TTP*** Time to progression was defined as the time from date of randomisation to date of documentation of tumour progression. • ***QoL***
Notes	• Level of blinding not clear; • ~60% of women had measurable disease based on RECIST; • Treatment was given until progression, intolerable toxicity or physician/patient desire for removal from study.	• Included women who had received two previous lines of chemotherapy (~15% of women); • Both treatments were administered every 3 weeks for a minimum of six cycles unless there was progression, unacceptable toxicity or patient refusal. After six courses the patients could continue therapy for three further cycles if, in the opinion of the attending physician, further clinical benefit could be expected.

[a] Carboplatin dose was calculated based on the Calvert formula using glomerular filtration rate calculated from serum creatinine values according to the method of Cockroft and Gault.

Abbreviations used in table: AUC, area under the curve; GCIG, Gynecologic Cancer InterGroup; OS, overall survival; PFS, progression-free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to progression; vs, versus.

Appendix 13. Quality assessments of two additional RCTs included in the network meta-analysis

Question	How is the question addressed in the study?	ERG's assessment (yes/no/not clear/NA)
***Alberts* et al.**[55]		
Was randomisation carried out appropriately?	Study described as randomised but method of randomisation not reported	Unclear
Was the concealment of treatment allocation adequate?	Not reported	Unclear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Patients in the PLDH plus carboplatin group were slightly older than patients in the carboplatin alone arm (median age: 66.9 years for PLDH plus carboplatin vs 62.5 years for carboplatin alone). Median platinum-free interval was longer in the PLDH plus carboplatin group compared with the carboplatin alone group (430 days vs 382 days).	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Not reported. However, the ERG considers that the primary outcome assessed (OS) is an objective outcome and, as such, should the study be an open-label study, there is a low risk of bias.	Unclear
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	A larger proportion of patients in the PLDH plus carboplatin group than in the carboplatin alone group discontinued protocol treatment because of an adverse event (48% vs 23%).	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	There is no evidence to suggest this.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The study does not specify that it has carried out an ITT analysis. However, all randomised patients have been included in analysis of OS.	Unclear

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Was randomisation carried out appropriately?	Patients randomised by a central data centre; no additional details reported.	Unclear
Was the concealment of treatment allocation adequate?	Not reported	Unclear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	More patients with ECOG performance status 2 were included in the carboplatin alone group, but the authors report that this difference was not statistically significant.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Not reported. However, the ERG considers that the outcomes assessed are objective outcomes and, as such, should the study be an open-label study, there is a low risk of bias.	Unclear
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	There is no evidence to suggest this.	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The efficacy analyses were carried out on the ITT population. Safety analysis was carried out on the safety population, which included all patients who received at least one dose of the study drug.	Yes
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination. Abbreviations used in table: ECOG, Eastern Cooperative Oncology Group; ERG, Evidence Review Group; ITT, intention-to-treat; MS, manufacturer's submission; PFS, progression-free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; vs, versus.		

Appendix 14. Selected distributions for the ERG base case PSA

Input	Selected distribution
Average body weight of UK cohort	Normal
Average BSA	Normal
First cycle administration cost	Gamma
Subsequent cycle administration cost	Gamma
Number of minutes pharmacy time (each infusion)	Normal
Cost of pharmacy time per hour	Gamma
Weekly supportive PFS cost	Gamma
Weekly supportive PD cost	Gamma
PFS utility	Beta
PD utility	Beta
Cost of palliative care (total per patient)	Gamma
Post-progression treatment total cost per patient (placebo)	Gamma
Post-progression treatment total cost per patient (bevacizumab)	Gamma
Cost of thrombocytopenia (Grade 3)	Gamma
Cost of thrombocytopenia (Grade 4)	Gamma
Cost of leukopenia (Grade 3)	Gamma
Cost of neutropenia (Grade 3)	Gamma
Cost of neutropenia (Grade 4)	Gamma
Cost of hypertension	Gamma
Cost of anaemia (Grade 3)	Gamma
Cost of neutrophil count decreased (Grade 3)	Gamma
Incidence of adverse events	Beta
Treatment effectiveness estimates (OS)	Estimates from the survival analysis varied using covariance information as per the manufacturer's model
Abbreviations used in table: BSA, body surface area; ERG, Evidence Review Group; PD, progressed disease; PFS, progression-free survival; PSA, probabilistic sensitivity analysis; OS, overall survival; UK, United Kingdom.	