[redacted]

01 November 2012

RE: Bevacizumab for the treatment of recurrent advanced ovarian cancer [ID490]

[redacted]

Please find below our response to the clarification questions from the ERG and the technical team at NICE received 18th October 2012. I would also like to advise you that our response contains no commercial or academic in confidence material and the confidential information checklist provided previously should be considered applicable here.

Please note that a substantial number of questions request additional analyses of data rather than clarification of issues in our original submission. As a result of resource constraints and the timelines attached to this part of the process we have prioritised those questions relating to points of clarity. If you require any further clarification or information then please do not hesitate to contact us.

Yours Sincerely,

[redacted]

Section A: Clarification on effectiveness data

A1. Priority question: Please supply the Clinical Study Report (CSR) for the OCEANS RCT.

We have included a copy of the report which was used when preparing the submission, and have also included the recently approved Summary of Product Characteristics. Please note 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.

A2. Priority question: Please complete the table below using data for women who received between 1 and 6 cycles of gemcitabine plus carboplatin in each arm, where n = number of events and N = number of people in the analysis.

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.

A3. Priority question: Please provide the mean duration of PFS (months) and of OS (months), with accompanying 95% CI, for the bevacizumab and placebo groups for the OCEANS investigator-assessed and IRC analyses based on analyses of data at clinical cut-off (17th September 2010).

The analyses of PFS and OS were conducted before all patients had progressed or died. Therefore the maximum PFS and OS values are unknown and a mean cannot be calculated.

The median duration of PFS and OS with accompanying confidence intervals are reported in Table 5 (p59) and Table 8 (p67). The IRC-assessed PFS is reported in Section 6.4.6.3 (p62); the IRC did not review overall survival.

A4. OCEANS is described as a double-blind, placebo-controlled RCT, but the ERG is unable to locate a description of allocation concealment and maintenance of blinding in OCEANS. Please describe how:

- **Allocation concealment was carried out;**
- **Blinding was maintained.**

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.

Blinding of the personnel, CRO, investigators and patients was maintained until disease progression at which point the investigators and patients may be unblinded; the Sponsor's personnel remained blinded to treatment assignments until database lock.

A5. In OCEANS, bevacizumab was added to second-line treatment with gemcitabine plus carboplatin as a maintenance therapy until disease progression (PD) or until unacceptable toxicity. The Summary of Product Characteristics for bevacizumab indicate that, when administered with carboplatin plus paclitaxel for first-line

treatment of ovarian cancer, after 6 cycles of treatment bevacizumab should be given as single agent until PD or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier. Please clarify how bevacizumab is anticipated to be used in UK clinical practice as a second-line adjunctive treatment to gemcitabine plus carboplatin.

- **Should bevacizumab be given as a single agent after 6 cycles of gemcitabine plus carboplatin?**
- **How long after completion of the gemcitabine plus carboplatin regimen should bevacizumab be administered? Is the maximum time of administration 15 months, as in first-line treatment?**

In the treatment of recurrent platinum sensitive ovarian cancer, bevacizumab is administered in combination with carboplatin and gemcitabine (GC) for between 6 and 10 cycles (depending on toxicity), followed by continued bevacizumab as a single agent until disease progression. Thus the maximum duration of administration of bevacizumab, after the period of combination with GC, will be according to the progression-free survival of each individual patient.

A6. In Section 6.3.5.4, it is noted that the OCEANS protocol did not restrict post-progression therapies for either treatment arm and, therefore, patients in both study arms could receive bevacizumab in third and subsequent lines of therapy. Please clarify how bevacizumab was used in third and subsequent lines of therapy. For example:

- **Was bevacizumab given as a maintenance treatment at all times?**
- **Was bevacizumab given as a monotherapy?**
- **Could bevacizumab be added to any other chemotherapy regimen?**
- **Were the same criteria applied for cessation of bevacizumab (administer until PD or unacceptable toxicity)?**

The timing and duration of bevacizumab in subsequent lines of therapy was according to each treating physician's individual discretion. Thus bevacizumab may have been given in combination with any chemotherapy regimen and also used as maintenance therapy post chemotherapy.

A7. Please complete the table below to provide updated data on the number of women receiving post-progression therapies using the data sets that form the first (17th September 2010) and third (30th March 2012) interim analyses of OS. In addition, please provide definitions for the types of therapy listed below in the context of the table:

- **Any subsequent anticancer therapy;**
- **Subsequent chemotherapy;**
- **Other chemotherapy.**

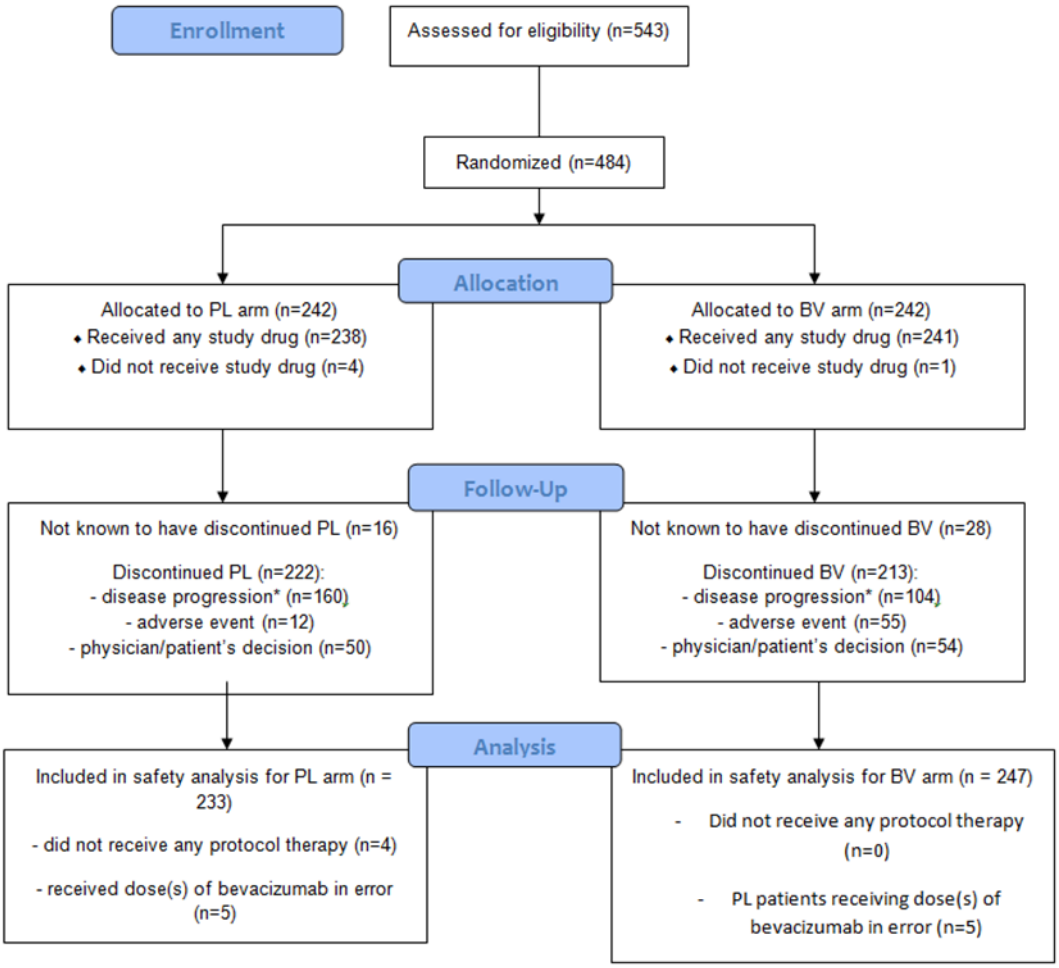
These data are not reported in the OCEANS CSR or elsewhere in the relevant publications.

A8. Please provide an updated Consort diagram (Figure 3) to illustrate:

- **The number of patients lost to follow-up;**

- **The patients included in the safety analysis sets (e.g. addition of patients receiving therapy to which they were not randomised, and exclusion of those not receiving one dose of study drug).**

An updated CONSORT diagram is provided below.



Study drug = bevacizumab/placebo; PL: gemcitabine+carboplatin+placebo; BV:gemcitabine+carboplatin+bevacizumab

Please refer to the answers for A11 and A22 for further discussion of follow-up and the safety analysis

A9. Figure 3 (Consort diagram) indicates that 55 patients in the bevacizumab group and 12 patients in the placebo group discontinued treatment due to an adverse effect. However, in Table 18, the figures reported for discontinuation due to an adverse event are 49 and 11 for the respective groups. Please clarify this potential discrepancy.

Please see our response to question A8.

A10. For the outcome of progression free survival, please complete the table below to indicate the total number of patients that were censored from each arm of OCEANS, and also to indicate the number of patients who discontinued treatment or were lost to follow-up, at the follow-up time point indicated.

The Kaplan-Meier curves for Investigator-assessed and IRC-assessed PFS have been presented, in an independent publication by the Investigators, in the peer-reviewed Journal of Clinical Oncology. We do not have access to the exact number of such events at each month of follow-up. We present below the numbers of patients at risk at 6-monthly intervals, as shown in Figs. 4 and 5 of the MS.

Number of patients at risk during study (242 per arm at commencement of observations)

Month of patient's follow-up	Censoring for patients without PD or death at time of last tumour assessment (at completion of study)		Censoring for patients receiving non-protocol-specified therapy	
	Placebo	Bevacizumab	Placebo	Bevacizumab
0	242	242	242	242
6	184	213	168	195
12	54	102	31	73
18	15	37	8	22
24	4	11	3	7
30	0	2	0	0

A11. Please clarify how many patients were lost to follow-up from each arm of OCEANS until clinical data cut off (from 17th April 2007 to 17th September 2010).

These data are not reported in the OCEANS CSR or elsewhere in the relevant publications.

A12. On page 56 of the submission, the percentage of patients in the placebo arm reported to have discontinued due to physician or patient choice is reported to be 20.7%. In Figure 3, the number of patients in the placebo arm who have discontinued due to physician or patient choice is given as 60, which the ERG calculates to be 24.8% of the patients randomised to placebo. Please clarify this potential discrepancy.

This is due to an incorrect entry for Figure 3; the relevant section should read "Discontinuation due to physician/patient's decision (n=50)", which equates to 20.7% of randomised patients in the PL arm. This has been corrected in the updated CONSORT flow diagram (see A8).

A13. Please populate the table below to provide additional data on PFS for the sensitivity analysis that included non-protocol therapies, where n = the number of events, and N = the number of people included in the analysis. Empty cells indicate requested data.

We have provided as much of the data as possible in the table below, but much of the data requested do not appear to be reported in the OCEANS CSR or elsewhere in the relevant publications.

	Placebo		Bevacizumab	
	n	N	n	N
Investigator-assessed				
Progression-free survival				
No. of patients with an event	**203 (83.9%)**	242	**174 (71.9%)**	242
Median PFS, months	8.4		12.4	
Mean PFS, months				
HR (relative to placebo)	0.524			
95% CI	0.425 to 0.645			
p value (log-rank)	p <0.0001			
Disease progression				
No. of patients with an event	**185 (76.4%)**	**242**	**146 (60.3%)**	**242**
HR (relative to placebo)				
95% CI				
p value (log-rank)				
Death				
No. of patients with an event	**2 (0.8%)**	**242**	**5 (2.1%)**	**242**
HR (relative to placebo)				
95% CI				
p value (log-rank)				

A14. Please populate the table below to provide additional information on PFS in the subgroups stratified by interval since last platinum exposure, where n = the number of events, and N = the number of people included in the analysis.

Characteristic	Placebo		Bevacizumab		Statistical analysis
	n	**N**	**n**	**N**	**HR (95% CI)**
Progression-free survival					
Subgroup of patients with partial platinum-sensitivity (6–12 months since last platinum exposure); reported to include 202 patients (pg 62 of submission)	**83**	102	**63**	100	0.41 (0.29 to 0.58)
Subgroup of patients with full platinum-sensitivity (>12 months since last platinum exposure); reported to include 282 patients (pg 62 of submission)	**104**	140	**88**	142	0.55 (0.41 to 0.73)

Bold text indicates requested data.

A15. In Table A1 (Unit costs of technology being appraised, pg 13 the mean treatment duration for bevacizumab is given as 7.5 months, which equates to 10.8 cycles on a 21-day cycle. These data are used to calculate the average cost of a course of treatment. However, in Table 16, the mean number of cycles of bevacizumab in OCEANS is reported to be 13.6 cycles, with a mean treatment duration of 42 weeks (ERG calculates this to equate to 9.8 months), and in Table 42 (pg 152) mean treatment duration of bevacizumab in OCEANS is reported as 11.71 months. Please clarify these potential discrepancies.

The data in Table 16 show the administration of bevacizumab to patients in the OCEANS clinical study. This was a selected patient population, which met all the inclusion and exclusion criteria required to enter the study. There were also regular clinical research monitoring visits to the study centres and a strict list of reasons why patients might halt study therapy. In routine clinical practice in the UK, the patient population may not be so strictly selected. Some less fit patients and a greater proportion of patients with disease at risk of early progression may receive bevacizumab. In addition, more patients may halt therapy before progression when they are not participating in a clinical study. Based on experience with other bevacizumab indications, the mean treatment duration estimated for bevacizumab in recurrent ovarian cancer in Table A1 has therefore been reduced to take account of a different patient population and different pattern of therapy in routine UK clinical practice.

The ERG is correct. There is a discrepancy in the mean treatment durations reported in Table 16 (from the CSR) and Table 42 (from the economic model). This 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

A16. Please populate the table below to provide additional information on the statistical testing of the difference between groups in discontinuation. In addition, please provide the number of patients in each arm who were receiving treatment at data cut off. In the table, n = the number of events, and N = the number of people included in the analysis. Empty cells indicate requested data.

These statistical tests have not been undertaken and we do not have access to the raw data to conduct these tests.

A17. Please populate the table below to provide additional information on the statistical testing of the difference between groups based on complete and partial response, where n = the number of events, and N = the number of people included in the analysis.

The patients with complete response and those with partial response were combined for the purposes of statistical analysis. No individual analyses were undertaken on each of these groups.

A18. For the subgroup analysis presented in Figure 5 (pg 64) of the submission, please complete the table below to provide the numerical values for the number of events

(n) in each group, and, for the subgroup based on interval since last exposure, the total number of patients (N) in each group. Empty cells indicate requested data.

Characteristic	Placebo		Bevacizumab	
	n	**N**	**n**	**N**
Age				
<65 years	**117**	149	**102**	157
≥65 years	**70**	93	**49**	85
ECOG				
0	**145**	185	**113**	182
1	**42**	57	**38**	59
Cytoreductive surgery for recurrent disease				
Yes	**16**	24	**15**	30
No	**171**	218	**136**	212
Primary site of disease				
Fallopian tube carcinoma	**11**	15	**9**	14
Ovarian carcinoma	**158**	207	**126**	200
Primary peritoneal carcinoma	**18**	20	**16**	28
Recurrence since last platinum therapy (months)				
6 – 12	**83**	102	**63**	100
>12	**104**	140	**88**	142
SLD of target lesions (mm)				
≤Median (59.0 mm)	**99**	126	**69**	118
>Median	**88**	116	**82**	124
CA-125 (U/mL)				
≤35 U/mL	**45**	63	**33**	57
>35 U/mL	**135**	167	**108**	171

Bold text indicates requested data.

Please note that the OCEANS CSR provides a breakdown of time to recurrence in terms of 6-12 and > 12 months, which does include the number of events. This differs from the breakdown requested, and from Figure 5 in the submission, which was obtained from the full publication of OCEANS (Aghajanian et al. 2012) and does not provide the number of events. The above table has been amended to provide the details for the stratified subgroup analysis of 6 – 12 months versus > 12 months.

A19. Please provide a more detailed description of how the IRC validated the outcomes of OCEANS. For example:

- **Did the IRC assess all scans generated during the trial, or validate a random sample of the data?**
- **How many experts formed the IRC?**

The IRC assessed data for each randomised patient (n= 484; see Figure 6 in the submission). The following information is provided in the OCEANS CSR regarding the IRC:

Section 3.1.1: Independent Review Committee

An IRC's assessment of PFS was added as a sensitivity analysis to evaluate the reliability of the primary endpoint of investigator-assessed PFS. The IRC also assessed objective response and response duration on the basis of radiographic and clinical evidence. The IRC used radiologic and clinical evidence to detect tumor progression. CA125 marker data were not sent to the IRC to determine progression status. Review was performed by two radiologists and adjudicated by a third radiologist if necessary. As a next step, an oncologist reviewed clinical data first and then reviewed both the radiologic and clinical evidence to make a final determination of response and progression status. The reviews were performed in a blinded fashion.

A20. Please clarify the rationale for the variation in definition of PFS between OCEANS investigator-assessed PFS and IRC-assessed PFS.

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

It is unknown why there is this discrepancy in definition in the protocol. We assume this is because the remit of the IRC was to examine data collected for patients only while they were on study.

A21. Please complete the table below to provide data on IRC-assessed PFS, objective response and duration of response, analogous to that presented for investigator-assessed outcomes reported for OCEANS. In the table, n = number of people with that event, and N = number of people in analysis. Empty cells indicate requested data.

These data do not appear to be reported in the OCEANS CSR or elsewhere in the relevant publications.

A22. Please clarify how the number of patients in the safety analysis in the bevacizumab group has been calculated. It is stated that the safety analysis comprises patients who have received one dose of study drug. The safety analyses include 247 patients in the bevacizumab group, but the ERG notes that;

- **242 patients were randomised to addition of bevacizumab to gemcitabine plus carboplatin;**
- **5 patients in the placebo arm were classed as protocol violations, having received doses of bevacizumab in error;**
- **1 patient randomised to the bevacizumab group did not receive any dose of study drug;**
- **1 patient in the bevacizumab group received study treatment, but not bevacizumab.**

Please clarify whether, for safety analyses, the bevacizumab group should comprise 245 patients.

No, the inclusion of 247 patients was correct. The points above are due to a reporting error, arising from confusion around the definition of 'BV' and 'PL' in the full text publication (Aghajanian, Blank, Goff, Judson, Teneriello, Husain, Sovak, Yi, & Nycum 2012), which was referred to in the context of the treatment arm in the body versus the context of bevacizumab and placebo alone in the flow diagram.

The correct safety information has been incorporated into the requested CONSORT diagram in A8) and is as follows:

- 242 patients were randomised to each arm
- 5 patients in the placebo arm received dose(s) of bevacizumab in error and were included in the bevacizumab arm
- One patient did not receive bevacizumab, however did receive carboplatin/paclitaxel

The primary safety population is defined as all patients who received at least one dose of protocol treatment; therefore this equates to 247 patients in the bevacizumab arm.

A23. Of the list of adverse events presented within the submission (Section 6.3.5.2), please define which events have been included in the category of "serious adverse events" and how these differ from adverse events classed as Grade 3–5.

The OCEANS protocol states the following regarding Serious Adverse Events:

Serious Adverse Events (Section 5.1.2)

An AE should be classified as an SAE if it meets the following criteria:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
- It is considered a significant medical event by the investigator on the basis of medical judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

All AEs that do not meet any of the criteria for serious should be regarded as **nonserious AEs**.

The terms "severe" and "serious" are not synonymous. Severity (or intensity) refers to the grade of a specific AE; for example, mild (Grade 1), moderate (Grade 2), or severe (Grade 3) myocardial infarction (see Section 5.2.2). "Serious" is a regulatory definition (see previous definition) and is based on patient or event outcome or action criteria usually associated with events that pose a

threat to a patient's life or functioning. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations from the Sponsor to applicable regulatory authorities."

A24. For adverse events (Tables 18–23 in the submission), please provide statistical significance testing of the difference between the groups for events categorised as bevacizumab-specific events (HR with 95% CI, and p value).

It is not possible to determine whether the differences between the bevacizumab and placebo arm for each named Adverse Event are statistically significant, because this type of multiple statistical testing on a single dataset requires a Bonferroni correction to reduce the p-value every time a significance test is conducted.

A25. Please list the adverse events that led to discontinuation of treatment in each arm of OCEANS, with a breakdown by adverse event type.

The following adverse events that led to study drug discontinuation are listed in the OCEANS CSR (Table 30; p79):

MedDRA System Organ Class MedDRA Preferred Term	No. (%) of Patients	
	CG + Pl (n = 233)	CG + Bv (n = 247)
Any adverse events	11 (4.7)	49 (19.8)
Blood and lymphatic system disorders		
Anemia	—	2 (0.8)
Neutropenia	1 (0.4)	4 (1.6)
Thrombocytopenia	2 (0.9)	4 (1.6)
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)
Hemoglobin decreased	—	1 (0.4)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)		
Glioblastoma	—	1 (0.4)
Tumor compression	1 (0.4)	—
Nervous system disorders		
Cerebral ischemia	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 ischemic attack	—	2 (0.8)
Renal and urinary disorders		
Hydronephrosis	—	1 (0.4)

MedDRA System Organ Class MedDRA Preferred Term	No. (%) of Patients CG + Pl (n = 233)	CG + Bv (n = 247)
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		
Dyspnea	—	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)

Bv = bevacizumab; CG = carboplatin + gemcitabine; MedDRA Medical Dictionary for Regulatory Activities; Pl = placebo; "— = 0(0.0); RPLS = reversible posterior leukoencephalopathy syndrome.

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 cutoff date (17 September 2010) were included in this analysis.

[a] One patient had encephalopathy of unknown etiology.

[b] Two were MRI-confirmed RPLS cases

A26. It is stated throughout the submission that OS data may be confounded as a result of post-progression bevacizumab use in the placebo arm.

- **Please clarify whether any analyses have been carried out to investigate the magnitude of any potential bias. For example, based on methods outlined in *DSU Report: Assessing methods for dealing with treatment switching in randomised clinical trials (July 2010)* (available at http://www.nicedsu.org.uk/Crossover-and-survival(2474846).htm)? If so, please provide this analysis for the latest time point (March 2012).**
- **Please provide OS estimates (with 95% CIs) excluding patients that went on to receive bevacizumab in both arms.**

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 data requested concerning survival of patients who did not receive bevacizumab after progression is of limited value as it is likely to be subject to significant bias and therefore is not supplied.

A27. Please clarify the statement that follows, taken from page 56 of the submission.

"One further patient in the BV arm received study treatment, but not bevacizumab." Did this patient receive gemcitabine alone, carboplatin alone, or gemcitabine plus carboplatin?

We are not able to access this individual patient's data within the required timeframe.

Section B: Clarification on cost-effectiveness data

B1. Please provide an updated model and incremental cost-effectiveness ratio (ICER) incorporating the following scenarios:

- **Modelling OS using Kaplan–Meier data from 30th March 2012;**
- **Modelling PFS using Kaplan–Meier data only (i.e. with no parametric modelling), either with more complete PFS data (if available) or using Kaplan–Meier data up to month 30 and assuming zero probability of being progression-free after month 30 (for both arms);**
- **Applying disutilities associated with adverse events, for example, using the reference identified by the ERG (Havrilesky,L.J. 2009 *et al.* Determination of quality of life-related utilities for health states relevant to ovarian cancer diagnosis and treatment; *Gynecol Oncol* 2009 May ; 113(2): 216–220. doi:10.1016/j.ygyno.2008.12.026.);**
- **Using 12 minutes additional pharmacy preparation time for bevacizumab as described in the submission (Section 7.5.5.5) as opposed to the 6 minutes additional pharmacy preparation time applied for bevacizumab in the model (£46 per hour of pharmacy time would equate to £9.20 per 12 minutes, not £4.60);**
- **Using the latest available data (30th March 2012) for estimates of post-progression chemotherapy, surgery and radiotherapy costs. Please report the total number of patients (N) who received post progression chemotherapy, radiotherapy and surgery at this time point for the placebo and bevacizumab arms of the study;**
- **Incorporating post-progression treatment costs at the time point when patients progress (i.e., ensuring that post-progression treatment costs are subject to a discount rate);**
- **Discounting final quality adjusted life years (QALYs) (rather than PFS patient numbers) and final total costs (rather than intermediate estimates).**

Please enable the model to assess each scenario individually and present ICERs for each individual scenario. In addition, please present an ICER following the combined application of all scenarios.

The requested scenarios represent a request for further analyses and data. They are not clarifications of the data presented in the submission. As stated in the discussion section of the submission,

> "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. However, it is worth noting that

subsequent analyses of the data have suggested that the OS benefit in this study is unstable, but that this may be confounded by the unrestricted use of subsequent therapies (Table 8 and Table 9)."

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. Furthermore, the sensitivity analyses already described in the submission clearly indicates that the incorporation of the other changes requested (i.e. utilities, administration costs, post-progression treatment costs and discount rates) is highly unlikely to change the decision outcome.

B2. Please provide a scenario analysis with an updated model and ICER in which only partially platinum-sensitive patients (relapse after first-line therapy between 6 and 12 months) from OCEANS are modelled. Please use the latest available data for PFS and OS.

This scenario analysis is a request for further data and analysis rather than a request for clarification of the submission and is not supplied.

B3. Please present updated probabilistic sensitivity analysis (PSA) which includes estimates of uncertainty for:

- **Treatment administration costs;**
- **Costs of post-progression therapies;**
- **Cost of palliative care.**

The model supplied in the submission incorporates uncertainty for treatment administration costs in the PSA. The uncertainty is bounded by the upper and lower quartiles of the NHS reference costs and is assumed to have a gamma distribution, in common with all other costs. This was not clear in the original submission.

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. We direct the ERG to the results of the deterministic sensitivity analyses where the effect of removing these costs was explored (Table 49, page 167) and found to change the incremental cost of treatment from £44,428 to £45,697 or £44,498, respectively. Therefore it is unlikely that these parameters will provide substantial additional information on the uncertainty of the model or affect the decision.

B4. Please provide the following versions of worksheet "KM OS" in the economic model:

- **OS Kaplan–Meier data from 30th March 2012 for all women (by arm of therapy);**
- **OS Kaplan–Meier data from 30th March 2012 for women who received between 1 and 6 cycles of chemotherapy (by arm of therapy);**
- **OS Kaplan–Meier data from 30th March 2012 for all women (by arm of therapy) as assessed by the IRC;**
- **OS Kaplan–Meier data from 30th March 2012 for women who received between 1 and 6 cycles of chemotherapy (by arm of therapy) as assessed by the IRC.**

Please see our response to question A2 and note that OS is independent of the IRC assessment of progression and therefore the third dataset requested is not appropriate.

B5. Please provide the following versions of worksheet "KM PFS" in the economic model:

- **The most recent PFS data for both arms, if available and different from the September 2010 data included in the model, for all women (by arm of therapy);**
- **The most recent PFS data for both arms for women who received between 1 and 6 cycles of chemotherapy (by arm of therapy);**
- **The most recent PFS data for both arms for all women (by arm of therapy) as assessed by the IRC;**
- **The most recent PFS data for both arms for women who received between 1 and 6 cycles of chemotherapy (by arm of therapy) as assessed by the IRC.**

Please see our response to question A2 and note that these requests are for further data and analysis rather than clarification of the submission and are not supplied.

B6. Please provide the Excel workbook described in Section 7.7.2 and 7.7.3 containing supplementary material worksheets "life years" and "QALYs" as the ERG cannot locate these.

These workbooks are supplied separately and were omitted from the original submission in error.

B7. Please provide a replica of Table B6 comparing clinical trial results from the most recently available data set (30th March 2012) with the model results (for the same time cut-off).

Please see our response to question B2.

B8. For post-progression therapy data used within the economic model submitted (September 2010):

- **Please confirm the total number of patients (N) in the bevacizumab and the placebo arm at this time point who received post-progression treatment. Please complete the table below:**

Post-progression intervention	Placebo (N)	Bevacizumab (N)
Chemotherapy		
Radiotherapy		
Surgery		

- **Please provide the full list of post-progression chemotherapy treatments (i.e., including therapies not expected to impact on survival) and the number of patients that received the treatment in each arm for this data set.**
- **Please indicate for therapies outlined in the worksheet "CHEMO" which and how many post-progression chemotherapy treatments were concomitant (i.e., where only one administration cost would apply). Please detail the combinations used and the number of patients receiving each combination.**

We refer the ERG to sheet “Post-Prog Treatments” in the Excel model provided in the submission which provides all the data requested.

B9. The figures presented in Table B10 “Summary of predicted resource use by category of cost” (pg 167) do not sum to the total figure presented at the bottom of the table. Please confirm that the mean supportive care cost of progressed disease should read £9,222 for bevacizumab plus carboplatin plus gemcitabine, and £10,533 for carboplatin plus gemcitabine to represent the figures presented in the economic model.

The ERG is correct. The discrepancy is due to differences in accounting for the cost of post-progression therapies which ought to have been included in the total supportive care cost of progressed disease.

B10. In Section 7.5.5.4, it is stated that “it was assumed the time taken to prepare carboplatin and gemcitabine in pharmacy would be 12 minutes, as determined in a prospective time-and-motion study conducted in the UK for oxaliplatin (Millar et al. 2008)”. Similarly, in Section 7.5.5.5, it is stated that bevacizumab would be associated with an additional 12 minutes of pharmacy preparation time, with the same reference cited in support of the statement.

- **The ERG was unable to validate the reported time taken to prepare carboplatin and gemcitabine or bevacizumab using the reference cited. Please clarify whether the reference is correct. If not, please supply an alternative reference in support of this statement.**
- **Please explain the rationale for assuming that the pharmacy preparation time would be similar for carboplatin plus gemcitabine, or bevacizumab when compared with the therapies in Millar (2008).**

This 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 and consequently the overall incremental costs of the addition of bevacizumab to gemcitabine and carboplatin.

Section C: Textual clarifications and additional points

Systematic review

C1. In the systematic review of the literature on the clinical effectiveness of interventions of interest, studies that include fewer than 200 patients have been excluded. Please clarify the rationale underlying this exclusion criterion.

This arbitrary threshold was chosen in order to focus on studies with a sufficient population size (i.e. at least 100 patients per arm) to provide robust efficacy data. This was particularly relevant to the non-RCT literature search, where small-scale uncontrolled retrospective/observational studies may not provide particularly informative data, and the network analysis (for which the excluded references are provided below), where the comparison of numerous small-scale trials may result in an even larger level of heterogeneity.

While this threshold was an exclusion criteria for each of the searches (excluding the GI perforation safety search), no results of the main RCT systematic review were excluded due to population size (Tables 57 – 61).

C2. In section 10.2.7, there is the statement relating to the systematic search of the Cochrane library that "No relevant RCTs were identified". Please clarify whether this statement means that no relevant RCTs additional to those identified by searches of EMBASE and MEDLINE were identified.

The statement related to the systematic search of the Cochrane library does mean that no relevant RCTs were identified from the Cochrane review, other than those previously identified by the ProQuest literature search (which included EMBASE and MEDLINE).

C3. Please clarify whether study selection (described in Section 6.2), and subsequent data extraction were carried out independently by two reviewers.

The study selection and data extraction was carried out by one reviewer.

C4. The table below lists those studies excluded from the network meta-analysis on the basis of including too few people (<200). Please provide full reference details and full publications for the excluded studies.

Publication author	Reference details
NUM	
2010	
Bafaloukos, D	Bafaloukos D, Linardou H, Aravantinos G, et al. BMC Med. 2010 Jan 7;8:3
Gonzalez-Martin, A	Gonzalez-Martin A, Casado A, Arranz J, et al. Annals of Oncology, suppl. SUPPL. 8 21 (Oct 2010): viii307.
Markman, M	Markman M, Moon J, Wilczynski S, et al. Gynecologic Oncology 116. 3 (Mar 2010): 323-325.
Nam, E	Nam E, Kim J, Kim J, et al. American journal of clinical oncology 33. 3 (Jun 2010): 233-7.
2008	
Alberts, D	Alberts D, Liu P, Wilczynski S, et al. Gynecologic oncology 108. 1 (Jan 2008): 90-4
2005	
Gonzalez-Martin, A	Gonzalez-Martin A, Calvo E, Bover I, et al. Ann Oncol 2005;16:749-55
2002	
de Jongh, F	de Jongh F, de Wit R, Verweij J, et al. Eur J Cancer 2002;38:2005-13

Additional clinical effectiveness clarifications

C5. Please clarify the term "not known to have discontinued" relating to the safety analysis. Does this statement mean that these patients were lost to follow-up?

We acknowledge the ambiguity of this wording, which was taken from the CSR and would like to clarify that it does not necessarily imply that these patients were lost to follow-up. For example, in Table 2 of the OCEANS CSR (Summary of Patient Disposition and Reasons for Treatment Discontinuation), these patients are reported as “not yet discontinued BV/PL”.

C6. Within the submission (pg 7), it is noted that patients with platinum-sensitive recurrent disease have a wider choice of subsequent therapies. It is also noted that, in the UK, gemcitabine plus carboplatin is not typically the first choice for second-line treatment of platinum-sensitive recurrent ovarian cancer. However, in Section 2.7, it is stated that the most appropriate comparator for the decision problem is 3-weekly gemcitabine plus carboplatin with no supporting statement to justify this choice. Please clarify why, of the treatment options available for platinum-sensitive disease, gemcitabine plus carboplatin is the most appropriate comparator for the decision problem that is the focus of this STA.

Although carboplatin-gemcitabine (GC) is not the most popular choice for second-line treatment for recurrent platinum sensitive ovarian cancer, it is the most appropriate comparator for this STA. The purpose of the STA is to determine the cost-effectiveness of bevacizumab in this setting and the only available Phase III clinical data are for GC plus bevacizumab versus GC plus placebo.

The indirect comparison of Phase III studies of other chemotherapy options in the recurrent platinum sensitive setting concluded that the levels of hetereogeneity between the four large studies were too high for an indirect comparison to provide relevant results. This made it impossible to compare bevacizumab plus GC with a different chemotherapy (section 6.6, page 71-80).

The most popular chemotherapy option for recurrent ovarian cancer, liposomal doxorubicin is currently unavailable and may not reappear on the market until the end of 2014. Thus a comparison against this therapy, even if there were clinical study data to support it, would have no relevance to current UK clinical practice.

C7. Please provide references to support each sentence in the paragraph below (reproduced from pg 18 of the submission):

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. This suggests that a total of approximately 2,100 patients should be eligible for second-line bevacizumab therapy in the UK.

Please find attached a data on file (Roche Products Limited. Data on file RXUKDONF00257. October 2012) and a reference to a British Heart Foundation monograph (Prevalance of CHD in all ages of women. British Heart Foundation Statistics Database. Morbidity: Figure 2.7 Prevelance of CHD, stroke, myocardial infarction and angina by age and sex, 2006, England. Page 50. Accessed February 2012 (http://www.bhf.org.uk/idoc.ashx?docid=76c0f867-46aa-425d-8a7e-862760819037&version=-1)) for the number of patients contraindicated for bevacizumab in support of this paragraph.

C8. In Section 8, the number of patients eligible for treatment with bevacizumab in England and Wales in year 1 has been calculated to be 1,804. However, in Section 2, the number of patients in the UK estimated to be eligible for treatment with bevacizumab is estimated to be 2,100. Please clarify how the number of 1,804 eligible patients in England and Wales has been reached; please provide details of a reference to support any assumptions made.

Ovarian cancer figures for Scotland in 2010 show 613 registered new cases and 387 deaths (ISD Scotland, 2012). Assuming that the majority of deaths are in patients with recurrent ovarian cancer, this gives a number of around 300 of eligible patients in Scotland, which is part of the UK.

Additional cost effectiveness clarifications

C9. Please provide the reference within the economic model for body surface area (BSA) presented in the "CHEMO" worksheet. In this worksheet, the reference cited for BSA is the full publication of the OCEANS RCT, but the BSA does not match to either the UK population BSA or OCEANS.

The number referred to is indeed incorrect and ought to be a direct link to the value reported on the "Model Inputs" sheet, BSA_new.

C10. Average weight data are used to estimate the weight of UK patients for the purposes of dosing costs. Please identify the source of the overall weight of the study population (68.15 kg) as the ERG is unable to locate this figure in the Sacco 2010 reference.

We address this in Section 7.5.5.1 of our submission (p146):

> "It should be noted that this study did not provide the weight and height of individuals and so these parameters must be imputed from the overall survey female population (68.15kg, 14.74kg) adjusted proportionately using the Du Bois & Du Bois BSA formula (Du Bois D. & Du Bois 1989) so that:
>
> Individual body weight = 68.15kg * (individual BSA / mean BSA)$^{(1/0.425)}$
>
> A consequence of this approach is to assume all patients are of equal height (160.05cm)."

C11. The sample size for carboplatin plus gemcitabine in the economic model is set as 251 (model inputs worksheet, cell C92, name s_com). The sample size for bevacizumab plus carboplatin plus gemcitabine in the economic model is set as 244 (model inputs worksheet, cell C93, name s_new). Please explain how these figures have been derived.

These numbers are included in error. They ought to be 242 and 242 respectively. We would like to point out that these numbers are only used to derive uncertainty in the adverse events of patients in the model and therefore do not have a substantial impact on the model results.