18 October 2012

National Institute for Health and Clinical Excellence

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London
WC1V 6NA

[redacted]

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[redacted]

Re: Single Technology Appraisal – Bevacizumab for the treatment of recurrent advanced ovarian cancer

The Evidence Review Group, BMJ-Technology Assessment Group (BMJ-TAG) and the technical team at NICE have now had an opportunity to take a look at submission received on the 24th September 2012 by Roche. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports. As you will only receive the evidence review group report 5 days prior to the Appraisal Committee meeting, you may want to respond to the points raised and provide further discussion from your perspective at this stage.

We request you to provide a written response to this letter to the Institute by 5pm on **01 November 2012**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

If you have any further queries on the technical issues raised in this letter then please contact [redacted]

Yours sincerely

[redacted]
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

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

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.

	Placebo		**Bevacizumab**	
	n	N	n	N
Investigator-assessed				
Progression-free survival (PFS)				
No. of patients with an event				
Median PFS, months				
Mean PFS, months				
Hazard ratio (HR; relative to placebo)				
95% CI				
p value (log-rank)				
Disease progression				
No. of patients with an event				
HR (relative to placebo)				
95% CI				
p value (log-rank)				
Death				
No. of patients with an event				
HR (relative to placebo)				
95% CI				
p value (log-rank)				
Overall survival (OS; based on data recorded at 17th September 2010)				
No. of patients with an event				
Median OS (95% CI), months				
Mean OS (95% CI), months				
HR (relative to placebo)				
95% CI				
p value (log-rank)				

OS (based on data recorded at 29th August 2011)				
No. of patients with an event				
Median OS (95% CI), months				
Mean OS (95% CI), months				
HR (relative to placebo)				
95% CI				

p value (log-rank)				
OS (based on data recorded at 30th March 2012)				
No. of patients with an event				
Median OS (95% CI), months				
Mean OS (95% CI), months				
HR (relative to placebo)				
95% CI				
p value (log-rank)				
Objective response rate				
No. of patients with objective response				
Complete response				
Partial response				
HR and 95% CI for objective response rate				
No. of patients not known to have an event				
Duration of response, months				
Median				
95% CI				
Mean				
95% CI				
Stratified analysis				
HR (relative to placebo)				
95% CI				
p value (log-rank)				
Unstratified analysis				
HR (relative to placebo)				
95% CI				
p value (log-rank)				

Independent-review committee (IRC) assessed				
Progression-free survival				
No. of patients with an event				
Median PFS, months				
Mean PFS, months				
HR (relative to placebo)				
95% CI				
p value (log-rank)				
Disease progression				
No. of patients with an event				
HR (relative to placebo)				
95% CI				

p value (log-rank)				
Death				
No. of patients with an event				
HR (relative to placebo)				
95% CI				
p value (log-rank)				
OS (based on data recorded at 17th September 2010)				
No. of patients with an event				
Median OS (95% CI), months				
Mean OS (95% CI), months				
HR (relative to placebo)				
95% CI				
p value (log-rank)				
OS (based on data recorded at 29th August 2011)				
No. of patients with an event				
Median OS (95% CI), months				
Mean OS (95% CI), months				
HR (relative to placebo)				
95% CI				
p value (log-rank)				

OS (based on data recorded at 30th March 2012)				
No. of patients with an event				
Median OS (95% CI), months				
Mean OS (95% CI), months				
HR (relative to placebo)				
95% CI				
p value (log-rank)				
Objective response rate				
No. of patients with objective response				
Complete response				
Partial response				
HR and 95% CI for objective response rate				
No. of patients not known to have an event				
Duration of response, months				
Median				
95% CI				
Mean				
95% CI				
Stratified analysis				

HR (relative to placebo)	
95% CI	
p value (log-rank)	
Unstratified analysis	
HR (relative to placebo)	
95% CI	
p value (log-rank)	
Placebo = carboplatin plus gemcitabine plus placebo Bevacizumab = carboplatin plus gemcitabine plus bevacizumab	

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).

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.

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?

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)?

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.

Type of therapy	Placebo	Bevacizumab	Relative risk (RR) (95% CI) p value
Any subsequent anticancer therapy			
Subsequent bevacizumab			
Subsequent chemotherapy			
Pegylated liposomal doxorubicin			
Paclitaxel			
Platinum agent			
Other chemotherapy			

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).

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.

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.

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		Discontinued (due to adverse effect or patient/physician choice) or lost to follow-up	
	Placebo	Bevacizumab	Placebo	Bevacizumab	Placebo	Bevacizumab
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
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27						
28						
29						
30						

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).

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.

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.

	Placebo		Bevacizumab	
	n	N	n	N
Investigator-assessed				
Progression-free survival				
No. of patients with an event		242		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				
HR (relative to placebo)				
95% CI				
p value (log-rank)				
Death				
No. of patients with an event				
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. Empty cells indicate requested data.

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)		102		100	0.41 (0.29 to 0.58)
Subgroup of		140		142	0.55

patients with full platinum-sensitivity (>12 months since last platinum exposure); reported to include 282 patients (pg 62 of submission)					(0.41 to 0.73)

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.

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.

Characteristic	**Placebo**		**Bevacizumab**		**Statistical analysis**
	n	N	n	N	HR (95% CI)
Discontinuation due to disease progression	160	242	104	242	
Discontinuation due to physician or patient choice	60	242	54	242	
Discontinuation due to an adverse event	12	242	55	242	
Number of patients receiving treatment at data cut off					

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.

Characteristic	**Placebo**		**Bevacizumab**		**Statistical analysis**
	n	N	n	N	HR (95% CI)
Investigator-assessed objective response rate					
Objective response	139	242	190	242	
Complete	22	242	42	242	

response					
Partial response	117	242	148	242	

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		149		157
≥65 years		93		85
ECOG				
0		185		182
1		57		59
Cytoreductive surgery for recurrent disease				
Yes		24		30
No		218		212
Primary site of disease				
Fallopian tube carcinoma		15		14
Ovarian carcinoma		207		200
Primary peritoneal carcinoma		20		28
Recurrence since last platinum therapy (months)				
<12				
12 to 24				
>24				
SLD of target lesions (mm)				
≤Median (59.0 mm)		126		118
>Median		116		124
CA-125 (U/mL)				
≤35 U/mL		63		57
>35 U/mL		167		171

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?

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).

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.

	Placebo		**Bevacizumab**	
	n	N	n	N
Progression-free survival				
No. (%) of patients with an event	148 (61)	242	119 (49)	242
Disease progression				
No. of patients with an event		242		242
HR (relative to placebo)				
95% CI				
p value (log-rank)				
Death				
No. of patients with an event		242		242
HR (relative to placebo)				
95% CI				
p value (log-rank)				

Objective response rate				
No. of patients with an event				
No. of patients not known to have an event				
Duration of response, months				
Median				
95% CI				
Mean				
95% CI				
Stratified analysis				
HR (relative to placebo)				
95% CI				
p value (log-rank)				
Unstratified analysis				
HR (relative to placebo)				

95% CI	
p value (log-rank)	

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.

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.

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).

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

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.

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?

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.

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.

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.

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.

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.

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.

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).

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.

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.

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).

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.

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.

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

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	
Gonzalez-Martin, A	
Markman, M	
Nam, E	
2008	

Alberts, D	
2005	
Gonzalez-Martin, A	
2002	
de Jongh, F	

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?

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.

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.

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.

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.

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.

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.