[redacted]

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BY EMAIL

13 March 2013

RE: Bevacizumab in combination with paclitaxel and carboplatin for the first-line treatment of ovarian cancer

Dear [redacted]

Thank you for the opportunity to comment on the ACD for the above technology appraisal.

We are disappointed the Committee has failed to appropriately consider the full impact of crossover in the GOG-0218 study in this ACD. Whilst the impact of crossover has been considered when evaluating the clinical effectiveness of bevacizumab (Section 4.7 of the ACD), this appears not have been considered when evaluating the cost-effectiveness of bevacizumab. We do not consider this to be reasonable.

In the GOG-0218 study **crossover to bevacizumab was permitted following progression** on chemotherapy. This is not representative of UK clinical practice, nor the decision problem set out in the NICE scope. As a result, median survival for patients randomised to chemotherapy in GOG-0218 does not reflect the decision problem.

Patients in the chemotherapy arm of G0G-218 experienced median OS of 40.6 months. This is significantly higher than the median survival observed for a matched population from the ICON7 study. In ICON7, a study conducted in the UK in which crossover was not permitted, median OS of 28 months was observed.

Furthermore, the median survival observed for patients randomised to chemotherapy in GOG-0218 is significantly higher than that seen in historical data for this patient population (FIGO III and IV with sub-optimal debulking) (Du Bois 2009).

We believe that this disparity was caused by one key differentiator between ICON7, GOG-0218 and this historical control data – the fact that bevacizumab use after first disease progression was

permitted in GOG-218. As a consequence, it is our belief that any analysis based upon the GOG-218 data that does not take this into account will result in the incremental survival benefit of bevacizumab being underestimated, and the ICER associated with bevacizumab relative to chemotherapy alone being significantly inflated.

Whilst the chemotherapy arm in GOG-218 is clearly confounded by crossover and therefore unrepresentative of the survival outcomes expected in current UK practice, data *is* available on the survival of patients given chemotherapy without bevacizumab use after progression. The ICON7 study was a UK MRC sponsored study conducted in the UK with the chemotherapy regimens used in the UK. The control arm from this study provides a clear proxy for an un-confounded control arm in UK clinical practice.

We have therefore conducted a sensitivity analysis utilising this proxy data in order to investigate the impact of a more representative chemotherapy control arm (an analysis similar to that conducted using the Bedikian 2011 data in the NICE appraisal of vemurafenib (TA258)). This analysis demonstrates that the ICER associated with bevacizumab in this setting is £45,896. We believe this estimate to be more representative of that expected in UK clinical practice where post-progression use of bevacizumab is not standard practice.

Furthermore, we have concerns that the ACD does not report the ICER estimated by Roche for the use of bevacizumab in the ICON7 study high-risk population. Whilst the clinical data for this study has been reported in the ACD, the equivalent cost-effectiveness data has not been reported. In the interests of transparency and in line with the requests of the UK clinical community we believe this information should be reported within the ACD. We therefore urge the Committee to review and report all the evidence submitted and discussed at the first Committee meeting, including the cost-effectiveness of all clinically relevant dosing regimens - given the need to appropriately consider the impact of crossover.

If any clarification or further analyses would aid the Committee in their deliberations we would be more than happy to provide it.

Yours Sincerely,

[redacted]

[redacted]

Roche Products Limited

1. **Has all of the relevant evidence been taken into account?**

The effect of crossover bevacizumab on OS in GOG-0218 has not been considered appropriately

The Committee discussed the difficulties associated with estimating the likely survival benefit of bevacizumab plus carboplatin and paclitaxel in GOG-0218 due to unrestricted use of bevacizumab in patients after progression (Section 4.7, p20), but the consequences of this uncertainty for the cost-effectiveness analysis were not covered in the ACD. If the survival benefit of adding bevacizumab to standard therapy has been underestimated in GOG-0218, this will have a considerable effect on the ICER calculated by any model reliant on data from this clinical trial.

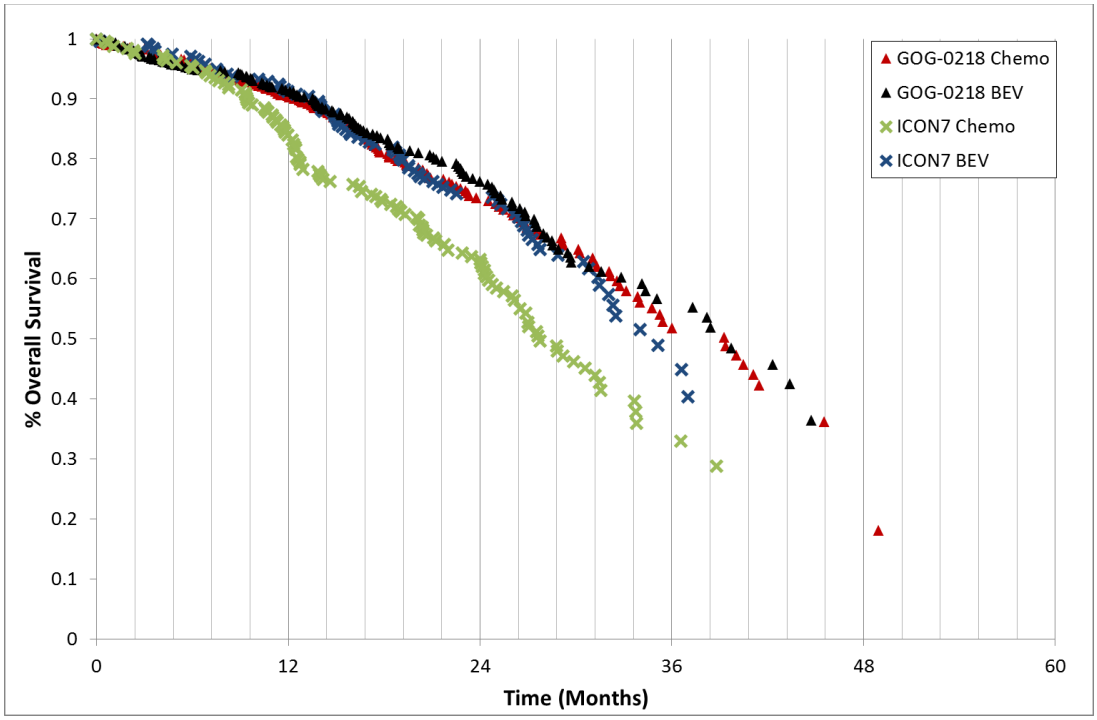
This issue is clearly illustrated in a comparison of the incremental QALYs observed in models based on the key trials; GOG-0218 and ICON7. It is worth noting that the incremental gains in QALYs before disease progression in both models are comparable (0.243 in GOG-0218 vs 0.252 in ICON7) and are reflective of comparable clinical gains in PFS (6 months increase in median PFS in GOG-0218, compared to 5.68 months in ICON7 HR subgroup). In contrast, there is a large difference in incremental QALYS after progression which may reflect the differences in study design which allowed patients in GOG-0218 to receive bevacizumab post progression (Table 1 below). In standard NHS practice bevacizumab is not given as a crossover therapy following disease progression, we therefore believe the post-progression period from ICON-7 provides a more representative evidence base on which to assess the efficacy of first line bevacizumab in real world UK clinical practice.

Table 1: Comparison of incremental QALYs in models based on key trial data (from Tables B7 and B8, p181 of original submission)

Health State	Incremental QALY	
	GOG-0218	**ICON7**
Cross-over	permitted	not permitted
PFS	0.243	0.252
PD	-0.055	0.309
Total	0.188	0.561

The potential consequences on overall survival of this difference in the treatment of patients after progression are illustrated when the survival curves for the 2 studies are compared on a single chart (Figure 1).

Figure 1: Overall survival of patients in GOG-0218 and ICON7 studies are different



The survival of patients randomised to receive bevacizumab in the high risk subgroup of ICON7 (which have similar baseline characteristics to the ITT population in GOG-0218) is indistinguishable from that of patients in GOG-0218 (regardless of initial treatment allocation) for at least the first 30 months. In contrast, patients in the high risk subgroup of ICON7 randomised to receive standard chemotherapy alone (i.e. carboplatin and paclitaxel), and restricted from receiving bevacizumab after progression, have a different survival expectation from the control arm in GOG-0218.

The exploratory analysis of 3 prospective randomized trials (AGO-OVAR, 3, 5 and 7) conducted by du Bois and colleagues (du Bois 2009) was referenced in our submission as supportive evidence of the most appropriate parametric function to extrapolate OS beyond the follow-up period of either GOG-0218 or ICON7. The results of the du Bois study have demonstrated that residual tumour following surgery is a prognostic factor for poorer outcomes in ovarian cancer patients (both PFS and OS). Median survival in patients (regardless of staging) without any visible residual disease was 99.1 months (95% CI, 83.5to -), for those with 1-10 mm was 36.2 months (95% CI, 34.6 to 39.4) and those with >10 mm residual disease was 29.6 months (95% CI, 27.4 to 32.2). Stratified analysis of PFS and OS by disease staging (FIGO IIB-IIIB, FIGO IIIC and FIGO IV) was also performed and it is the results of analyses of patients with advanced disease (FIGO IIIC and IV) which most closely conform to the licenced population.

The Kaplan-Meier survival curve of the ITT population of GOG-0218 randomised to receive chemotherapy is comparable to, or better than, that of patients with Stage IIIC disease with residual tumour after surgery (Table 2 and Figure 2), despite the presence of approximately 25% FIGO IV patients in the study cohort.

In comparison, the Kaplan-Meier survival curve of the expanded HR subgroup of ICON7 is as expected from a pooled population of FIGO IIIC and IV patients (Table 2 and Figure 3).

Table 2: Median OS for patients receiving chemotherapy in GOG-0218 is greater than expected from their baseline characteristics

Patient population	Reference	N	Median OS (months)
GOG-0218 ITT Chemotherapy	Table 15 of MS (p85)	625	40.6
ICON7 HR subgroup Chemotherapy	Table B4 of MS (p180)	251	27.76
FIGO IIIC (any residual tumour)	Table 3 of (du Bois 2009)	1293	34.2
FIGO IV (any residual tumour)		467	24.6

Figure 2: Overall survival in the chemotherapy arm of GOG-0218 is better than clinical expectation

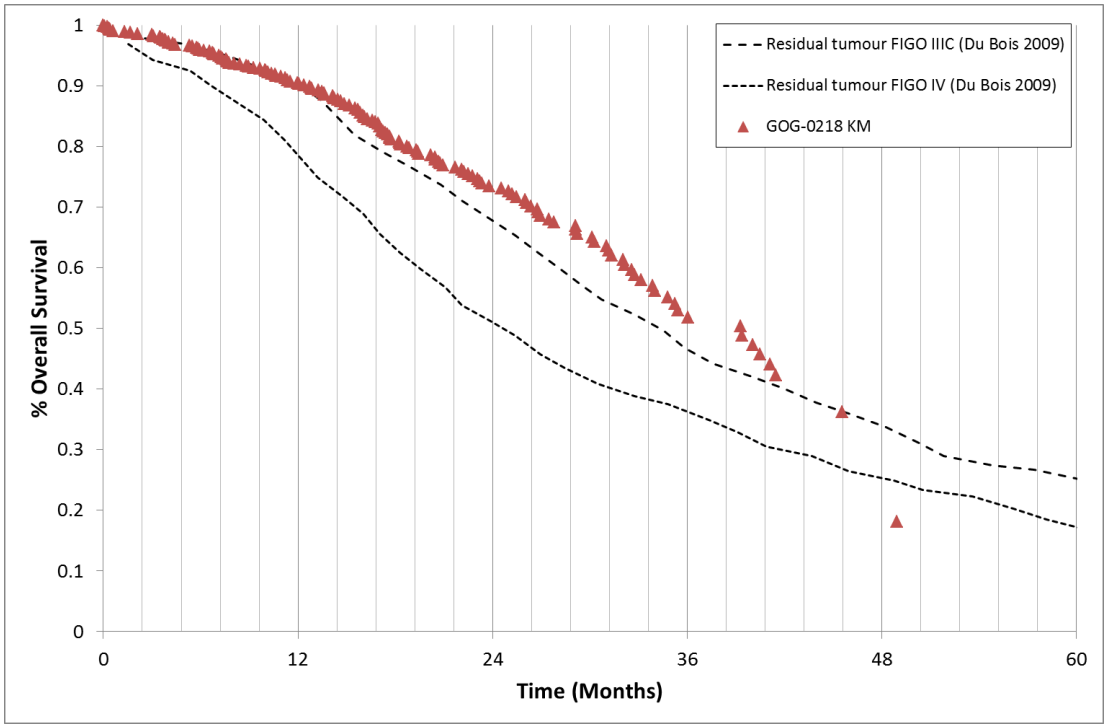
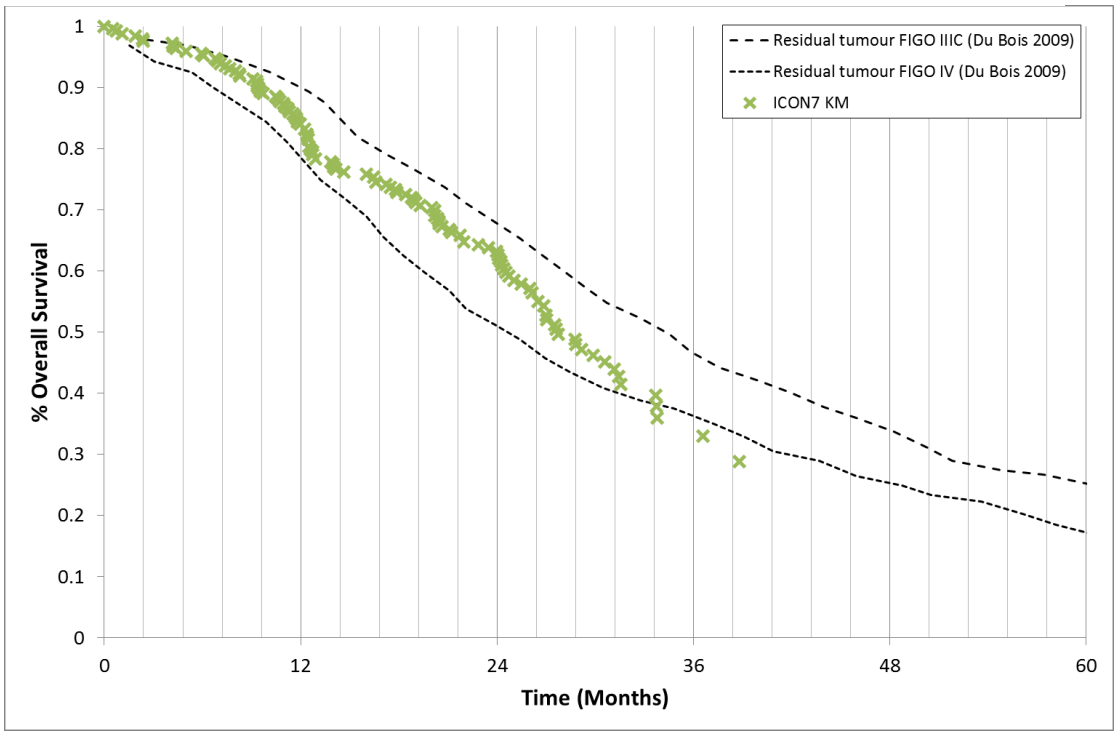


Figure 3: Overall survival in the chemotherapy arm of ICON7 is similar to clinical expectation



The high risk subgroup of ICON7 used in this analysis is broadly comparable (in terms of disease characteristics at baseline) to the ITT population of the GOG-0218 and therefore the most likely explanation for this difference in overall survival for the patients in the 'control' arms of the two studies is the exposure to bevacizumab of patients after progression in the GOG-0218 study.

In light of this, we have conducted a further sensitivity analysis on the economic evaluation of GOG-0218 to explore the assumption that the overall survival curves observed in ICON7 are more plausible given restrictions on bevacizumab to a first line treatment setting. Briefly:

- we used the GOG-0218 economic model which was submitted and incorporated the adjustments and corrections recommended by the ERG in their report to provide a 'baseline' ICER of £142,477/QALY (in agreement with Table 14 on page 46 of the ERG report).

- The OS curves for both treatment arms of the ICON7 study, as modelled by the log-logistic functions described in the original submission, were subsequently used in the 'updated' GOG-0218 model. Structurally therefore, the GOG-0218 model must be changed to a fully AUC model where the proportion of patients in the Progressed Disease state are defined as those still alive and not in PFS (i.e. PD = OS – PFS).

The results of this sensitivity analysis are provided in Table 3 and suggest the ICER for the addition of bevacizumab to standard chemotherapy as described in the GOG-0218 study could plausibly be as low as £46,000 per QALY. Further details of this analysis are provided in Appendix 1.

Table 3: Exploratory analyses of GOG-0218 economic model

Scenario	Treatment	Costs (£)	QALYs	ICER (£/QALY gained)
ERG base case	CPB	48,318	4.455	-
	CP	18,001	4.195	-
	Incremental	30,317	0.26	142,477
Overall survival from GOG-0218 chemotherapy arm replaced with ICON7	CPB	47,777	4.241	-
	CP	15,966	3.319	-
	Incremental	31,810	0.92	45,896

Please note that Section 4.16 of the ACD (p25) contains a factual error. The incremental QALY for the ITT population in the GOG-0218-based model is reported as 0.299. The correct figure from the original submission is 0.188.

2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The cost-effectiveness evidence for ICON7 has not been appropriately discussed

We believe that the ACD does not provide a complete account of the discussions of the cost-effectiveness evidence for ICON7 at the Committee meeting because it omits any estimate of the likely ICER for this study.

The importance of an estimate of cost-effectiveness as used by clinicians in practice was highlighted by the clinical specialists at the meeting (for example, to assist local applications for funding). Indeed, it was suggested by the NICE Programme Director that a statement about the cost-effectiveness of using bevacizumab as described in the ICON7 study could be included in the report, even though any recommendation to the NHS on implementation would be restricted to the licensed treatment dose and duration.

Furthermore, the ERG has provided a critique of the economic model using bevacizumab according to the ICON7 study in the Appendix to their report (pages 50-58) and it was the subject of much discussion during the meeting. The absence of a record of this discussion is not a transparent representation of the data presented and discussed by the Committee.

It seems unreasonable that clinical evidence from ICON7 is considered by the Committee to have

> *"… contributed to the body of knowledge about the efficacy of bevacizumab plus paclitaxel and carboplatin for advanced ovarian cancer." (Section 4.9, p21)*

but the cost-effectiveness model based on this evidence is

"… not relevant to the decision problem" (Section 4.16, p26)

This appears to be contrary to the Secretary of State's direction to NICE to consider the broad balance of clinical benefits and costs, specifically:

> *"(f) to look into and consider, for the purpose of advising the Secretary of State with regard to possible improvements in the provision of health services and in the effective use of available resources, such other matters as may be notified by the Secretary of State;"*
>
> (paragraph 4a, section 2 (1), Directions and Consolidating Directions to the National Institute of Health and Clinical Excellence 2005).

In the interest of transparency, completeness and consideration of current NHS practice we believe Roche's estimate of the cost-effectiveness of bevacizumab based upon the ICON-7 study should be reported in the ACD.

Median PFS gain in stage III patients with suboptimally debulked cancer

The report contains an arithmetical inaccuracy in several places (Sections 3.9 [p9], 4.11 [p23] and the summary of key conclusions [p29]). The difference in median PFS for stage III patients with suboptimally debulked cancer should be 6.8 months (10.1 months CP vs 16.9 months CPB7.5).

3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

No, in view of the comments and issues described above.

Appendix 1

Table 4 presents disaggregated outcomes and costs predicted by economic evaluations described in answer to Question 1. For consistency the time horizon has been set to 25 years in order to provide alignment with the recommendation of the ERG. Identical cells have been colour coded to aid comparison and to confirm expected changes to the ERG base case model of GOG-0218 (yellow cells) when OS is modelled using data from the ICON7 study (orange cells).

Table 4: Disaggregated outputs of economic models presented as evidence

	ERG base case			GOG-0218 PFS/ICON7 OS			ICON7 model		
	CPB	CP	Incremental	CPB	CP	Incremental	CPB	CP	Increment
Mean life years	4.455	4.195	0.260	4.241	3.319	0.922	4.241	3.319	0.922
Mean Time in PFS (yrs)	1.909	1.586	0.322	1.909	1.586	0.322	1.530	1.209	0.321
Mean Time in Progression (yrs)	2.546	2.609	-0.063	2.332	1.732	0.600	2.711	2.109	0.601
Mean QALYs	3.342	3.129	0.213	3.187	2.494	0.693	3.154	2.462	0.691
Mean QALY in PFS	1.497	1.239	0.258	1.497	1.239	0.258	1.189	0.934	0.255
Mean QALY in Prog	1.845	1.891	-0.045	1.690	1.255	0.435	1.965	1.529	0.436
Mean Total Cost (£)	48,318	18,001	30,317	47,777	15,966	31,810	35,291	16,968	18,323
Mean Cost of PFS incl. Cost of AE's (£)	35,765	5,304	30,461	35,765	5,304	30,461	19,454	1,798	17,656
Cost of Bevacizumab (£)	29,378	-	29,378	29,378	-	29,378	16,653	-	16,653
Administration Cost of Bevacizumab (£)	850	-	850	850	-	850	861	-	861
Cost of Carboplatin (£)	104	105	- 1	104	105	- 1	107	102	5
Cost of Paclitaxel (£)	123	123	- 1	123	123	- 1	121	118	4
Administration Cost of Carboplatin & Paclitaxel (£)	711	714	- 3	711	714	- 3	726	697	29
Mean Supportive Care Cost of PFS (Health State) (£)	1,023	851	173	1,023	851	173	820	648	172
Mean Supportive Care Cost of Progression (£)	12,553	12,697	- 144	12,012	10,662	1,349	15,837	15,170	668
Cost of AE's (£)	3,576	3,512	64	3,576	3,512	64	165	233	- 68
Cost per Life Year Gained (£)			116,686			34,483			19,863
Cost per QALY Gained (£)			142,477			45,896			26,507

CP: Carboplatin + Paclitaxel, CPB: Carboplatin + Paclitaxel + Bevacizumab,