NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Roche Products	**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 (**Error! Reference source not found.** not reproduced here). 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. 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 (not reproduced here).	Comments noted. The effect of crossover on overall survival in the GOG-0218 economic model was considered in further detail by the Appraisal Committee at its second meeting. Please see section 4.16 of the FAD.

Consultee	Comment	Response
	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, 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 not reproduced here). 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.	

Consultee	Comment	Response
	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 **Error! Reference source not found.** [not reproduced here] 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 [not reproduced here].	
	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.	Comment noted. The relevant sentence has been removed from the FAD.

Consultee	Comment	Response
Roche products	**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.	Comment noted. The Appraisal Committee considered the cost effectiveness of bevacizumab at its unlicensed dose of 7.5 mg/kg based on ICON7 at its second meeting. See FAD Sections 4.17 and 4.18.

Consultee	Comment	Response
	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).	Comment noted. These arithmetical inaccuracies have been corrected for in the relevant sections of the FAD.

Consultee	Comment	Response
Roche products	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** No, in view of the comments and issues described above.	Comment noted. The Committee agreed that the range of ICERs obtained from the cost-effectiveness model of bevacizumab plus paclitaxel and carboplatin were outside the range normally considered as a cost-effective use of NHS resources. It therefore concluded that bevacizumab within its marketing authorisation (that is, at a dose of 15 mg/kg), plus paclitaxel and carboplatin, would not be a cost-effective use of NHS resources for first-line treatment of advanced ovarian cancer compared with paclitaxel and carboplatin alone. See FAD section 4.15.

Consultee	Comment	Response
Target Ovarian Cancer	The committee reviewed evidence from two major phase III studies which evaluate the benefits of including bevacizumab in combination with carboplatin and paclitaxel for the first-line treatment of ovarian cancer, these are GOG-0218 and ICON7. To our knowledge these studies are the most relevant in the context of this appraisal. While we agree with the committee's conclusion that evidence from the GOG-0218 trial supports: • the clinical effectiveness of bevacizumab in first-line treatment of ovarian cancer • patient population in the trial generally represents those treated in secondary care in the UK While we understand that NICE can only appraise drugs within their marketing authorisation, we don't agree that bevacizumab is only clinically effective when given within its marketing authorisation. Data from ICON7 supports the clinical effectiveness for bevacizumab at a lower dose (7mg/kg), and highlights a group of high-risk patients who are likely to derive greater benefit from bevacizumab. Also, the ICON7 data is valuable in reflecting how bevacizumab is currently used in clinical practice in the UK. Given recent economic analysis by Scottish Medicines Consortium, there is also the potential that bevacizumab could be cost effective at the lower dose. Women will feel quite rightly that they have been served a great injustice, especially knowing that evidence exists to support that bevacizumab can be given at an effective and tolerable dose which is likely to be cost effective. Overall we are very disappointed with the committee's verdict not to recommend bevacizumab for first-line treatment of ovarian cancer. Sadly there have been no new drugs that extend the progression free survival interval following first-line treatment since the early 1990s. We believe that it is imperative that both NICE and the manufacturer Roche, work together to resolve the issues that have led to this decision.	Comment noted. The Appraisal Committee considered further whether it was able to issue guidance on the use of bevacizumab for the first-line treatment of advanced ovarian cancer at its unlicensed dose of 7.5 mg/kg at its second meeting. See FAD sections 4.17 and 4.18.
Ovacome	**Has all of the relevant evidence been taken into account?** We believe that all of the relevant evidence has been recorded. Naturally we wish that NICE would be able to take greater account of the issues raised and submitted by patients groups, and the innovative nature of this technology.	Comment noted.

Consultee	Comment	Response
Ovacome	Dose issues. The position of the committee; that it is unable to consider the lower dose of 7.5mg is confusing. The pre meeting briefing report states that "The summary of product characteristics for bevacizumab states that 'the recommended dose of bevacizumab is 15 mg/kg of body weight given once every 3 weeks'. The European Medicines Agency concluded that there was insufficient evidence of an acceptable balance of clinically relevant benefit to risk at the lower dose (7.5 mg/kg) used in the ICON7 study. Therefore, NICE is unable to produce guidance for the unlicensed dose of 7.5 mg/kg." However at the commencement of the meeting, the experts in the presence of the committee were told that the reason ICON 7/ the lower dose of 7.5 mg could not be considered was because NICE could not evaluate technologies outside of the licensed indication. The difference in these directions is significant. At the time of license there were less available results from the ICON 7 study than at the time of the NICE meeting, thus NICE would have been furnished with a higher level of evidence to be able to determine whether there is now sufficient 'evidence of an acceptable balance of clinically relevant benefit'. During the coffee break, I raised the question of perversity of this position with regard to the verbal direction given; that NICE are unable to consider technologies outside of the licensed indication. I suggested to Meindert Boysen that it was my belief that NICE had considered use outside of license when it reviewed PLDH, which is licensed at 50 mgs, but in fact used at 40mgs. Since that time, I have been unable to test the veracity of my recall as the TA in question – TA 45 has been removed from the NICE website. Similarly NICE guidance on the use of Paclitaxel in first line advocates its use in combination with Carboplatin, which is outside of licence.	Comments noted. The appraisal of pegylated liposomal doxorubicin hydrochloride (PLDH) for the treatment of advanced ovarian cancer (TA 45) considered the use of PDLH at its licensed dose of 50 mg per square metre of the patient's surface area. The appraisal of paclitaxel for the treatment of ovarian cancer (TA 55) recommended that paclitaxel in combination with a platinum-based compound or platinum-based therapy alone (cisplatin or carboplatin) are offered as alternatives for first-line chemotherapy (usually following surgery) in the treatment of ovarian cancer. Therefore, the wording of the guidance statement does not specify the exact platinum-based compound with which paclitaxel is recommended. However, it is acknowledged that the wording of the guidance statement is incorrect because it also recommends the comparator intervention in the appraisal, that is, a platinum-based therapy alone (cisplatin or carboplatin). It should be noted that NICE guidance should not make recommendations on the use of comparator technologies.

Consultee	Comment	Response
	TA55: 1.1 "It is recommended that paclitaxel in combination with a platinum-based compound or platinum-based therapy alone (cisplatin or carboplatin) are offered as alternatives for first-line chemotherapy (usually following surgery) in the treatment of ovarian cancer." The licence for Paclitaxel specifies its use in combination with Cisplatin. It is clear therefore that NICE has in the past recommended treatments outside of their licensed indication, and we therefore believe that the decision not to consider non licensed dosage in this instance, given the available evidence (ICON 7) is perverse.	
Ovacome	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The ACD examines the evidence fully at the dose of 15mgs; however we would advocate that cost effectiveness/ICER data of use at 7.5 mgs be published (as it is in the SMC guidance). Women are currently able to access Avastin (at 7.5 mgs) via the Cancer Drugs fund (CDF). The CDF ceases in March, and at present we are uncertain as to the details of its replacement. We anticipate that for the interim at least there is a possibility that clinicians may have to submit Individual Funding requests (IFR) as they currently do in Wales and Scotland. Having fuller details on the NICE determinations/ICERs at 7.5mgs, the UK preferred dose, would be useful to women in attempting to access treatment via an IFR.	Comment noted. Comment noted. The Appraisal Committee considered the cost effectiveness of bevacizumab at its unlicensed dose of 7.5 mg/kg based on ICON7 at its second meeting. See FAD Sections 4.17 and 4.18.

Consultee	Comment	Response
Ovacome	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** As previously submitted, we believe that NICE may have previously issued guidance for treatments outside of the licensed indication; however this matter requires further investigation. We believe that the guidance as it stands will cause significant distress to women affected by ovarian cancer as they perceive this treatment as being the most significant advance in the treatment of the disease in many years. There is the possibility that some will make considerable financial compromises to be able to access the treatment privately. We believe that an unintended consequence of the guidance as it stands will be to hamper further clinical research which would lead to understanding better when and for who Avastin would be most beneficial, as well as its use in potentially more active combinations. These studies would of course make the treatment more cost effective for the NHS.	Comments noted. The Committee agreed that the range of ICERs obtained from the cost-effectiveness model of bevacizumab plus paclitaxel and carboplatin were outside the range normally considered as a cost-effective use of NHS resources. It therefore concluded that bevacizumab within its marketing authorisation (that is, at a dose of 15 mg/kg), plus paclitaxel and carboplatin, would not be a cost-effective use of NHS resources for first-line treatment of advanced ovarian cancer compared with paclitaxel and carboplatin alone. See FAD section 4.15.

Consultee	Comment	Response
Ovacome	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** We believe that as a consequence of the guidance discrimination may occur. As previously stated the current lack of a clear replacement for the CDF in England, and the lack of a CDF in the rest of the UK will see an increase in the need to use IFRs to be able to access treatments. The individual funding request is a rigorous process. It is instigated by the clinician, however in many cases this is prompted by the informed patient. We believe that patients who are not able to access detailed treatment information outside of that given by the clinical team, and unable to research the treatment options available due to poverty, age or disability will be unaware that there are alternate treatments available, nor how they might be able to access them. As a consequence we believe that the ACD will cause a difference in the way women across the UK are treated based on their age and financial status. We have been unable to identify any research undertaken to establish whether the IFR is an intrinsically discriminatory process, however it is something that many in the cancer patient community believe to be the case.	Comment noted. NICE does not consider this to be a potential equalities issue.

Consultee	Comment	Response
Royal College of Physicians	**Outcome from appraisal** The results of GOG218 were reviewed at the NICE appraisal meeting on 20th November 2012 with immature data from ICON7 considered in support. *NICE concluded that bevacizumab plus paclitaxel and carboplatin was not a cost-effective use of NHS resources for first-line treatment of advanced ovarian cancer compared with paclitaxel and carboplatin alone.* **Response to NICE from NCRI/RCP/RCR/ACP/JCCO** The UK Gynaecological cancer community strongly disagrees with the NICE Initial Appraisal decision in which first-line bevacizumab was rejected outright and suggest that the lower 7.5mg/kg dose is instead considered for approval. Having examined the data from ICON7 and GOG218 in detail, we wish to highlight the following. **1. Clinical Efficacy of bevacizumab:** *A subject of discussion at the appraisal meeting was the poor overall survival in the ICON7 control arm compared to that of the GOG218 study, leading the committee to conclude the populations were incomparable.* The final analysis of GOG218 showed a median overall survival of 40.6 months with chemotherapy plus placebo, and 43.8 months with chemotherapy plus bevacizumab (during chemotherapy and as maintenance) to a total of 15 months (hazard ratio 0.88 (0.75-1.04), P = 0.0641. In ICON7 the median overall survival for the high risk group of patients (a similar population to those included in GOG218) who were treated with chemotherapy and bevacizumab, and then with bevacizumab as maintenance to a total of 12 months was 36.6 months, very similar to that seen in GOG218; however the median overall survival for the ICON7 control group patients in this category who received chemotherapy alone was 28.8 months. The better survival outcomes for those in the GOG218 control arm compared to those in the control arm of ICON7can be explained by the extent of cross-over that occurred in GOG218. In GOG218, patients within the study (recruited from USA, Japan and Korea) were unblinded at the time of progression or at the time of the initial analysis.	Comments noted. The Appraisal Committee considered the cost effectiveness of bevacizumab at its unlicensed dose of 7.5 mg/kg based on ICON7 at its second meeting. See FAD Sections 4.17 and 4.18.

Consultee	Comment	Response
Royal College of Physicians	It is estimated that 40% patients crossed over to bevacizumab, which was a requirement of the FDA. In contrast, in ICON7 (recruited from UK, other countries in Europe, Australasia and Canada) a very small percentage of patients crossed over to anti-angiogenic therapy post progression and such a crossover was strongly discouraged in the protocol. We feel that the extent of crossover in GOG218 not only resulted in better survival within its control arm but also diluted the biological effect of the agent resulting in a non-significant improvement in overall survival. **2. Preferred dose of bevacizumab** *Although the manufacturer (Roche) and clinical experts requested (letter to NICE) that the 7.5mg/kg dose of bevacizumab used in ICON7 be considered instead of 15mg/kg, this was refused on the grounds that bevacizumab had only been licensed by the EMA for use at 15mg/kg and the lower dose of 7.5mg/kg was outside the scope of the current appraisal.* Although we agree with the committee's findings that bevacizumab given at the licensed 15mg/kg dose to unselected patients with advanced ovarian cancer is not a cost-effective use of NHS resources, we are concerned by NICE's summary sentence. By stating 'NICE conclude that bevacizumab plus paclitaxel and carboplatin was not a cost-effective use of NHS resources for first-line treatment of advanced ovarian cancer compared with paclitaxel and carboplatin alone' this appears to preclude the evaluation of the drug at a lower and more cost effective dose. We strongly feel that bevacizumab at a dose of 7.5mg/kg should be approved for first line clinical use. This was the dose given in the ICON7 study, which has shown equal clinical efficacy and lower toxicity than the 15mg/kg dose given in GOG218. Moreover, ERG analysis of bevacizumab given at 7.5mg/kg in an unselected ovarian patient population results in an ICER of £77,884 per QALY gained over carboplatin and paclitaxel alone over a 10 year time horizon. We therefore consider that, in a selected (high-risk) population, as defined in ICON7 and balanced against the benefits of treatment, 7.5mg/kg <u>is</u> a cost-effective use of NHS resources.	

Consultee	Comment	Response
Royal College of Physicians	**In conclusion** We believe that the data from ICON7 and GOG218 are robust, and strongly point to a clinically significant biological effect from bevacizumab. The economic analyses conducted with the ICON7 dose and duration of bevacizumab, set against the improvement of outcome seen for high risk patients, also suggest that this is cost-effective. We see the addition of bevacizumab to front-line treatment of patients with ovarian cancer as a vitally import step-change in their management and an opportunity to improve the prognosis of this aggressive disease. In the interests of our patients, we strongly oppose the decision made by NICE at its Initial Appraisal and ask for the opportunity to re-present the efficacy and economic evidence for bevacizumab 7.5mg/kg given alongside and after first-line chemotherapy in patients with high risk ovarian cancer with the aim of obtaining its approval in this selected patient group.	

Comments received from commentators

Commentator	Comment	Response
Commissioning Support Appraisals Service	We are in agreement with the recommendation in the ACD not to recommend bevacizumab for this indication as on the basis of the evidence considered it is unlikely that this treatment can be considered clinically and cost effective in real life clinical practice. • **This technology is not a cost effective use of NHS resources.** The manufacturer's base-case ICER estimate was about £144,000 per QALY gained. • **No overall survival benefit has been shown from adding the licensed dose of bevacizumab to carboplatin and paclitaxel.** The manufacturer suggested this may be due to patients in the pivotal GOG-0218 trial switching over from the control group to receive bevacizumab after disease progression. The Committee judged that the effect of bevacizumab on overall survival was uncertain, as it was not clear how many patients crossed over, and what impact this had on the survival analyses. • **Adding bevacizumab to carboplatin and paclitaxel increases progression free survival (PFS) by 6 months.** This data came from the censored analysis of PFS from the GOG-0218 trial, which the Committee judged to be the most relevant to the UK. • **Evidence on the effects of the licensed dose and treatment duration for bevacizumab come from one phase III trial (GOG-0218).** The Committee judged this trial to be well-designed. Similar results were found in a trial which used a lower unlicensed dose of bevacizumab for a shorter period of time (ICON-7). • **There were no new safety concerns raised by the trial, and the side effects of adding bevacizumab were considered by the Committee to be acceptable and manageable.** Side effects that occurred in over 10% more people with add-on bevacizumab than with carboplatin and paclitaxel alone included: stomatitis, dysarthria, headache, epistaxis and hypertension. Grade 3-5 side effects at least 1% more common with add-on bevacizumab were: hypertension, gastrointestinal perforation and non-central nervous system bleeding.	Comments noted.

Commentator	Comment	Response
	• **The cost of adding bevacizumab is about £36,078 per patient.** This is based on a patient weighing 65kg receiving 15mg/kg bevacizumab every 3 weeks for 14 treatment cycles. • **In England and Wales the incremental cost of adding bevacizumab could be £28.3 million in year five after implementation.** This cost assumes about 2,089 women being eligible for bevacizumab and half of them receiving it in year five.	

Commentator	Comment	Response
Southampton Health Technology Assessments Centre (SHTAC)	SHTAC has identified a few points which may need clarification: 1. In sections 3.7 to 3.10, CPB7.5 should read CPB7.5+. 2. In section 3.9, the following text seems to imply that the groups were compared with each, and also it does not take into account that the HRs for two of the analyses show non-significant effects: "These analyses showed that the stage III patients with optimally debulked cancer derived a smaller improvement from the treatment (difference in median PFS of 1.6 months based on CP 17.7 months (n=368) and CPB7.5 19.3 months (n=383); HR 0.89, 95% CI 0.74 to 1.07) compared with stage III patients with suboptimally debulked cancer (difference in median PFS of 5.8 months based on CP 10.1 months (n=154) and CPB7.5 16.9 months (n=140); HR 0.67, 95% CI 0.52 to 0.87) or stage IV cancer (difference in median PFS of 3.4 months based on CP 10.1 months (n=97) and CPB7.5 13.5 months (n=104); HR 0.74, 95% CI 0.55 to 1.01)." (p.9) 3. Also in section 3.9 it is also not clear what is meant by the following text: "No statistical tests of interaction were presented by the manufacturer for these subgroup data." (p.9) 4. In section 4.10 the following sentence implies that PFS in the chemotherapy arm in the ICON7 trial ITT population was worse than in the chemotherapy arm of the GOG trial in the ITT population (censored data), but it was not (ICON7 17.4 vs GOG 12). It was only worse when comparing the 'high risk' subgroup from ICON7 with the GOG censored ITT analysis (ICON7 10.5 vs GOG 12): "The Committee also noted that PFS in the chemotherapy comparator arm was worse in ICON7 than in GOG-0218, which could affect interpretation of the results." (p.22) 5. In section 4.11, the difference in median PFS for the ICON7 high risk subgroup should read 5.5 months. (p.22)	Comments noted. The relevant sections of the FAD have been amended.

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional	1	We are very disappointed that NICE's agreed procedures meant that NICE were not able to fully consider evidence from the ICON7 trial in this appraisal. This large well-conducted trial provides important, relevant evidence on the effectiveness of bevacizumab in ovarian cancer. ICON7 compared standard chemotherapy alone with standard chemotherapy+bevacizumab+continuation bevacizumab (up to 18 cycles of bevacizumab) using 7.5mg/kg. ICON7 more closely reflects clinical practice in the UK and it is possible that had NICE had been able to fully appraise the bevacizumab dose and schedule used in ICON7 they may have been able to come to a different conclusion. We believe NICE should be able to take into account all the available high quality evidence. ICON7 was an academic-led study and if such studies are to be able to contribute to NICE Technology Appraisals, they must not be disregarded just because they examine questions that are slightly different to the license application made by the manufacturer. To ignore the relevant evidence from ICON7 is to do a disservice to the 1528 women who took part in the trial, and to the thousands of women who are diagnosed with ovarian cancer each year	Comments noted. The Appraisal Committee considered further whether it was able to issue guidance on the use of bevacizumab for the first-line treatment of advanced ovarian cancer at its unlicensed dose of 7.5 mg/kg at its second meeting. See FAD section 4.18.
NHS Professional	1	There should be a comment on the ICON 7 subset analysis that shows a clear overall survival benefit for poor prognosis patients when half dose bevacizumab is used	Comment noted. The Appraisal Committee considered further whether it was able to issue guidance on the use of bevacizumab for the first-line treatment of advanced ovarian cancer at its unlicensed dose of 7.5 mg/kg at its second meeting. See FAD section 4.18.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
NHS Professional	4	There is strong evidence that half the licensed dose is as effective as 15mg/kg. It would be helpful to be able to take a statement from NICE to regional CDF committees acknowledging this particularly since there are good data to show an overall survival benefit in poor prognosis patients at this lower dose. The ICER for this dose would also be helpful to put into the NICE document. Such a statement from NICE does not have to be a recommendation but merely an acknowledgement of the existence of the data and their validity. Such an approach does not breach the NICE terms of reference which do not allow recommendations relating to non-licensed doses.	Comment noted. The Appraisal Committee considered the cost effectiveness of bevacizumab at its unlicensed dose of 7.5 mg/kg based on ICON7 at its second meeting. See FAD Section 4.17.
NHS Professional	7	The consideration of the data in relapsed disease is urgent. There is a current need in this situation.	Comment noted. NICE is currently appraising bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer as part of its work programme.
NHS Professional	1	I accept this for 15mg/kg and all patients but I would hope a positive decision could be given for using 7.5 mg/kg in ICON7 defined high risk patients.	Comment noted. The Appraisal Committee considered further whether it was able to issue guidance on the use of bevacizumab for the first-line treatment of advanced ovarian cancer at its unlicensed dose of 7.5 mg/kg at its second meeting. See FAD section 4.18.
NHS Professional	3	It would be very useful if an ICER for the high risk patients defined in ICON7 and using 7.5 mg/kg could be included.	Comment noted. The Appraisal Committee considered the cost effectiveness of bevacizumab at its unlicensed dose of 7.5 mg/kg based on ICON7 at its second meeting. See FAD Section 4.17.

Role*	Section	Comment	Response
Patient	1	What can I say to try to persuade such learned bodies to continue using Bevacizumab in some shape or form? To reach the decision you have, you must have considered all angles, but it would be a shame if the main reason for discontinuing were due to cost-effectiveness alone. Just one year ago, Avastin was hailed as a third component of treatment that could improve ovarian cancer treatment for the first time in 15 years, offering hope for treating the deadliest of gynaecologic cancers, according to researchers. What has gone wrong? If even the unlicensed dose of 7.5 mg/kg was being administered effectively in ICON7, might it not be possible to use an unlicensed dose in order to keep costs down? We as ovarian cancer patients are offered so little hope compared with most other cancer sufferers. It would seem as though you have just taken away one of the last straws that many ovarian cancer sufferers had been clutching. I am sure that most of us would be more than prepared to put up with negative side-effects, just to stay alive.	Comments noted. The Appraisal Committee considered further whether it was able to issue guidance on the use of bevacizumab for the first-line treatment of advanced ovarian cancer at its unlicensed dose of 7.5 mg/kg at its second meeting. See FAD section 4.18.
Patient	2	I am one of the patients who received Bevacizumab in the ICON7 trial. I had grade 3, FIGO stage iiB clear cell carcinoma of the ovary. I am truly grateful to the medical profession who allowed me to take part in this trial and find it very sad that other ovarian cancer sufferers may not be able to avail themselves of this drug. From the product characteristics, I was only too aware of the adverse reactions associated with the treatment but, given the alternative likelihood of possibly dying earlier from ovarian cancer, I was prepared to clutch at any straws and it was worth the risk. As it turned out, throughout my treatment I was able to lead a normal life, with my adverse reactions being no more than neutropaenia, severe constipation. chemo-fog, loss of hair and occasionally feeling sorry for myself. After coming out of one 10-hour treatment, I drove 300 miles the same evening. I can only say that the dose of all three drugs in my case must have been perfect for I am here today, partly thanks to the excellent care I received all round, combined (I am convinced) with feeling very positive as a result of all the warmth and love from my friends	Comment noted. The Appraisal Committee considered further whether it was able to issue guidance on the use of bevacizumab for the first-line treatment of advanced ovarian cancer at its unlicensed dose of 7.5 mg/kg at its second meeting. See FAD section 4.18.
Patient	3	I would rather have a few unpleasant side-effects and a greater hope of staying around for a while longer than have foregone Avastin and its side-effects. Provided it is not fatal, an SAE is a small price to pay for staying alive.	Comment noted. The Committee heard from the patient experts that patients often choose to tolerate serious side effects in the hope of gaining additional PFS at its first meeting. See FAD section 4.3