National Institute for Health and Clinical Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Bevacizumab for the treatment of recurrent advanced ovarian cancer

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from *BMJ-TAG* to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 5pm, *6th December 2012* using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The attached proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Discussion of the preferred treatment options in the UK

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 10 In the critique of the decision problem (Section 1.1), the ERG states *"The ERG's clinical expert fed back that paclitaxel plus carboplatin would be the preferred treatment… particularly for patients who relapse > 12 months after completion of first-line chemotherapy"* However, there is no acknowledgement of the overall proportion of patients for whom this may be suitable.	An additional sentence should be added to reflect the full opinion of the clinical expert (as described on p23), that although paclitaxel plus carboplatin is the preferred choice for recurrent platinum-sensitive ovarian cancer in the UK, *"… it is unsuitable as a second-line regimen for ~50% of patients because of associated neurotoxicity"*.	The omission of the clinical expert's caveat that the preferred chemotherapy option is not appropriate for half of all patients distorts the availability of treatment options available.	No change required; not a factual error.

Issue 2 Discrepancy in reporting of the number of chemotherapy cycles in the OCEANS trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 10, 13, 48, 58 and 76 In several parts of the report, gemcitabine and carboplatin are reported as having being administered for a	Amend *"maximum of 10 cycles"* to	This amendment more accurately reflects the study protocol and the licensed indication for bevacizumab in	No change required; not a factual error. The ERG considers that the instances highlighted by the

"maximum of 10 cycles", whereas the treatment duration was actually 6 cycles, with the option to continue up to 10 cycles.	*"6 – 10 cycles"*	recurrent ovarian cancer.	manufacturer should be considered in the context of the full text in which they appear in the ERG report. The ERG highlights throughout the report that OCEANS was designed such that patients would receive six cycles of gemcitabine plus carboplatin but, if the assessing investigator deemed it necessary, and the study Sponsor approved, patients could receive up to 10 cycle

Issue 3 IRC-assessed ORR and duration of response incorrectly referred to as "sensitivity analyses"

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 10, 11, 13, 49, 54, 59, 76 and 153 Throughout the report, the exploratory IRC-assessed PFS, ORR and duration of response (DOR) are all referred to as sensitivity analyses, which is only correct for PFS.	When discussing IRC-assessed ORR and DOR, these should be referred to as "exploratory analyses" instead of "sensitivity analyses".	While IRC-assessed PFS, ORR and DOR were all evaluated as exploratory analyses, the term "sensitivity analysis" is only correct for IRC-assessed PFS. Only IRC-assessed PFS was evaluated as a sensitivity analysis to confirm the robustness of the primary endpoint.	The ERG thanks the manufacturer for the clarification. Text discussing the IRC-determined analyses has been amended in line with the manufacturer's correction. The ERG notes that text on page 49 has not been corrected. In this section, only IRC-determined PFS is discussed in the context of a sensitivity analysis. The relevant text reads: The MS indicated that, to evaluate the robustness of the primary

			endpoint, a sensitivity analysis was added in which an independent-review committee (IRC) assessed PFS. The IRC also assessed ORR and duration of response based on radiographic and clinical evidence; the IRC did not evaluate OS.

Issue 4 QALY gains in different health states

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15 The ERG estimates that: *"… approximately 90% QALYs were a function of the OS gain, and approximately 10% QALYs were a function of PFS gain."*	The words "PFS" and "OS" should be switched in this sentence and the paragraph re-phrased accordingly.	Table B8 in our submission clearly shows that the QALY gain of adding bevacizumab to Gemcitabine/Carboplatin is 0.298 overall and is comprised of 0.263 in PFS (88.3%) and 0.035 in PD (11.7%).	No change required; not a factual error. The manufacturer has misunderstood the point raised by the ERG. The ERG's point is that 90% (and 10%) of the QALY gain was a **function** of OS (and PFS). Rather than the health state in which QALYs were accrued. To clarify, these numbers were calculated by setting OS to be the same for both arms, which resulted in a QALY gain in the bevacizumab group of 0.03. Subsequently, PFS was set to be the same for both arms, which resulted in a QALY gain for the bevacizumab group of 0.27. From this, the ERG ascertained

			that difference in OS was responsible for 0.27 of the 0.30 QALYs gained (90%) and the difference in the PFS was responsible for 0.03 of the 0.30 QALYs gained (10%).

Issue 5 Reference to "inconsistency in the proportion of patients achieving complete response" as a key issue

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 16 The summary of the key issue of investigator-assessed versus IRC-assessed objective response rate (ORR) is not aligned with the balance of the ERG report.	The key issue on p16 should be removed or amended to reflect the overall context of the ERG report, placing greater emphasis on the commonly used, and clinically relevant, endpoint of ORR than on complete responders alone.	Various parts of the report suggest that the difference between complete responders is not a key issue:- *"The results of the sensitivity analysis for ORR carried out by the IRC are in agreement with the results of the investigator-assessed analysis. The ERG notes that the proportion of patients classified as achieving an objective response is comparable for the investigator assessed and IRC-determined analyses" (Page 59)* *"The guidance from the FDA indicates that, when complete and partial responses are combined, ORR is a direct measure of antitumor activity of a drug." (Page 60)* In the context of recurrent ovarian cancer, where it is accepted that treatments are unlikely to be curative and the aim of treatment is palliation of symptoms and prolongation of symptom-free interval, shrinkage of lesions (as defined by ORR) is likely to be of more importance to patients than whether the lesions disappear completely. The agreement between ORR assessment by the Investigator and the IRC, which both confirm >20% increase in ORR for patients given bevacizumab versus placebo, shows that the term 'Response' was correctly applied at the Investigator sites to	No change required; not a factual error. The ERG acknowledges the manufacturer's comments on the outcome of ORR. However, based on comments received from clinical experts, the ERG considered it important to highlight the considerable disparity between the investigator-assessed and IRC-determined proportion of patients achieving complete response (investigator-assessed; 17.4% with

		virtually all patients. The inconsistency between the complete responses reported by Investigators and the IRC is not of major importance when, as shown above, it is accepted that • ORR is a direct measure of anti-tumour activity and • there is agreement between ORR as assessed by Investigators and by the IRC	bevacizumab vs 9.1% with placebo; IRC-determined analysis; 0.8% with bevacizumab vs 1.2% with placebo).

Issue 6 Reference to "the trial" of bevacizumab in front-line advanced ovarian cancer

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 29 and 48 Bevacizumab in front-line ovarian cancer is discussed in passing at two points in the report. However, this refers to *"the trial evaluating… bevacizumab in the first-line treatment of advanced ovarian cancer"* There are two studies in the first-line setting.	Amend *"the trial"* to *"one of two trials"*	While ICON7 is a relevant and important study, which most closely represents the use of bevacizumab in UK clinical practice, it is worth noting that this was one of two trials included in the Avastin SmPC. The licensed dose of bevacizumab in advanced ovarian cancer as a front-line therapy is based upon the other RCT, GOG-0218.	The ERG thanks the manufacturer for the clarification. Text on pages 29 and 48 has been amended accordingly.

Issue 7 Source of cost data for carboplatin

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 117 *"The ERG notes that the manufacturer used public list prices from the BNF for bevacizumab and carboplatin, and a drug price obtained from the CMU eMit for the cost of gemcitabine."*	This sentence should be corrected to read: "The ERG notes that the manufacturer used public list prices from the BNF for bevacizumab, and a drug price obtained from the CMU eMit for the cost of gemcitabine **and carboplatin**."	We acknowledge the error identified by the ERG. However we feel it is important to state that it is our intention to use CMU eMit as a source of costs wherever possible as it represents the cost of drugs available to the majority of the NHS and is therefore most relevant to the decision problem (please see previous appraisals of bevacizumab in 1L OC [ID435], mBC [TA263], CRC [TA212]). Furthermore, it is worth noting that the cost of carboplatin and gemcitabine, as acknowledged by the ERG, does not have a large impact on the ICER.	No change required; not a factual error. The ERG notes that the cost of a 600 mg vial used in the model matches that reported in the BNF (£260), rather than that reported in CMU eMit (£33.35).

Issue 8 Indirect comparisons between bevacizumab and comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 69-75 The ERG provides an opinion on our reasons for believing that an indirect comparison of the 4 studies identified for treatment options in recurrent ovarian cancer was not appropriate and presents the results of a Bayesian network meta-analysis.	We suggest this analysis is either removed or a more appropriate discussion of the limitations of the analysis be included here and provided in the executive summary.	Indirect comparisons are only relevant and useful if existing heterogeneities are small and fully understood. However, there are several sources of heterogeneity in the proposed indirect comparison that we believe the ERG has incorrectly dismissed as having negligible impact. • Patients are not comparable.	No change required; not a factual error. The ERG considers that the heterogeneity among the trials included in the NMA has been discussed in the submitted report. In

"…(the ERG) asserts that the trials are sufficiently comparable to facilitate an adjusted indirect comparison, with accompanying critical assessment of the impact that any potential bias may have on the results." (page 72) *"Although the ERG considers the analysis to represent a methodologically robust assessment, it should be stressed that the analysis is exploratory, and, as such, the results should be interpreted with caution. In addition, the ERG is uncertain about the direction of overall bias in the analysis". (page 73)*		CALYPSO and ICON4 recruited patients who had previously received more than 1 line of therapy (about 20% in CALYPSO). Furthermore, the treatment response in these patients is uncertain. • Clinical endpoints used in these trials are not comparable even though they are described as "PFS" OCEANS and CALYPSO both used the RECIST criteria for disease progression, but CALYPSO included non-measurable disease in about 40% of the patients. In contrast, OCEANS excluded non-measurable disease. • The degree of blinding in the studies. It is widely acknowledged that PFS is subject to bias in open-label studies (Freidlin et al., (2007) J.Clin. Oncol. 25(15):2122-6). OCEANS is the only double-blinded trial in these set of studies. These sources of heterogeneity are important enough to conclude that an indirect comparison of these studies will not provide a meaningful result.	addition, the ERG has stressed that the analysis is exploratory and should be interpreted with caution.