National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

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

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Roche Products	This topic is appropriate	Comment noted. No action required.
	NCC for Cancer	This is an appropriate topic given the low rates of overall survival for women with advanced/metastatic ovarian cancer who receive current standard treatments	Comment noted. No action required.
	MRC Clinical Trials Unit	Referral of this topic to NICE for appraisal is appropriate – it has already become relevant to UK clinical practice following initial reporting of the GOG 218 trial, and depending on further results from that trial and reporting of the ICON 7 trial, is likely to become of increasing importance.	Comment noted. No action required.
	CSAS	This STA is appropriate given the assessment of bevacizumab for a range of different indications and research assessing its use as a treatment for metastatic ovarian cancer.	Comment noted. No action required.
	NCRI Gynaecological Clinical Studies Group/RCP/RCR/ACP/JCCO	Very important topic. Results of the first RCT, GOG 218 show significant extension of PFS.	Comment noted. No action required.
	Royal College of Nursing	This is an appropriate topic given the low rates of overall survival for women with advanced/metastatic ovarian cancer who receive current standard treatments.	Comment noted. No action required.

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	Target Ovarian Cancer	Yes this is an appropriate referral. There have been no new life extending treatments in ovarian cancer in over a generation. The disease is characterised by late stage diagnosis with poor survival rates. It is imperative that effective new treatments are developed and made available.	Comment noted. No action required.
	NHS Waltham Forest	This STA is appropriate given the assessment of bevacizumab for a range of different indications and research assessing its use as a treatment for metastatic ovarian cancer.	Comment noted. No action required.
Wording	Roche Products	The wording should reflect treatment of 1st line ovarian cancer, irrespective of stage of disease in accordance with the potential licensed indication.	NICE can only appraise technologies within their licensed indication. Bevacizumab (in combination with paclitaxel and carboplatin) currently holds a UK marketing authorisation for the front-line treatment of advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian cancer.
	NCC for Cancer	It is difficult to comment on the wording until the details of the UK license are known but it is probably safe to assume that the current wording is correct.	Comment noted. No action required.

Section	Consultees	Comments	Action
	CSAS	The wording is appropriate	Comment noted. No action required.
	NCRI Gynaecological Clinical Studies Group/RCP/RCR/ACP/JCCO	Yes	Comment noted. No action required.
	Royal College of Nursing	The appraisal does not reflect the continued use of single agent chemotherapy and possibly should be 'Bevacizumab in combination with paclitaxel and/or carboplatin…' (see comparators)	NICE can only appraise technologies within their licensed indication. The wording of the licence is bevacizumab is in combination with paclitaxel and carboplatin.

Section	Consultees	Comments	Action
	Target Ovarian Cancer	Target Ovarian Cancer is aware that some women receive Carboplatin as a single agent chemotherapy. However Target Ovarian Cancer is not aware of any data that compares Carboplatin with Bevacizumab with Carboplatin alone or Carboplatin plus Paclitaxel with Bevacizumab with Carboplatin alone. The majority of women with ovarian cancer that is advanced/metastatic would receive a combination therapy. Target Ovarian Cancer is aware that the ICON 7 trials which are due to announce results in early October will include patients who have stage I-IIa high grade ovarian cancer, and women with stages IIb-IV any grade. The scoping meeting should consider whether or not it is appropriate to widen the current remit from advanced/metastatic. As far as we understand it is not yet clear which patient groups will be included in the license application.	NICE can only appraise technologies within their licensed indication. The wording of the licence is bevacizumab is in combination with paclitaxel and carboplatin. Bevacizumab (in combination with paclitaxel and carboplatin) currently holds a UK marketing authorisation for the front-line treatment of advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian cancer.
	NHS Waltham Forest	The wording is appropriate	Comment noted. No action required.

Section	Consultees	Comments	Action
Timing Issues	Roche Products	The timing is appropriate.	Comment noted. No action required.
	NCC for Cancer	Yes	Comment noted. No action required.
	CSAS	Bevacizumab does not currently have marketing authorisation in the UK. The timing is appropriate given that bevacizumab is being considered for different indications and the research assessing its use as a treatment for metastatic ovarian cancer.	Comment noted. No action required.
	NCRI Gynaecological Clinical Studies Group/RCP/RCR/ACP/JCCO	If a license is granted through the EMA at the end of the year there will be considerable public and professional pressure to access the drug. It should be noted that the results of the second trial, ICON 7 are due to be made public on 11 Oct 2010. Neither GOG 218 or ICON 7 have mature survival data at the moment	NICE aims to provide guidance to the NHS as close as possible to the time of marketing authorisation.
	Royal College of Nursing	Yes	Comment noted. No action required.
	NHS Waltham Forest	Bevacizumab does not currently have marketing authorisation in the UK. The timing is appropriate given that bevacizumab is being considered for different indications and the research assessing its use as a treatment for metastatic ovarian cancer.	Comment noted. No action required.

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	Target Ovarian Cancer	It is imperative that this appraisal is carried out as swiftly as possible, so that , if appropriate, women can access this drug without delay. However there needs to be a clear understanding of what evidence is available (GOG -0218 trial) and what will be forthcoming and when (ICON 7) so that a decision on timing can be made that has the potential to open up access to this drug if effective to the widest possible group.	NICE aims to provide guidance to the NHS as close as possible to the time of marketing authorisation.
Additional comments on the draft remit			

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Roche Products	No comment	Comment noted. No action required.
	NCC for Cancer	The incidence figure of 40% for advanced stage (3&4) disease is too low. The sentence “In stage III, the cancer has grown outside the pelvis into the abdominal cavity or affects lymph nodes” should read “In stage III, the cancer has grown outside the pelvis into the abdominal cavity or affects the para-aortic lymph nodes.” The sentence “Standard treatment for ovarian cancer consists of surgery to determine the type and stage of the disease and to remove as much of the cancer as possible.” should read “Standard treatment for ovarian cancer consists of surgery to determine the type and stage of the disease and to remove as much of the cancer as possible although increasingly chemotherapy is being given before surgery.”	The background section has been revised with an updated figure for the incidence of advanced disease. The other two suggested amendments have been made to the scope.

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	MRC Clinical Trials Unit	Since the introduction of platinum based chemotherapy - no major improvements proven and clinically accepted. The role of intraperitoneal chemotherapy and dose fractionated weekly IV chemotherapy may give big advantages, trials have suggested this (NCI alert re IP therapy and JGOG trial in Lancet earlier this year) but questions remain and these approaches are still being investigated.	Comments noted. The background section provides a brief overview of the disease and current standard treatments. It does not include treatment under investigation.
	CSAS	The background information appears to be complete	Comment noted. No action required.
	NCRI Gynaecological Clinical Studies Group/RCP/RCR/ACP/JCCO	See timing issue above	Comment noted. No action required.
	Royal College of Nursing	The background information does not make standard treatment clear in relation to stage III and above (the definition presented for advanced/ metastatic disease). The background information suggests standard treatment is to have surgery followed by chemotherapy but the 'population' does not mention surgery – there are a significant number of women who do not have surgery before chemotherapy. This may need some clarification/ consideration.	The background section has been amended to clarify that some women have chemotherapy before surgery.
	Target Ovarian Cancer	The second paragraph is not clear and potentially misleading. There is clear evidence now that ovarian cancer is not asymptomatic (Goff 2004 & 2007, Hamilton 2009). The statistics used are not clear - they should be - the number of cases of ovarian cancer in total, the number of stage III and IV cases, and then the number of deaths. The current wording implies more deaths than incidence and is thus confusing.	The second paragraph in the background section has been amended.
	NHS Waltham Forest	The background information appears to be complete	Comment noted. No action required

Section	Consultees	Comments	Action
The technology/ intervention	Roche Products	Where it is stated that "Bevacizumab does not have a UK marketing authorisation for the treatment of metastatic ovarian cancer", the term 'metastatic' should be removed to reflect our proposed marketing authorisation. In the clinical trials where bevacizumab has been studied, the population was not restricted to 'newly diagnosed' patients, nor were they restricted to 'stage III and IV' ovarian cancer. It should be noted that the intervention of bevacizumab in combination with paclitaxel and carboplatin will be followed by a period of maintenance therapy with bevacizumab monotherapy.	The technology section has been amended as suggested.
	NCC for Cancer	Yes.	Comment noted. No action required.
	MRC Clinical Trials Unit	Details of dose and duration may be important to state, the US GOG218 trial used a higher dose for longer than the European/Australian/Canadian ICON7 trial.	Details of the dose and duration of treatment of the intervention are not included in scopes.
	CSAS	The technology is described accurately	Comment noted. No action required
	NCRI Gynaecological Clinical Studies Group/RCP/RCR/ACP/JCCO	Yes	Comment noted. No action required
	Royal College of Nursing	Yes	Comment noted. No action required
	NHS Waltham Forest	The technology is described accurately	Comment noted. No action required

Section	Consultees	Comments	Action
Population	Roche Products	The population under consideration need not be newly diagnosed. As mentioned above, the disease should be stated as 'ovarian cancer' irrespective of stage of disease.	Comment noted. No action required.
	NCC for Cancer	We are not aware of any evidence to select specific sub-groups of advanced ovarian cancer for separate assessment. However, general oncological principals would suggest that the benefit of adding bevacizumab to standard chemotherapy would be greatest in those patients with a higher chance of benefit from chemotherapy and with better outcomes. This would be patients in whom successful, surgical tumour clearance (debulking) had been undertaken.	Consultees at the scoping workshop discussed the inclusion of a subgroup of women who had surgical cure with no macroscopic or microscopic tumour left, (that is absence of residual disease). They agreed that this was a suitable subgroup.
	MRC Clinical Trials Unit	Restriction to stage III and IV may not cover the patient population who could benefit, stage II and high risk stage I patients are now being included in trials of first line therapy along with patients with more advanced disease. I would suggest that the scope is extended to this population, not sure how this fits in with recommendations for platinum/paclitaxel combinations first line and what the 'standard' non trial background chemotherapy should be for patients with early stage disease.	Comment noted. No action required.
	CSAS	The population is women with grade III or IV ovarian cancer who have not received chemotherapy. The scope mentions in the background, but could specify here too, that 40% of women will present with grade III or IV disease.	This level of detail is not included under population.
	NCRI Gynaecological Clinical Studies Group/RCP/RCR/ACP/JCCO	Yes- appropriate to all groups of patients with advanced ovarian cancer who have undergone primary surgery	Comment noted. No action required.

Section	Consultees	Comments	Action
	Royal College of Nursing	As above (background information)	Comment noted. No action required
	Target Ovarian Cancer	See comments above about the forthcoming announcements of ICON 7 results. If data is likely to be robust at all stages then the population group should be all women who are eligible to receive chemotherapy. If that data will not be robust for the earlier stage patients, then the existing population should be retained as there is data from the GOG trial.	Comment noted. No action required.
	NHS Waltham Forest	The population is women with grade III or IV ovarian cancer who have not received chemotherapy. The scope mentions in the background, but could specify here too, that 40% of women will present with grade III or IV disease.	This level of detail is not included under population.
Comparators	Roche Products	No comment.	Comment noted. No action required.
	NCC for Cancer	The UK standard treatment for advanced ovarian cancer is carboplatin + paclitaxel therefore the choice of comparator regimen is appropriate. However, a significant minority of patients in the UK receive single agent carboplatin. Therefore it would be helpful to UK practice to also use carboplatin as a comparator and to assess any evidence of benefit from adding bevacizumab to single agent carboplatin if this is within the UK license.	Single agent chemotherapy is included as a comparator (cisplatin or carboplatin with or without paclitaxel).
	MRC Clinical Trials Unit	Trials have added bevacizumab to the international standard of carboplatin and paclitaxel, which can be described as best alternative care.	Comment noted. No action required.
	CSAS	Platinum-based chemotherapy (cisplatin or carboplatin with or without paclitaxel), without bevacizumab are appropriate comparators	Comment noted. No action required.

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	Welsh Assembly Government	The UK standard treatment for advanced ovarian cancer is carboplatin + paclitaxel therefore the choice of comparator regimen is appropriate. However, a significant minority of patients in the UK receive single agent carboplatin. Therefore it would be helpful to UK practice to also use carboplatin as a comparator and to assess any evidence of benefit from adding bevacizumab to single agent carboplatin.	Single agent chemotherapy is included as a comparator (cisplatin or carboplatin with or without paclitaxel).
	Royal College of Nursing	Single agent platinum is included as a comparator which is appropriate but some women with advanced/metastatic disease continue to have single agent carboplatin in accordance with NICE Technology Appraisal No 55. This may need some clarification/ consideration.	Single agent chemotherapy is included as a comparator (cisplatin or carboplatin with or without paclitaxel).
	Target Ovarian Cancer	The most appropriate comparator is Cisplatin or Carboplatin with Paclitaxel	Comment noted. No action required.
	NHS Waltham Forest	Platinum-based chemotherapy (cisplatin or carboplatin with or without paclitaxel), without bevacizumab are appropriate comparators	Comment noted. No action required.
Outcomes	Roche Products	No comment.	Comment noted. No action required.
	NCC for Cancer	Yes	Comment noted. No action required.
	MRC Clinical Trials Unit	Care should be taken on definition of progression free survival - does this include CA125 as well as clinical, radiological or histological progression? We have seen clear evidence of non proportional hazards so effect of treatment over time would be an important consideration.	Comments noted. This level of detail is not included in scopes.

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	CSAS	The outcome measures are appropriate for this technology and indication.	Comment noted. No action required.
	Royal College of Nursing	Yes	Comment noted. No action required.
	NHS Waltham Forest	The outcome measures are appropriate for this technology and indication.	Comment noted. No action required.
Economic analysis	Roche Products	No comment.	Comment noted. No action required.
	CSAS	The detail of the economic analysis is clear and appropriate for the review.	Comment noted. No action required.
	Royal College of Nursing	Seems appropriate	Comment noted. No action required.
	NHS Waltham Forest	The detail of the economic analysis is clear and appropriate for the review.	Comment noted. No action required.
Equality and Diversity	Roche Products	No comment.	Comment noted. No action required.
	NCC for Caner	None	Comment noted. No action required.
	Welsh Assembly Government	No	Comment noted. No action required.
	Royal College of Nursing	No suggestions	Comment noted. No action required.

Section	Consultees	Comments	Action
Innovation	Welsh Assembly Government	There has been no significant change in the 1st line treatment of advanced ovarian cancer over the last 15 years. This has been due to the failure of any new chemotherapy drug to show improved benefits. This is in contrast to significant improvements made in many other solid tumours. Bevacizumab has a different mechanism of action to standard chemotherapy drugs and has shown anti-tumour activity in animal models and initial clinical studies of ovarian cancer. Therefore there is the possibility that this technology will lead to a significant and much awaited improvement in patient outcomes.	Comments noted.
Other considerations	Roche Products	No comment	Comment noted. No action required.
	NCC for Cancer	No suggestions	Comment noted. No action required.
	MRC Clinical Trials Unit	Subgroups of patients who express VEGF more highly may be more likely to benefit. No marker has been developed to date, but patients with ascites/pleural effusions, may over express VEGF and could be considered a subgroup. If effective, this could be considered a step change, but full data on the 2 main trials (GOG218 and ICON7) have not yet emerged.	Consultees at the scoping workshop explained that there is no marker for VEGF overexpression and so it would be difficult to define this subgroup of women.

Section	Consultees	Comments	Action
	Welsh Assembly Group	*Are there any subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately?* I am not aware of any evidence to select specific sub-groups of advanced ovarian cancer for separate assessment. However, general oncological principals would suggest that the benefit of adding bevacizumab to standard chemotherapy would be greatest in those patients with a higher chance of benefit from chemotherapy and with better outcomes. This would be patients in whom successful, surgical tumour clearance (debulking) had been undertaken. *Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* I am not sufficient aware of the method of calculating QALYs to answer this question	Consultees at the scoping workshop discussed the inclusion of a subgroup of women who had surgical cure with no macroscopic or microscopic tumour left, (that is absence of residual disease). They agreed that this was a suitable subgroup. Comment noted. No action required
	Royal College of Nursing	Recent studies of inhibitors of angiogenesis have shown promising results in the management of advanced cancer. The progression free survival rates for women with ovarian cancer have remained stagnant for many years and the use of such agents may increase the time to remission and improve overall survival rates.	Comment noted. No action required

Section	Consultees	Comments	Action
Questions for consultation	Roche Products	Yes. There is considerable clinical and pre-clinical evidence to suggest that ovarian cancer is a disease that is driven by Vascular Endothelial Growth factor (VEGF) and high expression of VEGF correlates with worse survival in this disease. Bevacizumab, which binds VEGF, is a therapy directly targeted against a key driving factor for ovarian cancer. Bevacizumab will be the first anti-VEGF agent to be licensed for the treatment of ovarian cancer and it represents a step-change in the management of the disease, from non-specific chemotherapy to a targeted therapy. *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.* There are two large RCTs for bevacizumab in combination with paclitaxel and carboplatin: GOG-218 and ICON 7. The ICON 7 trial includes patients with early stage ovarian cancer (Stage I and II) as well as later stages (III and IV) also covered by GOG-218.	Comments noted.
	NCC for Cancer	Overall survival, progression-free survival and quality of life are the most relevant endpoints and will be available from the randomised clinical trial data. Time to subsequent therapy could be useful but we are not sure if this information is available.	Comment noted. No action required

Section	Consultees	Comments	Action
Additional comments on the draft scope.	Target Ovarian Cancer	Target Ovarian Cancer believes it is imperative that the scope is considered very carefully to ensure that there is balance between potentially (if the data shows effectiveness) - opening up access to an effective new drug to as many women as possible and ensuring that there are not delays in the appraisal process, which would deny women access to a potentially beneficial treatment.	NICE aims to provide guidance to the NHS as close as possible to the time of marketing authorisation.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Bristol-Myers Squibb Pharmaceuticals
Department of Health
Macmillan Cancer Support
MHRA
NHS Quality Improvement Scotland
Pfizer Ltd
Public Health Wales NHS Trust