National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Bevacizumab for the treatment of recurrent advanced 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	Royal College of Pathologists	Yes	Comment noted.
	Roche Products	Yes	Comment noted.
	Target Ovarian Cancer	Yes we believe it is important that this topic is assessed in a timely manner, in line with the market authorisation.	Comment noted.
	Royal College of Physicians	Angiogenesis is a key component driving ovarian cancer and anti-angiogenic therapy with the VEGF inhibitor, bevacizumab has shown clear evidence of activity (response and prolonged PFS in phase II non randomised trials). The single agent response data is greater in ovarian cancer than most other tumours. Control of disease, maintaining stability after chemotherapy for recurrence would be a key advance in the management of advanced ovarian cancer	Comment noted.
Wording	Roche Products	Yes	Comment noted.
	Target Ovarian Cancer	We are not certain why both the terms relapsed and recurrent are used. Either would suffice in this instance.	Comment noted. Following discussion at the Scoping Workshop it was agreed that including the term recurrent would suffice. The scope has been amended accordingly.
	Royal College of Physicians	Yes	Comment noted.

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Timing Issues	Roche Products	Please see regulatory timelines below.	Comment noted.
	Target Ovarian Cancer	Given there are limited options for women with relapsed ovarian cancer, and potential benefits for women through the use of this drug, we believe it is important to appraise this technology as soon as it is feasible to do so in an appropriate manner.	Comment noted. If this topic is referred to NICE by the Department of Health, it will be planned into the NICE work programme, taking the anticipated date of regulatory approval and UK launch into consideration.
	Royal College of Physicians	License submission likely in 2011 with possible approval mid/late 2012	Comment noted.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Royal College of Pathologists	I would delete "occurring in different parts of the ovary" from the first sentence as the theory for the aetiology of ovarian cancer is the surface epithelium or epithelial inclusion cysts.	Comment noted. The background section has been amended to indicate that ovarian cancer represents a group of different tumours that arise from diverse types of tissue contained within the ovary.
	Roche Products	No comment	Comment noted.
	Target Ovarian Cancer	90% of women diagnosed with early stage ovarian cancer are reporting symptoms to their GP (Hamilton et al, BMJ 2009, Target Ovarian Cancer Pathfinder Study 2009). Therefore we do not agree with the statement that ovarian cancer may be asymptomatic in the early stages. We suggest you refer to the recently published clinical guidance CG122 for appropriate wording, and correct identification of symptoms, which would also include urinary frequency and urgency, together with a qualifying statement about frequency of	Comments noted. The background section of the scope has been updated to maintain consistency with CG122.

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		symptoms. Paragraph 2 in cites English and Welsh stats, then UK stats. We would recommend consistency. CG122 again is a good source for this information, or the Cancer Research Website. Paragraph 3 uses out of date survival statistics. There are currently two different stats being used in this area - one is based on the International Cancer Benchmarking Partnership Study data from the Lancet in 2010 - which says 36% five year survival, and Cancer Research UK use ONS data, which says 41%. The differences are due to differences in weighting and inclusion or otherwise of zero survival patients. The ICBP figure is good for comparisons with other countries, the CRUK data for inter cancer comparisons within the UK.	
	Royal College of Physicians	NICE TA 91 is very out of date and needs to be reviewed urgently	Comment noted. The review of TA 91 has been planned into the NICE work programme and a decision is expected in November 2012.
The technology/ intervention	Roche Products	It should be noted that in contrast to current wording, bevacizumab has only been studied in Phase III clinical trials in combination with carboplatin plus paclitaxel in a 1st line setting and in combination with carboplatin plus gemcitabine in a 2nd line (platinum sensitive) setting. There are no trials in combination with docetaxel in ovarian cancer and so this treatment regimen should be removed from current wording. We would ask for the amendment of the phrase "Bevacizumab in combination with standard platinum-based therapy" to "Bevacizumab in combination with platinum-based therapy" in the interest of clarity.	Comment noted. The GOG-0213 trial is currently ongoing in patients with platinum-sensitive recurrent ovarian, primary peritoneal, or fallopian tube carcinoma which compares paclitaxel or docetaxel *and* carboplatin, with paclitaxel or **docetaxel** *and* carboplatin *and* bevacizumab. Therefore there is a trial where docetaxel is being compared with

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			bevacizumab and therefore removing docetaxel from the description of clinical trials is not required. The wording of the intervention has been changed to bevacizumab in combination with platinum-based therapy. Please note that guidance will only be issued in accordance with the marketing authorisation.
	Royal College of Physicians	Yes	Comment noted.
Population	Roche Products	Yes the population is defined appropriately.	Comment noted.
	Target Ovarian Cancer	Data exists also for the use of Bevacizumab in patients with Primary Peritoneal Cancer and Fallopian Tube Cancer which are treated in the same manner.	Comment noted. Following discussion at the Scoping Workshop, the population has been expanded to include women with recurrent platinum-sensitive or partially platinum-sensitive advanced epithelial ovarian, fallopian tube or primary peritoneal cancer.
	Royal College of Physicians	Yes	Comment noted.
Comparators	Roche Products	We propose that the following be added to the list of comparator technologies: Gemcitabine in combination with carboplatin Trabectedin	Comment noted. As NICE Technology Appraisal No. 222 does not recommend the use of trabectedin for ovarian cancer, it is not routinely used

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			in UK clinical practice and therefore should not be included in the list of comparator technologies. It was agreed at the Scoping Workshop that gemcitabine in combination with carboplatin was a relevant comparator, although it is not commonly prescribed in clinical practice. It has been added to the list of comparators in the scope.
	Target Ovarian Cancer	The comparators given are the standard treatments currently used in the NHS. For first line treatment of ovarian cancer, Bevacizumab has been used with these comparators. However from what we understand, the main data in relation to relapsed ovarian cancer is comparing it to a combination of platinum and gemcitabine (OCEANS study). Gemcitabine is not routinely given in the UK.	Comment noted. It was agreed at the Scoping Workshop that the scope should list the following comparators for both platinum sensitive and partially platinum sensitive ovarian cancer: • Paclitaxel in combination with a platinum compound • Gemcitabine in combination with carboplatin • Pegylated liposomal doxorubicin hydrochloride in combination with a platinum compound • Platinum-based

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			chemotherapy as monotherapy
	Royal College of Physicians	The comparator in the 'OCEANS' trial is an acceptable chemotherapy regimen (Carboplatin and Gemcitabine), licensed in the UK but not part of the TA 91 appraisal. GOG 213 includes carboplatin and paclitaxel with or without bevacizumab, but it has not yet reported.	Comment noted. It was agreed at the Scoping Workshop that the scope should list the following comparators for both platinum sensitive and partially platinum sensitive ovarian cancer: • Paclitaxel in combination with a platinum compound • Gemcitabine in combination with carboplatin • Pegylated liposomal doxorubicin hydrochloride in combination with a platinum compound • Platinum-based chemotherapy as monotherapy
Outcomes	Roche Products	Yes	Comment noted.
	Target Ovarian Cancer	Yes	Comment noted.
	Royal College of Physicians	PFS clearly important with OS trend; there is always a danger of confounding OS due to cross over, additional therapies, including other vascular targeting	Comment noted.

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		drugs (within clinical trials)	
Economic analysis	Roche Products	No comment	Comment noted.
	Target Ovarian Cancer	None	Comment noted.
Equality and Diversity	Roche Products	No special equality considerations	Comment noted.
	Target Ovarian Cancer	None identified	Comment noted.
Innovation	Roche Products	We consider this technology to be innovative due to its specific mode of action, i.e. binding VEGF, a well known driver of the growth of ovarian cancer. This is the first anti-VEGF agent to show activity in the treatment of ovarian cancer. VEGF is also a major causative factor in the development of ascites in ovarian cancer patients. This technology, by binding VEGF, also reduces the development of ascites in ovarian cancer patients. The benefit to patient experience of reducing the development of ascites by this technology, which decreases the need to drain ascites fluid, is unlikely to be adequately included in the QALY calculation. There are published case-reports of the efficacy of bevacizumab in reduction of ascites.	Comment noted. The Committee will consider the innovative nature of bevacizumab, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the QALY measure. No action required.
	Target Ovarian Cancer	This is the first time a maintenance therapy and non chemotherapy approach is being adopted in ovarian cancer, which is notoriously hard to treat successfully. Women who relapse face a very difficult future with the focus being on managing rather than curing their disease. As such they have very few options, and this new approach is welcomed.	Comment noted.
	Royal College of Physicians	Yes, but full results ie mature OS data would allow a fuller and more meaningful evaluation	Comment noted.
Questions for consultation	Roche Products	Pegylated liposomal doxorubicin hydrochloride is a relevant comparator and we understand it is not restricted to women who are allergic to platinum compounds.	Comment noted. Discussion at the Scoping Workshop indicated that pegylated liposomal doxorubicin

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			hydrochloride is a relevant comparator and would be given in combination with carboplatin rather than as monotherapy in clinical practice in the UK, It was noted that combination use was within the license for pegylated liposomal doxorubicin hydrochloride. It has been included as a comparator in the scope.
	Target Ovarian Cancer	As far as we understand, Pegylated Liposmal Doxorubicin Hydrochloride is generally used as a 'last resort' in terms of treating women who have become resistant or allergic to platinum. With regard to subgroups, we are not aware at this point in time of any, but there may be data on this in the forthcoming Journal of Clinical Oncology June 20th 2011 edition, which is providing an update on both the ICON 7 and OCEANS study using Bevacizumab	Comment noted. Discussion at the Scoping Workshop indicated that pegylated liposomal doxorubicin hydrochloride is a relevant comparator and would be given in combination with carboplatin rather than as monotherapy in clinical practice in the UK. It was noted that combination use was within the license for pegylated liposomal doxorubicin hydrochloride. It has been included as a comparator in the scope.
Additional comments on the draft scope.	Roche Products	None	Comment noted.
	Target Ovarian Cancer	We welcome the fact that NICE is considering this as a potential technology appraisal. Often the news of relapsed disease can be even more devastating than the initial diagnosis, and as such, this drug potentially could offer hope, and medical benefits at this extremely distressing time when options are	Comment noted. If this topic is referred to NICE by the Department of Health, it will be planned into the NICE work

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		limited.	programme, taking the anticipated date of regulatory approval and UK launch into consideration.
	Royal College of Physicians	We have just had an update of ICON 7 at ASCO and the first results of bevacizumab in recurrent ovarian cancer: For ICON 7 we still see a significant affect on PFS. In terms of increase, this amounts to 2.4 months increase in PFS, as before with the maximum difference occurring at 12 months, the time at which bevacizumab stops. Whilst there are still too few events to comment on OS, it is possible to make some comment on the survival results of the poor prognosis patients (with macroscopic residual disease) with greater clarity; there have been more events in this group. Here there is an 8 month difference in median survival which is a significant difference and an improvement in the 1 year survival. It does appear at the moment that it is this group that may have the greatest benefit from bevacizumab. The optimum length of treatment remains unanswered and a new trial is being launched to compare 15 months (the GOG 218 length of treatment) and GOG dose – 15 mg/kg with a treatment to progression (or 24 month treatment). Final OS results of ICON 7 will be available in 2013. GOG 218 will work to a similar or slightly shorter time frame but there will be a much greater degree of cross-over in GOG studies and this could confound the survival results. In recurrent disease (first relapse), the OCEANS study demonstrated a highly significant improvement in PFS of 4 months, increased response rate with combination therapy and a non-signifcant trend for increase in OS. The data are not yet sufficiently mature to draw conclusions about survival. Taken together the emerging data suggest that the benefit of bevacizumab is likely to be greatest in women with bulk disease, whether in the primary setting or at relapse. The mature OS data for both studies will help shape views but in	Comments noted.

Section	Consultees	Comments	Action
		both first line and relapse the drug has clear evidence of activity	

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

Royal College of Nursing
Healthcare Improvement Scotland (formerly NHS Quality Improvement Scotland)
Marie Curie Cancer Care
The Public Health Wales Trust
Welsh Government
Department of Health
Medicines and Healthcare products Regulatory Agency (MHRA)

NATIONAL INSTITUTE FOR HEALTH CLINICAL EXCELLENCE

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Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:

1.	National Cancer Intelligence Network Gynae Clinical Reference Group	Target Ovarian Cancer		Not added	The NCIN are part of the NationalCancer Research Institute – this organisation is already automatically on the matrices for all oncological appraisals. Therefore NCIN cannot be added as a separate group.
2.	Please add National Forum of Gynaecological Oncology Nurses	The Royal College of Nursing		Added	This organisation has an area of interest closely related to this appraisal topic and meets the selection criteria to participate in this appraisal. National Forum of Gynaecological Oncology Nurses has been added to the matrix of consultees and commentators under 'professional groups'.

3.	National Site Specific Group for Gynaecological Cancers	Target Ovarian Cancer		Not Added	This is a regional cancer network. As per the technology appraisal process unless the PCT's listed for this appraisal nominates the cancer network to take part on their behalf, National Site Specific Group for Gynaecological Cancers cannot be added.
4.	List of Comparator Manufacturers: Accord Healthcare (carboplatin, gemcitabine,paclitaxil, pegylated liposomal doxorubicin hydrochloride) Celgene (paclitaxil Eli Lilly (gemcitabine) Hospira UK (carboplatin, gemcitabine paclitaxel) Sun Pharmacuticals (gemcitabine, paclitaxil)	NICE secretariat		Added	These organisations have an area of interest directly related to this appraisal topic and meet the selection criteria to participate in this appraisal. They have been added to the matrix under 'comparator manufacturers'.