Healthcare Improvement Scotland

NICE Health Technology Appraisal - 2nd ACD on Topotecan and others for recurrent ovarian cancer	
TO: NICE **15 December 2015**	**FROM: Healthcare Improvement Scotland**

They have not included the SAPPROC study. Although it does not compare between the agents in the appraisal it is a randomised study of weekly paclitaxel +/- saracatanib in platinum resistant recurrent ovarian cancer and therefore gives data on response, PFS and OS for weekly paclitaxel 80mg/m2. (A randomised placebo-controlled trial of weekly paclitaxel and saracatinib (AZD0530) in platinum-resistant ovarian, fallopian tube or primary peritoneal cancer I.A. McNeish et al Annals of Oncology 2014.) I do not think this would change the conclusions significantly but would support the inclusion of the unlicensed dose and schedule that is in routine clinical use.

They have not considered the use of dose dense platinum regimens in the platinum resistant setting.

They have not included any data from trials including bevacizumab. I understand that bevacizumab was not included in this analysis but nevertheless I think it needs to be noted in the discussion that the combination of bevacizumab/carboplatin/gemcitabine has improved PFS over carboplatin/gemcitabine and at present this is the only licensed combination that includes bevacizumab**.** In the platinum resistant setting they have not considered the Aurelia trial which showed improved PFS with the addition of bevacizumab to PLDH, Weekly paclitaxel or weekly topotecan. This is more relevant since it has been approved by the SMC for use in the first line treatment of platinum resistant disease.

In Scotland women with platinum sensitive relapse will receive combination platinum based therapy where their performance status allows and after discussion, they accept the increased toxicity. The choice of combination depends on prior toxicities and co-morbidities. Not all centres have access to carboplatin/PLD on their formularies, although individual requests can be made, so in these centres carboplatin/paclitaxel is standard therapy but where carboplatin/PLD is available this may be standard based on the CALYPSO trial. Women with hypersensitivity to paclitaxel or persistant neuropathy may be treated with carboplatin and gemcitabine. As a result I am not clear that it is appropriate to use single agent carboplatin as the comparator in the cost-effectiveness analysis but overall would be happy with the conclusion that now includes carbo/PLDH as well as carboplatin/paclitaxel

One concern remains that there is a variation in the baseline characteristics of the trials included. The RR, PFS and OS is likely to be lower in trials that include patients beyond 1st relapse compared to 1st relapse only. The time to progression following last platinum is a very important prognostic factor but it is a continuous variable and the way that progression is defined eg clinical symptoms, CA125 criteria or RECIST will affect the prognosis of the group included in the trial as progression by CA125 may occur many months before clinical or radiological progression. Prior therapy is also important hence one reason why an overall survival advantage might not have been seen in the carboplatin/gemcitabine v carboplatin where it was seen in the ICON 4 study of carboplatin/paclitaxel v carboplatin is that in ICON 4, the majority of patients had not received prior taxane where as in the gemcitabine study they had received prior taxane and might therefore have had more resistant disease.
I am not familiar with the methodology of network analyses but as I understand it they have not compared platinum based and non platinum based therapies in the platinum sensitive group. This would be very interesting as an important question is whether PLDH/trabectadin is as effective as PLDH/carboplatin. This is the subject of an ongoing randomised trial but in the absence of this data this would be a useful comparison. This is particularly important for patients with platinum sensitive disease who are platinum allergic. At present the recommendation is for the use of PLDH or paclitaxel alone in this group as trabectadin/PLDH was not cost effective compared to single agent PLDH but really for this group the comparator should be a platinum/combination ie if using a platinum combination as the comparator, which of PLDH, paclitaxel or trabectadin+PLDH is better for women who cannot receive platinum?

Overall I think the conclusions are sound but would like to see the option for carbo/gemcitabine for those where PLDH/carbo or paclitaxel/carbo is not appropriate: eg taxane sensitivity or neuropathy where PLDH cannot be given eg due to cardiac history or prior exposure to anthracyclnes in any guidelines based on this appraisal.

Q Are the patient pathways and treatment options described in the assessment applicable to NHSScotland. If not, how do they differ in Scotland?

There are some differences in Scotland compared to England. Carboplatin/PLD is not routinely available in all centres for platinum sensitive treatment. Carboplatin/gemcitabine/bevacizumab is not available in Scotland. It was previously available in England via the Cancer Drug Fund but this has now been removed from the CDF, however bevacizumab is available in combination with weekly paclitaxel

(approved by the SMC) for the treatment of first relapse in platinum resistant disease and this needs to be taken in account in any guidelines.

Q Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? If so, please describe what these changes would be.

I do not think there would be a significant change to current practice in Scotland for the first line treatment of platinum sensitive relapse as this broadly follows clinical practice. It may increase the use of carboplatin/PLDH compared to carboplatin/paclitaxel, where this has not been routinely available**.**

In platinum resistant disease women may now receive weekly paclitaxel plus bevacizumab (see above).

It is important to emphasise that this is only guidance for first relapse. Clinical judgement must be allowed in subsequent lines of therapy as there is very limited evidence to support practice but nevertheless a clinical need for subsequent lines of therapy and these should not be restricted on the basis of this guidance.

Q Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? If yes, please explain why this is the case.

No apart from that in platinum resistant disease women may now receive weekly paclitaxel plus bevacizumab (see above)

Comment provided to healthcare Improvement Scotland by Professor Nick Reed, Consultant Clinical Oncologist, Beatson Institute

The management of relapsed ovarian cancer has changed considerably over the past 20 years evolving from single agent carboplatin to platinum-based combinations for platinum sensitive disease whereas the use of platinum alone is reserved for those less fit all with poor performance status. In platinum resistant disease non-platinum agents such as liposomal doxorubicin and weekly paclitaxel are more commonly used. The recent recognition that bevacizumab improves the year progression free survival is probably come to late for this consideration. For platinum sensitive disease for many years carboplatin and paclitaxel was the standard of care but the Calypso study showed a noninferiority for carboplatin and liposomal doxorubicin hence it has generally replaced the former regime is the standard of care particularly if there is persisting neuropathy or other toxicity. Carboplatin and gemcitabine is also an important invaluable alternative schedule particularly in those with hypersensitivity and form the backbone of a number of studies including Oceans. We would therefore challenge the view that gemcitabine should not be used for ovarian cancer relapse. It is worth pointing out that grossly all clinicians use Caelyx at a dose of 40 mg/m² rather than the licensed 50 mg/m² .

These alternative schedule should be approved for use and certainly on the formulary for the West of Scotland. Clinician should be given licensed to use which ever of the 3 regimes they feel most appropriate in platinum sensitive disease taking into account the previous schedules and current toxicities.

Withdrawal of the approval of topotecan is relatively little consequence since it is rarely used, trabectedin is still being investigated although some important new data suggest that it may be more useful in patients known to

have a BRCA mutation. New data will emerge over the course of the next few years but there is a reasonable case to consider its use in platinum' partially sensitive disease in the 6-12 month window. However there are ongoing trials such as INNOVATYON which are addressing this and will provide further information in due course.

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Over the course of the past 10 years most of these drugs have become generic in the cost of dramatically reduced therefore affecting the value for money and cost effectiveness her calculations furthermore Caelyx is used at a dose 20% less in the manufacturers licensed schedule. Many patients receiving gemcitabine will also finish up with dose reductions which will lead to a lower cost

The summaries do not take into account changes in clinical usage in practice, the availability of generic combinations and relative reductions in the price of the drugs

For the reasons given above, I believe that there is flawed interpretation of the data and that the recommendations are too restrictive. These drugs are prescribed by a limited number of clinicians experienced in the treatment of gynaecological cancers and who behaves very responsibly and are aware of many of the issues regarding cost effectiveness. Evidence from clinical practice in Scotland would support responsible prescribing by the oncology community

Q Are the patient pathways and treatment options described in the assessment applicable to NHSScotland. If not, how do they differ in Scotland?

There are clear pathways for prescribing of these drugs by the 3 cancer network's in Scotland and there is remarkable concord between them. Clinicians will often determine which schedule is used dependent on prior toxicity and patient's performance status and it is essential that some flexibility is retained to allow clinicians to adapt treatment according to these predictive factors. The CMGs reflect this and it is hoped that this flexibility will be continued.

Q Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? If so, please describe what these changes would be.

Some of the restrictions would have potential negative effects particularly if it was insisted that we used the higher dose of Caelyx which is associated with higher toxicity as well as unnecessarily higher cost. Restriction on the use of gemcitabine would affect some clinical trials were carboplatin and gemcitabine is the standard of choice but would also affect patients with pre-existing neuropathy or hypersensitivity who were unsuitable treatment with paclitaxel. Withdrawal of topotecan will another very minor effect since there its use has been very limited in the past few years. Weekly paclitaxel has relatively little evidence base to support it from large randomised trials but again it is become the backbone of treatment particularly in platinum resistant cases and refractory disease at a later stage although this is outwith the considerations of the document.

Q Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? If yes, please explain why this is the case.

I think most of these are being covered by the points raised above

Q Please add any other information which you think would be useful to the Appraisal Committee, or helpful to us in guiding the Scottish response to this assessment.

It is important that the responsibility of the oncology community who treat ovarian cancer is recognised. We will all work within carefully scripted CMGs which have been approved by the 3 Scottish networks which represent multidisciplinary working groups. These are carefully controlled and not abused. Virtually all of the drugs discussing this document are now generic and cost saving have substantially increased over the course of the past decade.