NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

RPP decision paper

Review of TA284; Bevacizumab in combination with paclitaxel and carboplatin for the first-line treatment of advanced and/or metastatic ovarian cancer, and TA285; Bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer

Final recommendation post consultation
The guidance should be transferred to the 'static guidance' list.

1. Background

These appraisals were issued in May 2013.

At the GE meeting of 12 April 2016 it was agreed that we would consult on the recommendations made in the GE proposal paper. A four week consultation has been conducted with consultees and commentators and the responses are presented below.

2. Proposal put to consultees and commentators

The guidance should be transferred to the 'static guidance' list.

3. Rationale for selecting this proposal

TA284 - Since the publication of TA284, additional data have been reported from 2 of the trials considered as part of the original appraisal: GOG-0218 and ICON7.

The results from GOG-0218 (Randall 2013) represent an exploratory subgroup analysis of people with stage IV disease; confirmatory studies are required to strengthen Randall et al.'s conclusion that bevacizumab is more effective in people with stage IV disease. In addition, this analysis may not address the uncertainty in the survival benefit of bevacizumab. Considering these limitations, and the high

incremental cost effectiveness ratio (ICER) for bevacizumab in the overall patient population, this exploratory subgroup analysis does not warrant a review of the guidance.

The ICON7 trial investigated an unlicensed dose of bevacizumab; the committee is unable to issue guidance on a technology used outside the terms of its marketing authorisation.

TA285 - Since the publication of TA285 final survival data from the OCEANS clinical trial have been published, which show no significant benefit in favour of bevacizumab. Results from an additional randomised phase III trial (GOG-0213) have also been reported. These data may lead to an extension to the marketing authorisation for bevacizumab for treating ovarian cancer.

4. Summary of consultee and commentator responses

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Respondent: Target Ovarian Cancer **Response to proposal:** Disagree To date NICE has only reviewed bevacizumab in the context of its licensed dose of 15mg/kg. Bevacizumab was licensed at this level based on a pivotal Phase III US trial. However, a contemporaneous MRC Phase III trial in the UK – ICON 7 – showed similar benefit at half the dose – 7.5mg/kg. As the Cancer Drugs Fund is able to consider cancer drugs for off-license use, it was able to approve bevacizumab for the first line treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancer at Stage IV or Stage III with sub-optimal debulking or neo-adjuvant chemotherapy. Prior to the 2015 delisting process, the Cancer Drugs Fund also approved bevacizumab in combination with carboplatin and gemcitabine chemotherapy for recurrent platinum sensitive ovarian cancer. Separately, in 2015 bevacizumab was approved by the Scottish Medicines Consortium for use in combination with carboplatin and paclitaxel, for the first-line treatment of advanced (Stage IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer and for use in combination with paclitaxel for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens. The remit of the Cancer Drugs Fund in England is now changing and all cancer drugs currently funded through this will be expected to go through the NICE appraisal process within a two year window. In light of this, and the Scottish Medicines Consortium's approval of bevacizumab in 2015, subsequent to the original NICE 2013 decision, it would be highly appropriate for NICE to review TA284 and TA285.	**Comment from Technology Appraisals** Response noted. In its appraisals of health technologies, the committee is unable to issue guidance on a technology used outside the terms of its marketing authorisation. Exceptionally, the Department of Health may direct the Appraisal Committee to make recommendations about a technology outside of the terms of its marketing authorisation, but has not done so in this case (see Guide to the methods of technology appraisal section 6.1.12). A cost-effectiveness analysis based on the ICON7 would be outside the scope of an appraisal of bevacizumab, because ICON7 investigated a dose of bevacizumab that is not licensed in the UK. NICE is not influenced by the recommendations of other health technology appraisal bodies. The consultee is correct that drugs transferring from the old Cancer Drugs Fund (CDF) will all be appraised by NICE, over the next 18 months. A separate process has been developed for drugs currently in the CDF: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/cancer-drugs-fund However, because only an **unlicensed** dose of bevacizumab is available on the CDF, it will **not** transition into the NICE appraisal process via this route.

Respondent: Ovarian Cancer Action **Response to proposal:** Agree (with caveat) Ovarian Cancer Action has discussed this with one of our research Scientists. We acknowledge that Aviation is not currently recommended as a first line treatment in advanced ovarian cancer, but do have access to it with firstline with carbo/taxol via the CDF in patients with stage 4 disease, or stage 3 disease with macroscopic residual disease after surgery. It has been a while since the CDF paid for the use of Avastin with gem/carbo in the second line setting. Currently we understand that data on Avastin in both settings is relatively strong, but does not pass the cost effectiveness analysis. Although there is no new data yet, the icon8B study is looking again at Avastin in the first line setting either with a weekly or 3-weekly chemo and may add more weight to the use of Avastin in this setting. However these results are likely to still be a few years coming. Moving both TA284 and TA285 to the static list would not represent a problem, so long as it can be transferred back to the active list as soon as any new evidence, such as that from the icon8B study, becomes available.	**Comment from Technology Appraisals** Response noted. Once guidance has been on the static list for 5 years, NICE decides whether it is still appropriate to keep the topic on the static list (this is called a static list review). If it is decided that the evidence base has changed significantly, then a full review proposal is developed to assess whether an update of the guidance is required (see chapter 6 of NICE's guide to the processes of technology appraisal). Topics on the static list can be considered for review before 5 years has passed, if any new evidence becomes available that is likely to lead to a change in the existing recommendations.

Respondent: Roche Products **Response to proposal:** Partially agree **TA284** Avastin® (bevacizumab) has been available in England via the National Cancer Drugs Fund (CDF). Over a thousand applications have been made to the National CDF to treat women with stage III suboptimal (> 1cm residual disease) or Stage IV disease with Avastin. This demonstrates how Avastin is considered an important treatment option for patients by their treating clinicians.	**Comment from Technology Appraisals** **TA284** Response noted. NICE is unable to issue guidance on a technology used outside the terms of its marketing authorisation (that is, at the dose available on the Cancer Drugs Fund). The exploratory subgroup analysis was not

Since Avastin continues to be available on the CDF in this indication (albeit at an unlicensed dose), Roche can understand why NICE would prefer not to review the guidance at this point in time. Maintaining access to treatment is important and therefore the suggestion to place Avastin on the static list for this indication needs to take into consideration how patients retain access to this treatment (i.e. through the CDF or NHS England). However, should patients lose access to this treatment option (given the uncertainty in the current CDF reform) then it is important that Avastin will be reviewed again by NICE. To support this re-review, we highlight once more the GOG-218 subgroup analysis in the stage IV group that was described in the initial document submitted to NICE in January 2016. GOG-0218 study has shown improvements in median PFS (3.3 months ($p<0.0003$)) in the Carboplatin+ Paclitaxel+ Bevacizumab (CPB15+) treated stage IV patients compared to the Carboplatin+ Paclitaxel+ Placebo (CPP) arm. This compared to an increase of 3.8 months in the ITT population, although the HR was more favourable for the stage IV population (0.64 vs. 0.72). In terms of median OS, an improvement of 7.8 months in the CPB15+ treated stage IV patients compared to the CPP arm. This compared to an increase of 3.2 months in the CPB15+ ITT population versus the CPB15+ arm. Here, the hazard ratio for the stage IV subgroup was more favourable than the ITT population, 0.72 vs 0.88, with a statistically significant OS. HRQL improvements over the course of treatment and following study completion were similar across the ITT and stage IV populations. These results confirm that patients with stage IV ovarian cancer are likely to derive greater clinical benefit from the addition of Avastin to chemotherapy, than those patients with less widespread disease[i]. Furthermore we are aware that Public Health England have been conducting work[ii] looking at the overall survival of patients treated with Avastin through the CDF, which may be useful when assessing the overall cost effectiveness.	considered to be of substantial nature to warrant an appraisal review. In addition, the new evidence does not address the uncertainty in the survival benefit of bevacizumab, attributed to uncertainty related to the extent to which patients received bevacizumab after progression in GOG-0218, and the impact of this. Finally, given the high incremental cost effectiveness ratio for bevacizumab, incorporating the new evidence into the model is unlikely to change the committee's conclusion about the cost effectiveness of the technology. It is therefore recommended that TA284 be transferred to the static list.

TA285 In relation to Avastin in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive ovarian cancer (PSROC), a change in its license due to the GOG-213 trial is a potential scenario. Therefore Avastin for this indication may need to be reviewed in the context of this trial when a new license is received (PSROC filing based on the GOG-213 data is planned for submission in the EU in October 2016), and a fuller picture of the impact on the cost-effectiveness this data has can be established. In summary, moving Avastin for this indication to the static list should be reviewed by NICE as Avastin may be granted a marketing authorisation extension within the next months with more up to date clinical and economic evidence.	**TA285** Response noted. Topics on the static list can be considered for review if any new evidence becomes available that is likely to lead to a change in the existing recommendations.

Respondent: Novartis **Response to proposal:** No comment	**Comment from Technology Appraisals** Noted.

Respondent: Pfizer **Response to proposal:** No comment	**Comment from Technology Appraisals** Noted.

Paper signed off by: Janet Robertson – Associate Director, 1 June 2016

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[i] Outcome differences in patients with advanced epithelial ovarian, primary peritoneal and fallopian tube cancers treated with and without bevacizumab. L Randall et al doi:10.1016/j.ygyno.2013.04.139

[ii] An evaluation of Bevacizumab treatments for patients with colorectal or ovarian cancers funded through the Cancer Drugs Fund (CDF) in England. Michael W Health economics, cost and value - 3, 14/06/2016, 13:30 - 15:00