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22 January 2013

Dear Sir or Madam

Re: Single Technology Appraisal (STA) - Bevacizumab in combination with paclitaxel and carboplatin for the first-line treatment of ovarian cancer [ID435] - Appraisal consultation document (ACD)

I write on behalf of the NCRI Gynaecological Cancer Clinical Studies Group/RCP/RCR/ACP/JCCO who collaborate and submit joint responses to NICE oncological consultations. We are grateful for the opportunity to respond to the above ACD and would like to make the following comments.

Outcome from appraisal
The results of GOG218 were reviewed at the NICE appraisal meeting on 20th November 2012 with immature data from ICON7 considered in support. *NICE concluded that bevacizumab plus paclitaxel and carboplatin was not a cost-effective use of NHS resources for first-line treatment of advanced ovarian cancer compared with paclitaxel and carboplatin alone.*

Response to NICE from NCRI/RCP/RCR/ACP/JCCO
The UK Gynaecological cancer community strongly disagrees with the NICE Initial Appraisal decision in which first-line bevacizumab was rejected outright and suggest that the lower 7.5mg/kg dose is instead considered for approval. Having examined the data from ICON7 and GOG218 in detail, we wish to highlight the following.

1. Clinical Efficacy of bevacizumab:
A subject of discussion at the appraisal meeting was the poor overall survival in the ICON7 control arm compared to that of the GOG218 study, leading the committee to conclude the populations were incomparable.

The final analysis of GOG218 showed a median overall survival of 40.6 months with chemotherapy plus placebo, and 43.8 months with chemotherapy plus bevacizumab (during chemotherapy and as maintenance) to a total of 15 months (hazard ratio 0.88 (0.75-1.04), P = 0.0641. In ICON7 the median overall survival for the high risk group of patients (a similar population to those included in GOG218) who were treated with chemotherapy and bevacizumab, and then with bevacizumab as maintenance to a total of 12 months was 36.6 months, very similar to that seen in GOG218; however the median overall survival for the ICON7 control group patients in this category who received chemotherapy alone was 28.8 months.

The better survival outcomes for those in the GOG218 control arm compared to those in the control arm of ICON7can be explained by the extent of cross-over that occurred in GOG218. In GOG218, patients within the study (recruited from USA, Japan and Korea) were unblinded at the time of progression or at the time of the initial analysis. It is estimated that 40% patients crossed over to bevacizumab, which was a requirement of the FDA. In contrast, in ICON7 (recruited from UK, other countries in Europe, Australasia and Canada) a very

small percentage of patients crossed over to anti-angiogenic therapy post progression and such a crossover was strongly discouraged in the protocol. We feel that the extent of crossover in GOG218 not only resulted in better survival within its control arm but also diluted the biological effect of the agent resulting in a non-significant improvement in overall survival.

The fact that there was minimal crossover within ICON7 suggests that the 28.8 month overall survival within its control group realistically mirrors the expected survival of a poor prognosis subgroup of ovarian cancer patients denied bevacizumab treatment. In consideration of these factors, bevacizumab is a clinically effective treatment for patients with high risk ovarian cancer.

2. Preferred dose of bevacizumab

Although the manufacturer (Roche) and clinical experts requested (letter to NICE) that the 7.5mg/kg dose of bevacizumab used in ICON7 be considered instead of 15mg/kg, this was refused on the grounds that bevacizumab had only been licensed by the EMA for use at 15mg/kg and the lower dose of 7.5mg/kg was outside the scope of the current appraisal.

Although we agree with the committee's findings that bevacizumab given at the licensed 15mg/kg dose to unselected patients with advanced ovarian cancer is not a cost-effective use of NHS resources, we are concerned by NICE's summary sentence. By stating 'NICE conclude that bevacizumab plus paclitaxel and carboplatin was not a cost-effective use of NHS resources for first-line treatment of advanced ovarian cancer compared with paclitaxel and carboplatin alone' this appears to preclude the evaluation of the drug at a lower and more cost effective dose.

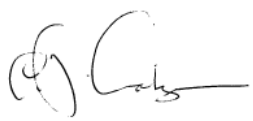
We strongly feel that bevacizumab at a dose of 7.5mg/kg should be approved for first line clinical use. This was the dose given in the ICON7 study, which has shown equal clinical efficacy and lower toxicity than the 15mg/kg dose given in GOG218. Moreover, ERG analysis of bevacizumab given at 7.5mg/kg in an *unselected* ovarian patient population results in an ICER of £77,884 per QALY gained over carboplatin and paclitaxel alone over a 10 year time horizon.

We therefore consider that, in a selected (high-risk) population, as defined in ICON7 and balanced against the benefits of treatment, 7.5mg/kg is a cost-effective use of NHS resources.

In conclusion

We believe that the data from ICON7 and GOG218 are robust, and strongly point to a clinically significant biological effect from bevacizumab. The economic analyses conducted with the ICON7 dose and duration of bevacizumab, set against the improvement of outcome seen for high risk patients, also suggest that this is cost-effective. We see the addition of bevacizumab to front-line treatment of patients with ovarian cancer as a vitally import step-change in their management and an opportunity to improve the prognosis of this aggressive disease. In the interests of our patients, we strongly oppose the decision made by NICE at its Initial Appraisal and ask for the opportunity to re-present the efficacy and economic evidence for bevacizumab 7.5mg/kg given alongside and after first-line chemotherapy in patients with high risk ovarian cancer with the aim of obtaining its approval in this selected patient group.

Yours faithfully



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