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BY EMAIL

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RE: Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer

Dear Kate,

Please find below our response to the second clarification question from the ERG received 20th January 2012. I would also like to advise you that our response contains no commercial or academic in confidence material and the confidential information checklist provided on Wednesday 25th January should be considered applicable here.

We hope this feedback helps clarify the issue raised by the ERG. If you require any further clarification or information then please do not hesitate to contact us.

Yours Sincerely,

[redacted]

Question:-

It is felt that while the subgroup used in the economic model almost reflects the indication for capecitabine, it is a narrower and more specific population than that specified in the licensed indication for bevacizumab in combination with capecitabine. Capecitabine is indicated for the treatment of metastatic breast cancer after the **failure of taxanes and an anthracycline-containing regimen**, while bevacizumab in combination with capecitabine is indicated for the first-line treatment of those with metastatic breast cancer for whom treatment with other chemotherapy options including **taxanes or anthracyclines is not considered appropriate**.

The ERG and the NICE technical team would like further clarification relating to **either** the clinical effectiveness data for the subgroup used in the economic model accompanying the submission **or,** preferably, additional cost-effectiveness data for the Intention-to treat/safety population in the RIBBON-1 trial.

Answer:-

An anthracycline or a taxane is the initial choice of first-line therapy for patients with metastatic breast cancer, based on the relative efficacy of the different therapies; anthracyclines better than taxanes much better than capecitabine (NICE CG81). During recruitment to the RIBBON-1 study, patients could be assigned to anthracycline or taxane therapy in one half of the study, or to capecitabine in the other half of the study, according to the Investigator's choice of therapy for individual patients. Thus the recruiting clinicians made the decision, before patients entered the capecitabine part of the study, that an anthracycline or a taxane was not appropriate as first-line therapy for their mBC. This designation of "not appropriate" may have been for a number of reasons and these reflected the individual clinicians' judgement of each patient. Anthracycline or taxane therapy may not have been appropriate either due to patients recurring after prior exposure to anthracycline and taxane therapy (patient had "failed" these therapies) or for reasons related to the more benign tolerability profile of capecitabine This improved tolerability profile allows patients with residual toxicity from earlier therapies, or those who

cannot/will not undergo particular toxicities, or those with less good performance status, to be treated with capecitabine.

The points above show that, for all the capecitabine patients in the ITT population of RIBBON-1, anthracycline and taxane therapy were not considered appropriate, but this consideration may have encompassed several different patient profiles. The patients who had previously “failed anthracycline and taxane therapy” were a subgroup of the ITT “not appropriate” population and these conform to a stricter population, defined by the failure of previous anthracycline and taxane therapy to control their disease. Only these patients conform to the licensed indication for Xeloda. The clinical effectiveness of bevacizumab in these patients was described in the submission on page 53 (PFS) and page 60 (OS) and the data informing the Kaplan-Meier survival curves were provided in the economic model.

As the submission shows, the clinical efficacy of capecitabine plus bevacizumab in the ITT population, where all the patients are considered not appropriate for anthracycline and taxane therapy, is not better than clinical efficacy in the subgroup of patients who have previously received adjuvant taxane and anthracycline therapy and have failed. Thus any cost-effectiveness analysis for patients who are considered “not appropriate” for anthracycline and taxane therapy would be less favourable than the analysis for the patients who have “failed” anthracycline and taxane therapy. Since the submitted health economic analysis calculated an ICER of approximately £77,000 per QALY for the “failed anthracycline and taxane therapy” subgroup, analysis of the ITT population would result in a larger ICER and therefore clearly not considered to be a cost-effective use of NHS resources.