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Dr. Carol Longson,
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Dear Carole,

re: Single Technolcogy Appraisal (STA)
Gemcitabine for the treatment of metastatic breast cancer.

Thank you for asking me to comment on the appraisal consultation document (ACD)and evaluation report for the above appraisal on behalf of the National Cancer Research Institute Breast Cancer Clinical Studies Group.

With respect to the ACD:

(i) I believe that all of the evidence relevant to the appraisal has been taken into account.

(ii) I believe that the summary of the clinical effectiveness of the Gemcitabine/Paclitaxel combination under estimates the potential clinical benefit of this combination for patients with metastatic breast cancer. Although there is considerable evidence that combination chemotherapy for metastatic breast cancer improves the response rates when compared with single agent chemotherapy treatment, there are very few trials that have shown improved survival in patients with metastatic breast cancer treated with combination chemotherapy compared with single agent treatment. The JHQG trial[1] which compared Gemcitabine/Paclitaxel (GT) with Paclitaxel (T) in patients with metastatic breast cancer who had received previous anthracycline based chemotherapy in the adjuvant treatment setting is only the second trial to my knowledge to show a survival benefit for combination over single agent chemotherapy in metastatic breast cancer. The only other study to have demonstrated a survival benefit for combination chemotherapy in patients with metastatic breast cancer is the study by O'Shaughnessy and colleagues[2] which compared Docetaxel mono therapy with Docetaxel/Capecitabine combination therapy. The combination of Docetaxel and Capecitabine has been approved by NICE for the treatment of locally advanced or metastatic breast cancer in people for whom anthracycline containing regimens are unsuitable or have failed.

Balancing efficacy and safety is a key goal in delivering a positive risk benefit profile for patients with metastatic breast cancer and therefore the toxicity profile of treatment is an important factor in determining the optimum combination therapy. At present the most widely used first line chemotherapy treatment for

metastatic breast cancer in patients who have previously received an anthracycline in the adjuvant treatment setting is single agent Docetaxel. In clinical practice the toxicity of combination treatment with Docetaxel and Capecitabine makes it difficult to deliver without significantly compromising patients quality of life. Docetaxel (100mg per m^2) iv mono therapy has been shown to be more active than Paclitaxel (175mg per m^2) three weekly mono therapy, but is also more toxic[3].

As metastatic breast cancer is incurable and the average survival for patients with visceral metastases is less than two years, therapies that result in a survival benefit can confer a significant advantage to patients in this situation. The results of the JHQG trial demonstrate a 20% incremental increase in survival time of patients treated with the combination of Paclitaxel and Gemcitabine compared with single agent Paclitaxel. The toxicity profile of this treatment is generally favourable. Although myelosuppression is greater in the Gemcitabine/Paclitaxel group, the rates of febrile neutropenia in this group (the only clinically significant effect of myelosuppression) was only 5%, which is significantly lower than that reported for single agent Docetaxel in other trials.

The availability of a tolerable combination chemotherapy regimen that confers a survival benefit to patients with metastatic breast cancer previously exposed to an anthracycline combing regimen in the adjuvant setting would be of a significant benefit to this patient population. It would be particularly applied to patients with visceral disease who are of good performance status and have good organ function. I believe that it would be used in preference to the more toxic Docetaxel/Capecitabine regimen.

As there are no randomised trials comparing Gemcitabine plus Paclitaxel with Docetaxel mono therapy or the Docetaxel/Capecitabine combination, comparisons between these treatments rely on indirect, cross trial comparisons. There is some heterogeneity between these trials in terms of the number of prior chemotherapy regimens that patients may have received. Summaries of the baseline characteristics of patients entering these studies are broadly similar with the exception that the median Karnofsky performance status of patients entered into the JHQG trial[1] was 70% whereas the median Karnofsky performance stats score for patients in the other two trials was 90%. Performance status is closely correlated with the patient's well-being, their ability to tolerate chemotherapy treatment and also their response to treatment. In this context, the results of the JHQG trial demonstrating survival benefit for the Gemcitabine/Paclitaxel combination in a group of patients with a generally poorer performance status, with very manageable toxicity, is an impressive result.

It would not be possible to formally assess the heterogeneity between the characteristics of the patients in the different study populations, nor to adjust for differences in baseline characteristics without access to individual patient data from each of these trials. I therefore believe that the economic analysis presented by the manufacturer linking these trials through the common comparator arm of single agent Docetaxel was appropriate and the only methodology which could be employed given the available data. I do not believe there is any way in which such a cross trial comparison can be undertaken whilst preserving the benefits of randomisation.

The cost effectiveness analysis for Gemcitabine/Paclitaxel combination therapy is significantly influenced by the acquisition cost of Paclitaxel. As this drug is now off patent and non proprietary formulations of Paclitaxel are available, the cost of this drug has fallen substantially. The current cost of Paclitaxel to my hospital Trust is nearly 50% of the price quoted in the ACD (paragraph 2.3). This significantly impacts on the overall drug cost of combination therapy and it is currently comparable to the cost of single agent Docetaxel. There are some additional costs involved in delivering this treatment, particularly as patients need to return for Gemcitabine on day eight and administration of Paclitaxel and Gemcitabine together on day one would take around four hours compared with one hour administration time for single agent Docetaxel. Despite this, the costs are still likely to substantially lower than those that have been used in the economic analysis that was undertaken by the ERG and I think that it is important that this is fully appreciated by the appraisal committee.

(iii) In the light of my previous comments, I believe that the provisional recommendations of the appraisal committee should be reviewed. The availability of the Gemcitabine/Paclitaxel combination for appropriate patients with metastatic breast cancer would be of signifcant clinical benefit and I believe would satisfy the requirements for cost effectiveness given the current acquisition cost of a non proprietary Paclitaxel.

Yours sincerely

References.

(1) Albain KS, Nag S, Calderillo-Ruiz G, Jordaan JP, Llombart A, Pluzanska A et al. Global phase III study of gemcitabine plus paclitaxel (GT) vs. paclitaxel (T) as frontline therapy for metastatic breast cancer (MBC): First report of overall survival. J Clin Oncol 2004; 22(14): 5S.

(2) O'Shaughnessy J, Nag S, Calderillo-Ruiz G, Jordaan J, Llombart A, Pluzanska A et al. Gemcitabine plus paclitaxel (GT) versus paclitaxel (T) as first-line treatment for anthracycline pre-treated metastatic breast cancer (MBC): interim results of a global phase III study (abstract 25). Proceedings of the American Society of clinical Oncology 2003; 22:7.

(3) Jones SE, Erban J, Overmoyer B, Budd G, Hutchins L, Lower E et al. Randomized Phase III Study of Docetaxel Compared With Paclitaxel in Metastatic Breast Cancer. J Clin Oncol 2005; 23(24): 5542-5551.