Reviewer's report

Title: FemZone Trial: a randomized phase II trial comparing neoadjuvant letrozole and zoledronic acid with letrozole in primary breast cancer patients

Version: 2 Date: 6 June 2013

Reviewer: Nigel Bundred

Reviewer's report:

This is an interesting Phase II study which did not complete recruitment and therefore any conclusions about it must be limited.

The paper is well-written but it is disappointing that there is no biological data, rather than just clinical endpoints as this would have made the whole paper more interesting.

There is not a lot that one can draw in terms of efficacy, from a trial in which only 168 out of the expected 858 patients were recruited. In many ways, the paper reflects this.

It is somewhat disappointing that there is no comment as to why patients declined entry to the trial or why clinicians declined to offer them the trial and randomise them.

The final point of the authors is that there is a difficulty in clinical assessment of response and this is correct. In some way, it diminishes the message of the paper.

All patients seem to have undergone surgery (although this is not clearly stated in the manuscript) and one arbiter of response would be median tumour size and tumour grade, and whether there were any changes in grade from the core biopsies. It is disappointing that this is not clear either in the manuscript or the subsequent tables, in which the logistic models and the tumour response is ultimately dependant on what percentage ended up with a mastectomy versus wide local excision/breast conserving surgery and did any patients experience a downgrade of their final tumour grade?

I would personally expect to see clear detail on the surgical treatment of these patients as part of a revision, in which the eventual surgery and various tumour grades was compared between the core biopsy (on which presumably the diagnosis was made) and the final surgical pathology.

The model appears based on radiological tumour size change rather than final pathological tumour size and for those cases where patients have discordance between the radiological and final pathology size, the final pathology size is more value but appears to be unclear here.

At the very least, a comparison of the final pathology size versus radiological size
prior to surgery, should be available. How did the pathology relate in terms of changes in the stroma, which zoledronic acid has been said to affect, compared to those treated with Letrozole alone. It would also be interesting to know whether side-effect profile related to tumour response as there has been considerable data in the literature with other drugs, that patients who have side-effects are more likely to have a tumour response.

In short therefore, I have some issues about the methods used to assess response and how they relate to final tumour pathological size.

The data given the low numbers randomised, has wide margins of error and does not allow the authors to provide any firm conclusions on increased response rate with a combination as they themselves note.

The limitations are clearly stated and the discussion and conclusions are balanced, except for my concerns about the pathological assessment.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.