**Reviewer's report**

**Title:** Analysis of and prognostic information from disseminated tumour cells in bone marrow in primary breast cancer. Report of a prospective observational study

**Version:** 1  **Date:** 9 April 2012

**Reviewer:** Jean-Yves Pierga

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Report on Falck et al

The authors report the follow-up of a large series of early breast cancer patients who had DTC detection in their bone marrow at time of surgery. This paper could add new information about prognostic value on DTC detection. However, several points have to be clarified and revised.

**Major Compulsory Revisions**

1/ From a methodological point of view, it is not acceptable that the results of two different methods, used sequentially and not concomitantly on different samples, can be mixed for the analysis. The vast majority of the patients were screened by immunofluorescence. The results for DFS and OS should be given only for the IF methods. For the ICC method, the number of patients is too small to draw definitive conclusion (74 patients). Even if a subgroup analysis was performed, it is not appropriate to pool the two methods in the same analysis. This IF procedure was not used in the metaanalysis published by Braun et al in 2005 and is outside recommendations of the consortium published in 2006 by Fehm et al in Cancer 2006. Did the authors compare the detection rate one the same samples with the two techniques (IC and IF)?

2/ More than one hundred patients had bone marrow sampling without any result. This is a very high percentage and is astonishing. What are the reasons for not being able to handle the samples? At least more detailed explanations should be given.

3/ 76 healthy people had bone marrow aspiration. What are the reasons to perform bone marrow aspiration in healthy people? This an invasive procedure and usually used in hematologic disorders or non solid cancerous diseases? Was there a specific inform consent signed by these healthy people?

4/ Median follow-up is not clearly given. As the last patients were included in 2003, one could expect a median follow-up of mere than 7 years.

5/ What is the justification of sternal double aspiration? In the majority of the studies, bone marrow aspiration was performed from bilateral iliac crest. Is the term sternal crest appropriated?

6/ Epithelial cell were detected in healthy control but surprisingly not in the control slide of the patients. Control patients without cancer were tested in
several series of the metaanalysis (Braun 2005) with a rate of detection inferior to 5%. In the present series, if you discard ambiguous cases, 19/73 (26%) positive cases rate is not statistically different from patients in the study (38%), p = 0.055.

7/ The authors should cite the recent studies of large series on DTC detection of Giuliano in JAMA with more than 3000 patients, confirming prognostic value of DTC detection (Giuliano, Hawes et al. 2011) or Molloy (Molloy, Bosma et al. 2011)

Minor Essential Revisions

1/ In the discussion, reference 22 is cited as a negative study on prognostic value of DTC detection However, there is a trend and the study as not the power (less than 100 patient s) to conclude with only 8 events.

2/ Figure 3: the morphological criteria of the ICC stained cell are not very convincing with the same tumour size than haematopoietic cells and nuclear size not clearly enlarged.


Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests