Reviewer's report

Title: Immunohistochemical subtypes predict the clinical outcome in high-risk node-negative breast cancer patients treated with adjuvant FEC regimen

Version: 2

Date: 16 June 2015

Reviewer: Sofia Torres

Reviewer's report:

1) Summary and Strengths: This is a review of a retrospective study that included 757 patients with node-negative breast cancer treated with adjuvant FEC between 1998 and 2008, in a single institution in France. The primary objective was to identify clinico-pathological predictors of disease-free survival in this cohort of patients. There was no comparison group.

The study asks a relevant clinical-question: can we identify patients with node-negative breast cancer who would benefit from a more aggressive chemotherapy treatment? The study question and results are well summarized in the abstract. The methods are appropriate and well described and the data is sound. There was an extensive bibliographic search to support the study rational and discussion of results and the authors clearly acknowledge the work upon they are building.

2) Major Compulsory Revisions

The major limitation of the present manuscript is that the authors do not adequately discuss the limitations (and strengths) of the present study design to answer the research question. This was a retrospective (therefore non-randomized, subject to confounding and bias), single-centre, single group, cohort study. The authors did not discuss of the quality of the data sources (completeness/missing data, validation of the data) or possible bias and confounding factors (that may explain some of the results obtained). Since the present study design does not allow to establish causality, authors should be careful not to make strong causal statements. A final paragraph stating the overall implications of the study/ future research could be added.

Other suggestions:

Page 6, line 14: please clearly state what are the primary and secondary objectives/ outcomes.

Page 6, lines 18-19: the authors indicate that the data was collected from a prospectively maintained institutional database. I suggest describing the data source (the quality of the data used might be a strength that the authors did not mention in their discussion): is it an administrative or clinical database? Who collects the data? Is the data validated? Is there any missing data?

Page 8, line 24: suggest STROBE guidelines instead
Page 12, line 12: OS is one of the secondary outcomes, but no results are presented
Page 13, lines 11 to 14 and Page 14, lines 19 to 21: how do the authors explain these results?
Page 15, line 15: In conclusion, our results suggest a relative...

3) Minor Essential Revision
Page 3, Title: should indicate that this is a retrospective study
Page 3, line 10: the term “Prospective data collection” is misleading
Page 3, line 11: suggested modification “clinico-pathological characteristics and treatment information.”
Page 3, line 12: SBR not previously defined
Page 3, line 13: “were estimated” using the Kaplan-Meier Method?
Page 5, line 5: please review reference; study cited investigated the benefit of the addition of CMF to surgery
Page 5, line 13: please review reference, EBCTG 2005 showed this
Page 6, line 8: please define high-risk
Page 6, lines 8-9: “treated with adjuvant FEC chemotherapy”
Page 6, line 11: please clarify the meaning of “expansive” in this sentence
Page 6, lines 18 to 24: sentence is too long, suggest breaking and separating inclusion and exclusion criteria for the study.
Page 8, line 11: only median and ranges, counts and frequency were used
Page 8, line 12: suggest adding counts and frequency after categorical, using the term continuous instead of quantitative, and adding median and ranges after continuous.
Page 8, line 19: compared among immunohistochemical subtypes using the log-rank test?
Page 10, line 22: “instead” not “in place”
Page 11, line 1: “DDFS” not “DFS”

4) Discretionary Revisions:
Page 5, line 24 and page 6 line 2: should be consistent with the terms-anthracycline/taxane-based
Page 7, line 19 and 20: for consistency, please add “all grades”, after HER2-negative and after HER2-positive
Page 8, line 1: can explain here that these are the high-risk features
Page 10, line 1: suggest using the term clinico-pathological predictors of DFS
Page 10, line 2: In the univariate analysis (and every time the term is used after this)
Page 10, line 8: In the multivariate / adjusted analysis (and every time the term is used after this)

Page 10, line 12-13: suggest “were independently associated with an adverse outcome” instead

Page 10, line 18: suggest using the terms predictive or associated with instead of prognostic

Page 11, line 21: suggesting the these patients might…

Page 23, Table 2: suggest removing the 5-year DFS column from the table. The same for page 25, table 4.

**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 in relation to this paper.

Financial disclosures not related with this paper: I have received honoraria from BMS and payment for travel, accommodations and other expenses from BMS and Roche Farmaceutica Química, Celldex and Astra-Zeneca. I have received fellowship support from Genomic Health.