Author's response to reviews

Title: Treatment patterns, clinical outcomes and health care costs associated with HER2-positive breast cancer with central nervous system metastases: a French multicentre observational study

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Version: 2 Date: 3 October 2013

Author's response to reviews: see over
Editorial Office Comments

1. Please include the 'Role of the funding source' in your CI statement. This has been done.

2. Conclusions:
   This should state clearly the main conclusions of the research and give a clear explanation of their importance and relevance. Summary illustrations may be included. We have rewritten the Conclusion so that these requisites are more explicitly met.

3. Tables:
   Please ensure that the order in which your tables are cited is the same as the order in which they are provided. Every table must be cited in the text, using Arabic numerals. Please do not use ranges when listing tables. Tables must not be subdivided, or contain tables within tables. Please note that we are unable to display vertical lines or text within tables, no display merged cells: please re-layout your table without these elements. Tables should be formatted using the Table tool in your word processor. Please ensure the table title is above the table and the legend is below the table. For more information, see the instructions for authors on the journal website. This has been corrected.
Reviewer 1

Major Compulsory Revisions

1. Need to use the same acronyms all the time not keep changing as this is very confusing for the reader. For example, CNSM, CNS metastases. Don’t switch between BC and breast cancer. Given an example below – introduction first paragraph. We have standardized these. BC is used throughout and we have kept CNS metastases throughout. BC, HER2, GPA, DRG and CNS are now the only acronyms used.

Abstract.

2. First paragraph first line should read - breast cancer (BC). This has been corrected.

3. First paragraph third line – ‘diversified’ should use ‘diverse’. This has been corrected.

Introduction:

4. “In 2011, an estimated 53,000 new cases of breast cancer (BC) were diagnosed and almost 11,500 women died from BC in France [Error! Reference source not found.]. Between 5%-15% of new BC cases are diagnosed when already metastatic, when the estimated five year survival is 13% [1]. The apparent incidence of central nervous system (CNS) metastases in BC is increasing [Error! Reference source not found.]. This may be due to improved imaging and earlier detection of CNS lesions and also because of the availability of more effective systemic treatments that allow more patients to live long enough to develop CNSM [2,3]. In general, survival for BC patients with CNSM is poor, with one-year survival of approximately 20% [4]. See reply to Point 1. The problem with the reference citations has been resolved.

5. Paragraph 2: Line 7 – remove ‘cytotoxic’. This has been done.

6. Paragraph 2: Line 8 – add ‘has’ before ‘encouraged’. This has been done.

Patients and Methods

7. In Patient selection should be ‘healthcare resources’. This has been corrected.

Results

8. Don’t’ need Table1 if you are going to report all the results in the paragraph. We have removed from the paragraph of the Methods the data that do not directly relate to the subject matter. The Table has been retained. We believe that it will be simpler for the reader this way.

9. In Health-care resources used after CNSM diagnosis section you need to explain what you mean by lines of chemotherapy. It means a new treatment regimen introduced whenever significant progression of the disease was observed. This is now specified in the text.

‘Chemotherapy was mainly delivered as an outpatient procedure. RT was administered to 200 patients (91.7%), and included whole brain RT n (77.3%), stereotactactic radiosurgery (SRS)n (9.6%) or both n(6%). Patients received one cycle of RT (n, 86.8%), two cycles of RT (n, 12.5%) or second SRS (n, 1%). The median number of
fractions per patient was ten. Radiation therapy sessions were delivered on an outpatient basis for 80...

10. *Health Care Costs* The values in this section do not seem to be the same as in the figures. The values in the text refer to all BC patients, whereas those presented in the Figure compare patients with primary brain metastases and those with secondary brain metastases. This has now been specified in the text to avoid confusion.

**Figures and Tables**

11. Table 2 - Lines need to line up and actual numbers need to be quoted with percentages. This has been done.

12. Figure 1 – It is not clear what survival you are comparing. It is overall survival. This is specified in the Figure Title.

13. Figure 2 – Values do not match result section and not sure what you are comparing as no explanation or title. We are comparing primary and secondary brain metastases. This is specified in the Figure legend. It is now also specified in the text of the Results section to avoid confusion about what these values represent (the numerical values for this comparison are not given in the Results). See also reply to Comment 10.

**Discussion**

14. It wasn’t clear how the discussion related to the results. To make the relationship clearer, we have restructured the Discussion by reordering the material and adding some perspectives on the implications of the findings for the cost-effectiveness of therapies and on the pertinence of early diagnosis of CNS metastases (see Point 17 below).

15. You say that the women with CNS metastases are younger and hormone receptor negative but don’t give any comparison results. This statement does not refer to our work, as we only evaluated women with CNS metastases and not those without. In fact, this material relates more to the background of the study, so we have moved it to the Introduction.

16. It would be useful to change the US dollar figures to Euros so that an easy comparison could be made. This has been done.

17. While finding CNS metastases earlier may be a therapeutic benefit what about the additional costs of treatment that may occur because they live longer with their disease? This is indeed possible, and a statement to this effect has been added to the Discussion.
Reviewer 2

*Minor Essential Revisions*

1. Please introduce all acronyms before using them. Acronym use has been standardized and all are introduced at first appearance. See reply to Comment 1 of Referee 1.

2. There are some bookmarking errors in the document, so the inserted references do not appear. Please correct these. These have been corrected.