Author's response to reviews

Title: Brain metastases from breast cancer: prognostic significance of HER-2 overexpression, effect of trastuzumab and cause of death

Authors:

Romuald Le Scodan (lescodan@crh1.org)
Ludivine Jouanneau (ludivine.jouanneau@curie.net)
Christophe Massard (christophe.massard@igr.fr)
Maya Gutierrez (maya.gutierrez@curie.net)
Youlia Kirova (youlia.kirova@curie.net)
Pascal Cherel (pascal.cherel@curie.net)
Julie Gachet (jgachet@hotmail.fr)
Alain Labib (alain.labib@curie.net)
Emmanuelle Mouret-Fourme (emmanuelle.fourme@curie.net)

Version: 4 Date: 12 August 2011

Author’s response to reviews: see over
Brain metastases from breast cancer: prognostic significance of HER-2 overexpression, effect of trastuzumab and cause of death

To the Editor,

We are pleased to resubmit this manuscript for consideration in BMC Cancer.

BM patients with breast cancer are an heterogeneous group of patients. The aim of this study was to confirm, in a cohort of patients with BM from breast carcinoma, the beneficial effect of trastuzumab in patients with HER2-positive disease, and to analyze the cause of death. We report that BM patients with HER-2 overexpressing tumors treated by trastuzumab appears to be a clearly distinct subgroup of patients who can expect a median survival time of about 20 months and a 1-year survival rate of 60%. In our experience, about 60% of HER-2 positive patients treated with trastuzumab who died apparently succumbed from CNS progression. This information may be useful to tailor the therapy for subgroups of patients, to define homogeneous cohorts for prospective randomized trials, and to identify more precisely patients with relative good prognosis who could be treated with innovative approaches, in order to obtain better intra cerebral control.

Thank you for considering our resubmission.
Yours sincerely,

Romuald Le Scodan, M.D.
Breast Cancer Group of Institut Curie-René Huguenin Cancer Center.
Response to reviewers: First revision

Reviewer: Shaheenah Dawood

Review: “Brain metastases from breast cancer: prognostic significance of HER2 over expression, effect of trastuzumab and cause of death”
Scodan et al present the results of a study that looks at the prognostic outcome of women with breast cancer and brain metastases stratified by HER2 status and trastuzumab treatment. The paper is well written and adds to the growing literature in this field. My comments are as follows:

1. The authors calculate and report the progression free survival of brain mets. Since the timing of CT/MRI for assessment of brain met progression were not conducted at the same time in all patients lead time bias is introduced and this should be discussed in the discussion section of the manuscript. One of the main objectives of this study was to also assess cause of death and thus biases involved in its determination should be discussed.

We do agree with this comment. Patients were followed every month during the 6 months after the end of treatment and every 2 months beyond 6 months. Brain CT scan or MRI were planned 2 months after completion of WBRT and every 3 months thereafter, or when CNS progression was suspected. Unfortunately, not all patients underwent CT/MRI for assessment of BM, mainly because of declining performance status. We do also agree that the determination of the cause of death is difficult in this context.
Corrected.

2. Do the authors have information on how many of the patients went on to receive lapatinib upon development of brain mets?

Only two patients received lapatinib upon development of brain metastases.

3. Do the authors have the data to calculate the time to development of brain
metastases stratified by her2 status. It would be interesting to see if trastuzumab affects this parameter especially since the majority received trastuzumab before development of brain metastases.

Unfortunately, we do not have this information. It is also difficult to calculate the time to development of BM according to HER2 status or delivery of trastuzumab because trastuzumab could have been delivered in the adjuvant setting or at different moment of the metastatic disease, according to its acceptance in the adjuvant or metastatic setting.

4. For figure one please insert the numbers at risk.

5. There are too many tables. the authors may consider consolidating some of the results.

Reviewer: David Church

The authors provide a retrospective analysis of patients treated in their institution, which suggests favourable prognosis in patients with brain metastases from HER2 overexpressing metastatic breast cancer treated with trastuzumab. This is consistent with other retrospective studies previously published.

Major essential revisions:
1. the paper puports to report the prognostic effect of trastuzumab on the survival of patients with BM from MBC. However the group described as 'trastuzumab treated' actually refers to trastuzumab treatment during any stage of the disease course. Thus unless previous trastuzumab treatment is suggested to modify the survival of patients who develop brain metastases after discontinuation of therapy this analysis is problematic. Alternative analysis should be either:

   A. survival from time of BM: HER2 neg vs HER2 pos then subgroup analysis of HER2 pos treated with trastuzumab after BM vs not treated with trastuzumab after BM
B. survival from diagnosis of metastatic disease: HER2 neg vs. HER2 pos
trastuzumab treated vs. HER2 pos trastuzumab non-treated

Patients with HER2 pos disease not treated with trastuzumab were poorer PS and older- suggesting that the worse survival in this group is due to selection bias. Additionally these patients may have been treated pre-2001. Though a difference in survival was noted between patients with HER2 pos disease treated with trastuzumab after BM compared to those who stopped at diagnosis of BM this is not significant. Either the analysis should be revised including survival curves, or the conclusions of the paper should be modified, and the bias in the study explicitly stated. In particular the abstract wording implies trastuzumab therapy after diagnosis of BM and should be reworded.

“Trastuzumab treated” refers to patients receiving trastuzumab for metastatic disease. Corrected.

Because the survival advantage for patients with brain metastases from tumors that overexpress HER2 does not seem to be due to an intrinsic biologic advantage of HER2 overexpression, as patients with HER2-overexpressing tumors who did not receive trastuzumab had survival similar to that of patients with tumors that did not overexpress HER2, we considered that it was better to report survival according to HER2 and delivery of trastuzumab, and not only HER2+ vs HER2-.

The median survival time for HER-2 negative patients (n=78), HER-2 positive patients not treated with trastuzumab (n=20) and HER-2 positive patients treated with trastuzumab (n=32) were 5.9 months, 5.6 months and 19.53 months respectively. The 1-year survival rates were 26.1% (95% CI: 16.8 - 40.7), 29.2% (95% CI:17-50.2) and and 62.6% (95% CI : 47.2-83) respectively, (p< 0.004) (Table 2, Figure 1).

The median survival time for the 10 HER-2 positive patients who stopped trastuzumab before or after the diagnosis of BM and the 22 patients who continued a trastuzumab-based therapy after WBRT were 9.2 months and 20.9 months respectively (p> 0.1). The 1-year survival rates were 43.6 (95% CI: 21.8 - 87.4) and 87.1 (95% CI: 71.8 - 100), respectively (p= 0.13).
We do agree that patients with HER2 positive disease not treated with trastuzumab were poorer PS and older than those treated with trastuzumab. However, in multivariate analysis considering known prognostic factors, trastuzumab–based therapy was associated with a 51% reduction in the risk of death (multiadjusted hazard ratio: 0.49; 95% CI, 0.29-0.83).

2. the manuscript should state the status of extracranial disease in patients diagnosed with BM in each group- not just the trastuzumab-treated cohort. Was it responding/stable/progressive? The number of other extracranial metastatic sites
   Unfortunately, the status of extra cranial disease at the time of BM diagnosis was not prospectively recorded in our database. The number of extracranial metastatic sites are reported in table 1.

3. no information on treatment of patients after diagnosis of BM other than WBRT is mentioned. Were other therapies- surgery, stereotactic radiosurgery, hormone therapy, chemotherapy used? In what proportion of patients? In case of systemic therapy, did continued control of extracranial disease correlate with survival? Were there any documented intracranial responded to systemic therapy (presumably not)? This requires inclusion in table form.

   Only one patient was treated with stereotactic radiosurgery for a local brain failure. Other therapies such as chemotherapy or hormone therapy were also used but the description of all these treatments in this metastatic setting is not easy and is not the main goal of this article. We do agree that the relation between the control of extracranial disease and survival is a key question, but unfortunately, we do not have the data to answer this question.

Minor essential revisions:
1. p11 'in agreement with two previous reports...' should be three previous reports including Church DN et al 2008
Modification have been made.

2. Please use consistent nomenclature throughout manuscript: HER2, italics for gene, non-italics for protein; 95% confidence interval (CI); P or p for significance;

3. p6 selectionned? Please reword.
   Corrected.

4. p7 please note numbers in each group at first mention of groups
   Corrected.

5. p7 should read ‘more likely to have received’
   Corrected.

6. ‘brain failure’ should be changed to ‘progression within the brain’ or ‘CNS progression’
   Corrected.

11. BMBC ?
   Corrected: BM (brain metastases)

12. multiple ‘BM patients’ should be changed to ‘patients with BM’
   Corrected.

13. Tables: please make consistent and put P values on same lines. Please standardise no. of decimal places for P values. Percentages should be given to one decimal place.
   Corrected.

Response to reviewers: Second revision

Reviewer: Shaheenah Dawood
Reviewer’s report:
Scodan et al look at the prognostic significance of HER2 and trastuzumab among
women with breast cancer and brain metastases. My comments are as follows:

1. In the results section the author states that 10 patients with HER2 positive disease treated with trastuzumab had CNS progression however 11 died of CNS progression. The author needs to clarify this.

Ten patients had CNS progression based on last scannographic or MRI evaluation and 11 apparently /clinically succumbed from CNS progression.

2. The author has discussed in detail cause of death specifically related CNS progression among women with HER2 positive disease. However the author only mentions that 30 patients with HER2 negative disease had a follow up brain CT. Its important to elaborate on this cohort as well. How many had CNS progression?

Five patients had CNS progression at last radiologic evaluation but most patients, including those with clinically CNS progression and who died rapidly, had no scannographic evaluation; this cohort is thus not very informative in this retrospective setting.

3. How many of these patients had triple negative disease and what was the overall survival and cause of death in this cohort in comparison to the her2 positive cohort? The author has only eluded to this in the univariate analysis.

28 patients (table 1). Triple negative disease was not an independent prognostic factor in MVA.

4. Time to brain metastases is also important. The author states this for the whole group. It should also be mentioned split into the three groups. An accompanying figure would also be good.

This data will be describe further in a future studies.

5. The author needs to information on hormone receptor status and trastuzumab treatment in table 1.
Tumor HR status is described in table 1 and delivery of trastuzumab-base therapy is specifically described in table 2.

6. Numbers at risk should be inserted in figure one.
7. The authors states that patients with HER2 positive disease who stopped trastuzumab before BM had OS of 9 months compared to those who continued (20m). This would make an interesting point of discussion as the group that stops trastuzumab still does better than the non treated group.

We do agree with this comment, but given the retrospective nature of this study, this data need to be taken with caution and was not developed.

8. How many patients who had documented CNS progression stopped trastuzumab before BM and how many continued it?

Two patients with CNS progression stopped trastuzumab before progression.

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' below.

Reviewer's report
Title: Brain metastases from breast cancer: prognostic significance of HER-2 overexpression, effect of trastuzumab and cause of death
Version: 3 Date: 7 June 2011
Reviewer: David Church
Reviewer's report:
The authors have responded satisfactorily to almost all the comments made. However, the principal point has still not been addressed; the title and abstract
wording suggest impact of trastuzumab after brain metastases were diagnosed while the actual analysis is of trastuzumab treatment at any stage during the disease course. Providing the abstract wording is amended to make this clear I am happy for this to be accepted for publication.

We do agree with this comment: this point is clearly explained in the results/discussion section and the impact of trastuzumab after BM is not specifically suggest in our title.

**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 have previously received travel expenses and honoraria from Roche.
I have no other competing interests

Thank you for reconsidering our revised article.

R Le Scodan, on behalf of the Institut Curie Breast Cancer Group.