**Author’s response to reviews**

**Title:** Efficacy of T-DM1 for leptomeningeal and brain metastases in a HER2 positive metastatic breast cancer patient: new directions for systemic therapy. A case report and literature review

**Authors:**

Giuseppina Ricciardi (giusyricciardi81@hotmail.it)

Alessandro Russo (alessandro-russo@alice.it)

Tindara Franchina (tfranchina@unime.it)

Silvia Schifano (silviaschifano@hotmail.it)

Giampiero Mastroeni (giampieromastroeni@gmail.com)

Anna Santacaterina (anna.santacaterina@virgilio.it)

Vincenzo Adamo (vadamo@unime.it)

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**COMMENTS TO REVIEWERS**

Reviewer reports:

The authors present a case report in which a patient with HER2-positive breast cancer metastatic to the brain with leptomeningeal disease was treated systemically with a drug conjugate of Herceptin and DM1 (called T-DM1) with concurrent WBRT. They report that the patient had complete regression of the intracranial disease. While they focus on the small metastatic disease and LMD, they should shift the focus to the response to the LMD, which carries a terrible prognosis. They propose some theories about how this may have happened, and acknowledge that fact that a trial would be necessary to draw and real conclusions. However, since the patient is still on T-DM1 therapy and alive, is it possible to obtain CSF and measure if there are any drug levels in the CSF (suggesting blood brain barrier penetration)?
R: We appreciated your useful comments. However, the patient at the moment refuses further invasive procedures. Therefore, these data cannot be available at the moment.

I would also ask that the figures be edited slightly. So for the most recent MRI, please provide the same cuts as the pre-treatment MRI. I think this will send a more powerful message regarding the patient's response.

There are a number of grammatical errors in the manuscripts that will require editing. A few are listed below:

Line 43 - should read "We previously…"

Line 34 - please re-word the sentence to be more grammatically accurate.

Line 39 - should read "Recent preclinical work demonstrated…"

Line 51 - efficacy should be effect

I think with these corrections, the paper should be considered for acceptance.

R: Thank you for your comments. We corrected the mistakes.
1. In Background, trastuzumab does not alter the natural course of breast cancer; it alters the course of the disease after treatment. "Natural course" implies the course of the untreated disease.

R: Thank you for your comments. We corrected the mistakes.

2. In Background, it is not true that there are "no specific treatment options" for brain metastases because SRS is a specific treatment option for brain metastases. It may be true that there are no targeted systemic options for brain metastases from breast cancer.

R: Thank you for your comments. We corrected the mistakes.

3. In Background, "against" in line 51 should be "compared to".

R: Thank you for your comments. We corrected the mistakes.

4. In Case Presentation first page, line 22, Mib-1 should be MIB-1

R: Thank you for your comments. We corrected the mistakes.

5. In Case Presentation second page, when the patient was staged for leptomeningeal disease, did she have an MR spine? Did she have CSF analysis? If so, what did these studies show?
6. In the Case Presentation, clarify the radiation fractionation and technique-- 30 Gy in 10 fractions? Was some technique used to minimize dose heterogeneity?

R: Thank you for your comments. We included these data.

7. From the images provided, the cribiform plate and posterior orbits do not appear to have been covered by the radiation fields; these areas would be at risk in a patient with leptomeningeal dissemination. If the cribiform plate and posterior orbits were not intentionally covered, was this decision based on the concurrent use of T-DM1, the local WBRT practice, a negative CSF result, or some other clinical factor?

R: Thank you for your comments. We did not cover these areas as per local WBRT practice.

8. Figure 4 and 5 could be combined. Would be nice to show a similar slice of the brain MRI at early and later follow up, instead of a slice through the optic chiasm at an early time point and a slice through the inferior cerebellum at a later time point.

9. Figure 6 restates what is in in the text and could be deleted.

R: Thank you for your comments. However, this image was included, as per editorial policy of BMC Cancer.
10. Discussion might benefit from further elaboration of the results from references #45 and #46 and a comparison of those patients with the current patient. Some of the patients in reference #46 received WBRT, but none of those patients had leptomeningeal dissemination, which should be emphasized.

R: Thank you for your comments. We included these data.