Peer Review File

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Reviewer A

The contents of the biology and mechanism of Brain Metastases and the method of local treatment are about the overall Brain Metastases of Breast Cancer, and The contents of the biology and mechanism of brain metastases and the method of local treatment are about the overall brain metastases of breast cancer, the characteristic contents of the HER2 positive breast cancer are hard to find.
Reply 1: we provide to specify that local treatments are for overall brain metastases (lines 211-212). In the section 3 are already explained the mechanisms of CNS spreading in HER2+ BC.
And Focusing of the conclusion is limited to new anti HER2 Drugs.
Reply 2: we provide to implement this section.
Please check the basic spelling and form of the paper. ('stereotaxic' or 'stereotactic', 'versus' or 'vs', 'HER2' or 'HER-2', (HR, p-value) or (HR; p-value)
Reply 3: we provide to homologate all the terms in ‘stereotactic’ and ‘HER2+’ and punctuation.
Although it is a systemic review, it is difficult to identify original or new contents compared to other reviews already published.

Reviewer B

Where possible, reference original articles rather than reviews; other authors’ reviews are very useful to direct your reading and ensure that you haven’t missed out important data in your own review, but should ideally be referenced as “reviewed in x” where cited. Some additional specific comments:
1. Title: Given the discussion of treatment for LMD in section 5, please include this in your title
Reply 1: We provided to change title, including all CNS localizations.
Changes in the text: See **line 1-2**
2. Introduction; HER2+ is no longer associated with a poor prognosis, so please amend the 3rd line to add “historically”
Reply 2: We provided to modify the text, including the word “historically”.
Changes in the text: We provided to modify the text **(line 58).**
3. Introduction and abstract; brain mets now develop in up to 50%of patients with

HER2+ breast cancer due to better treatments for extracranial disease and the risk increases with each line of therapy.
Reply 3: we changed this data and we inserted new reference
Changes in the text: “Patients with HER2-positive (HER2+) metastatic breast cancer (mBC) develop BM in up to 55% of cases” **(lines 28 and 61)**
4. Methods: Again, add LMD/change to “CNS spread” or similar
Reply 4: we provided to modify the text, adding “leptomeningeal metastases”.
Changes in the text: “we describe the biology of onset of brain and leptomeningeal metastases” **(line 31-32)**.
5. Mechanisms: Please add a similar section for LMD
Reply 5: we provided to extend the paragraph on the onset mechanisms, also inserting the part relating to the LMD.
Changes in the text: please see lines **173-186**
6. Therapeutic strategies: The prognosis for patients with HER2+ brain mets has been demonstrably better than for HER2- brain mets, so please include this
Reply 6: we provided to add this data.
Changes in the text: please see line **201-203**
7. Therapeutic strategies: Please include the toxicity profile of WBRT after surgery in your second paragraph
Reply 7: we provided to add toxicity profile of WBRT after surgery.
Changes in the text: please see lines **230-233**
8. Therapeutic strategies: 7th paragraph: Please include the caveat that the studies you are discussing were not specific to breast cancer, let alone HER2+ breast cancer.
Reply 8: we provided to specify how requested.
Changes in the text: please see lines **215-216**
9. Trastuzumab-pertuzumab: I would argue that the CLEOPATRA data reinforce that effective systemic therapy delays time to brain metastases, as the CNS penetration of this regimen at standard doses is poor. I would add the results from the phase 2 PATRICIA study here rather than in your “new perspectives” section
Reply 9: we provided to underline the importance of an effective systemic therapy and we add a reference to PATRICIA trial, but this one remains in new perspective section.
Changes in the text: please see lines **287-290**
10. TKIs: Neratinib: Please include that patient with active brain metastases were not included in NALA. Please also discuss data from the TBRC 022 study of neratinib and cape/neratinib in brain metastases demonstrating significant activity.
Reply 10: we provided to specify how requested for NALA trial. Moreover, we add TBRC 022 study discussion and respective reference.
Changes in the text: please see lines **385-386** and **378-383**
11. TKIs: Tucatinib: Please include that HER2Climb was the first large randomised

study to include patients with active brain metastases
Reply 11: we provided to specify how requested.
Changes in the text: please see lines **398-399**
12. TKIs: Pyrotinib: This section is too brief. Please include the results from the PERMEATE study of this agent in brain metastases at the very least
Reply 12: we provided to add data of PERMEATE trial.
Changes in the text: please see lines **422-427**
13. TKIs: Please add a small section on the pan-HER inhibitor, poziotinib
Reply 13: we provided to add a section on poziotinib.
Changes in the text: please see lines **428-433**
14. TKIs: please add the toxicity that has hampered many of the TKIs (esp neratinib/pyrotinib/poziotinib) due to EGFR targeting
Reply 14: we provided to add toxicities after involved trial.
Changes in the text: please see neratinib-pyrotinib and poziotinib section
15. New perspectives: Please include the limited data available for both tucatinib and TDXd in LMD
Reply 15: we provided to add how requested on limited data for both tucatinib and TDXd in LMD.
Changes in the text: please see lines **450-463**
16. New perspectives: 5th paragraph: Please qualify that these data are from a pre-clinical model of breast cancer brain metastasis. What further research has happened since 2015 on this technology? See review by Behravan N et al, Life Sci 2022 to direct your search
Reply 16: we provided to specify that these data are for a preclinical model. We add some additional data on nanoparticles technology.
Changes in the text: please see lines **481** and **484-493**
17. New perspectives: Please clarify that Alliance A071701 is for parenchymal brain mets not LMD
Reply 17: we provided to specify how requested.
Changes in the text: please see line **496**
18. New perspectives: Please expand your search to include all ongoing studies in HER2+ breast cancer brain mets or LMD and tabulate the search results. Discuss new HER2 ADCs in development here please.
Reply 18: we provided to add more ongoing trial and a mention of new ADCs in ongoing section.
Changes in the text: please see table 3. See lines **500-502**.
19. Conclusions: Again, the prognosis of HER2+ breast cancer was poor historically, but now vastly exceeds that of TNBC, so please clarify this. Please also be more specific regarding the successes in brain disease (SRS, T-DXD, Tucatinib) and where the

challenges remain (brain progression after RT and these agents, LMD)
Reply 19: we provided to modify and insert in the paragraph more information about successes and challenges in the treatment of BMBC.
Changes in the text: please see lines **523-524, 526-528, 530-534 and 537-539.**