Peer Review File

Article information: https://dx.doi.org/10.21037/tbcr-23-26

Reviewer Comments

Reviewer A

Comment 1: There is insufficient detail to know whether the patient responded to pyrotinib or not. She may have responded top docetaxel and then to radiation therapy. CAn the uathors provide scans and timing of scans to document that the pyrotinib was responsible for the tumor shrinkages.

Reply 1: Thank you for your rigorous consideration. In the part of case presentation, we mentioned that when the patient was found to have relapse and metastasis with grade 3 anemia, so we chose single-agent pyrotinib. Lesions was found to shrink rapidly after 16 days of reexamination, and the efficacy was assessed as PR, which was also demonstrated in Fig1. Therefore, we can be sure that the patient had responded to pyrotinib.

Comment 2: There is no discussion of the data of tki levels in CSF. I know there is data on trasatuzumab as well as at least tucatinib. exploration of this issue would be helpful.

Reply 2: Thank you for your rigorous consideration. The idea is novel, and understanding the level of KTI in CSF can provide the most direct evidence for TKI to treat brain metastases, several previous studies have reported that trastuzumab and some TKI levels, such as tucatinib, lapatinib, and neratinib could be detected in cerebrospinal fluid, but pyrotinib has not been reported in the literature. It is hoped that more research will continue to learn more about TKI in the future. We have modified our text as advised (see Page 05, line 137~139).

Comment 3: There is no discussion of the various other TKIs (tucatinib, lapatinib, neratinib, etc). It wold be helpfuk to compare and contrast them with pyrotinib in terms of disease activity, toxicity, CNS penetration, etc. Certainly there is extensive data of CNS effects of tucatinib that could be contrasted with what is known about pyrotinib.

Reply 3: We gratefully thanks for the precious time the reviewer spent making constructive remarks. In the discussion section, we have added discussion of other TKIs, such as lapatinib, neratinib, and afatinib. In the HER2CLIMB Trial, tucatinib had approved the efficacy in HER2-positive advanced breast cancer patients with brain metastases. However, tucatinib had not been approved in China and the clinical benefit in the Chinese population cannot be determined. What's more, there is no head-to-head clinical trail of pyrotinib and tucatinib. We have modified our text as advised (see Page 05~06, line 166~177).

Comment 4: There are no multiple papers on T-Dxd CNS activity. These should be cited and discussed.

Reply 4: We gratefully appreciate for your valuable suggestion. We have made appropriate adjustments in our discussion of T-DXd. Based on the original Destiny-

Breast 01 study, we have added the results of the Destiny-Breast 02 and Destiny-Breast 03 study, which further supports the application prospect of T-DXd in HER2-positive advanced breast cancer patients with brain metastases. We have modified our text as advised (see Page 06, line 182~186).

Reviewer B

Comment 1: The 'Acknowledgments' section should also detail all funding sources for the work in question. There must be a section "Funding" within the "Acknowledgments" section. If the research was carried out without funding, "None" should be stated in this section.

Reply 1: Thank you for pointing out this problem in manuscript. We have added a section "Funding" within the "Acknowledgments" section. We have modified our text as advised (see Page 07, line 227).

Comment 2: Please indicate the originality of the figures and tables. If a figure, table has been previously published or has appeared in copyrighted form elsewhere, acknowledge the original source and submit written permission from the copyright holder (usually the publisher) to reproduce the material. Permission is required, regardless of authorship or publisher except for documents in the public domain. According to our policy, most of the adapted work will still need written permission from the copyright owner.

Reply 2: Thank you for your rigorous consideration. The figures and table are original and illustrated in the title page. We have modified our text as advised (see Page 01, line 15).

Comment 3: Manuscript categories that require a highlight box: Original Article, Systematic Review, Scoping Review, Clinical Practice Guideline, Expert Consensus, Case Report, Case Series and Surgical Technique.

Reply 3: Thank you for pointing out this problem. We have added a highlight box before the section of abstract in manuscript. We have modified our text as advised (see Page 02, line 24).

Comment 4: The article should include a statement that ethical approval was obtained (or a statement that it was not required and why), including the name of the ethics committee(s) or institutional review board(s), the number/ID of the approval(s), and a statement that the participants gave informed consent before taking part. Authors should also state that the study conformed to the provisions of the Declaration of Helsinki (as revised in 2013).

Reply 4: Thank you so much for your careful check. We have added ethical statement in the footnote. We have modified our text as advised (see Page 07, line 233~239).

capture the important effects of an intervention to the satisfaction of all end-user groups, so multiple endpoints are usually selected, which are categorized as primary, secondary, or tertiary. The primary endpoint(s) are typically efficacy measures that address the main research question. Secondary endpoints are generally not sufficient to influence

decision-making alone but may support the claim of efficacy by demonstrating additional effects or by supporting a causal mechanism (PMID: 31799474). Thus, ORR, PFS, and OS can all be designed as endpoints. (Line 538-539)

Comment 7: Please provide a more detailed description of ctDNA and treatment effects.
Reply 7: Thanks. And I have rewritten it. (Line 427)

Comment 8: the technical terms are different in each section.
Early TNBC, early stage TNBC
Reply 8: Thanks. I have unified them as eTNBC.(Line 82)

Comment 9: Are PD-1 and PD-L1 antibodies different drugs as a classification? (Line 79-80)?
Reply 9: Though PD-1 is predominantly expressed on the surface of T cells while PD-L1 is primarily expressed on the surface of tumor cells, I still believe that they can be classified into one category. The reason is that PD-1/PD-L1 therapy targets the same pathway, other than CTLA-4. Moreover, the combination of ipilimumab and nivolumab has shown efficacy in melanoma, kidney cancer, and rectal cancer (PMID: 31196207). But there is no successful example of PD-1 combined with PD-L1 inhibition therapy in solid tumors. This may reflect the fact that PD-1/PD-L1 monoclonal antibodies can be classified into one group at present. (Line 130)

Comment 10: I'm not at all familiar with the term "late TNBC"(Line 392). Please explain and cite or remove.
Reply 10: My apology, for confusing you with my presentation. I've changed my sentence and hope you can get my point. (Line 708)