

**Manuscript ID: 83163: Resubmission of the revised manuscript, Tyrosine kinase inhibitors and HER2-positive breast cancer.**

Dear Colleagues,

On behalf of all the authors, I sincerely thank the Reviewers for their positive remarks and insightful comments. Our point-by-point responses to the Reviewers comments are addressed below and also **incorporated** into our revised manuscript. These changes have significantly improved the quality of our manuscript.

**Reviewer 1 comments:** In this manuscript, the authors reviewed the tyrosine kinase inhibitors and HER-2 positive breast cancer. They intended to highlight the most recent findings associated with the most widely-studied TKIs and their clinical significance in improving the outcomes of HER-2 positive BC. Several suggestions as follows.

**Comment # 1:** One figure is recommended to add in the manuscript.

**Response:** *As Reviewer suggested, we have added a figure depicting a schematic representation of TKIs targeting EGFR and various HER family receptors, leading to the inhibition of downstream PI3K and MAPK pathways, resulting in the inhibition of the cell cycle progression and proliferation.*

**Comment # 2:** What about the progress of Tucatinib and Neratinib?

**Response:** *We have cited one additional paper on the neratinib + lapatinib combination in HER2 positive breast cancer. In addition, we have revised the paper to include the statistical information available in the literature about TKIs. The changes have been **highlighted**.*

**Comment # 3:** English language needs to be revised.

**Response:** *As per the Reviewer's suggestion, we have revised the English language. As we made several changes in response to the other Reviewers', to avoid any confusion, we are not highlighting the revised text for the English language.*

**Reviewer 2 comments:**

**Comment # 1:** Overall the title does not cover the topic of the subject as it outlines mostly current ongoing studies rather than discussing current treatment strategies and directions.

**Response:** *With all due respect, since it is not a comprehensive review article, our goal is to highlight the most recent findings on widely-studied TKIs as well as the ongoing clinical trials*

which are yet to be completed. If Reviewer agrees, we are thinking of the new title as “Tyrosine Kinase Inhibitors and HER-2 Positive Breast Cancer: A commentary on Literature Updates”.

**Comment # 2:** I would suggest the addition of a table similar to table 1 outlining the studies to date and summarizing their outcomes as making far clearer.

**Response:** *With all due respect, we would like to emphasize that there are other published review articles, including ours, outlining the impact of TKIs such as tucatinib, neratinib, lapatinib, etc. The goal of this invited commentary is to highlight the most recent findings on widely-studied TKIs and their clinical significance in improving the outcomes of HER-2 positive BC. Adding another table with similar published information will be repetitive. For this reason, we are not including another table to be within the word limit of a commentary. However, we have cited one additional paper on the neratinib + lapatinib combination in HER2 positive breast cancer. Also, we have included a figure depicting a schematic representation of TKIs targeting EGFR and various HER family receptors, leading to the inhibition of downstream PI3K and MAPK pathways, resulting in the inhibition of the cell cycle progression and proliferation.*

**Comment # 3:** I would also suggest that as the paper states that it is outlining the improvement and current situations with regards to TKI, rather than using general terms such as superior or improved survival etc., that more statistical information is presented when discussing the studies such as percentages or the amount of improvement.

**Response:** *As suggested by the reviewer, we have included the statistical information available in the literature about TKIs.*

**Comment # 4:** The authors mention that little has been published in the past few years. It may be worthwhile to remind readers of the impact of the covid pandemic on the clinical trials which may have delayed recruitment, analysis and follow up.

**Response:** *We respect the reviewer’s perspective and agree that covid pandemic has majorly impacted every aspect of life and work schedules. However, we feel a bit reluctant to add this statement as every clinical trial could have different issues.*

This manuscript has not been submitted or is in the review process in any other journal. All the authors have approved the final version of the manuscript. We sincerely hope that you would find this commentary suitable for consideration in WJCO.

Thank you very much,

Sincerely,

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