

February 26, 2020

Dear Dr. Tang:

We are pleased to submit the revised version of our manuscript entitled “**Narrowing the focus: Therapeutic Cell Surface Targets for Refractory Triple-Negative Breast Cancer**” for consideration for publication in World Journal of Clinical Oncology.

We would like to thank reviewers for their insightful comments and suggestions. We have responded to all questions (*Italics*) and have made modifications in the manuscript (highlighted) to address all concerns and suggestions raised by the reviewers. Below is a detailed response to reviewers.

Reviewer 1

The manuscript is about the state of art of the therapeutic approaches for the treatment of refractory Triple Negative Breast Cancer (TNBC), with a focus on the new developing ones. The manuscript deserves some minor revisions that are detailed below:

1. The tile of subsection “THE CASE FOR CELL-SURFACE TARGETING” needs to be contextualized to facilitate readers,e.g. The case for cell-surface targeting in breast cancer.

We thank the reviewer for the constructive comment. Breast cancer was added to the title of subsection. Please see page 4, line 78.

2. The frequency of Trop-2 expression in TNBC must be introduced in the appropriate section.

We have an “expression in TNBC” column in Table 2 and pointed out that Trop-2 is expressed in 75% of the TNBC in level of protein (ref 19 in new version). For more clarification and since the focus of the review is on TNBC, we changed the “Trop-2 is expressed on the cell surface of

85% of breast cancers” to “Trop-2 is expressed on the cell surface of 75% of TNBC patients”. The reference was changed accordingly. Please see page 5, line 102.

3. A comparison of LIN-1 expression by IHC between normal breast tissue and breast cancer one would appropriate. The authors have cited a comparison between normal breast tissue and prostate cancer one, that is out of the theme. This sentence needs to be revised or to be better explained.

As requested by the reviewer, this sentence was revised: the part of the sentence related to normal prostate was removed from the manuscript, instead the expression level of LIV-1 in TNBC was added. The references were changed accordingly. Please see Page 5, line 108.

4. The incidence of TNBC in Breast cancer diagnosis must be cited in the introduction, as well as, it would be important to know the % of refractory TNBC in all TNBCs.

This has been addressed at the bottom of page 2 and into page 3 of the introduction. There is no standard definition for treatment refractory TNBC, so we have cited the existing data regarding the early recurrence and mortality rates observed in TNBC.

5. In the table:
 - a. I suggest to use increase or decrease instead of arrows to be clearer for the readers.
Done (please see Table 1 and 2).
 - b. The type of shRNA or siRNA must be indicated, not simply shRNA ,siRNA. The same consideration for Ab (what kind of Ab? For which target?)
Done (please see Table 1).

Reviewer 2

Tafreshi and colleagues propose a review on a topic of great interest even if already well-illustrated in other publications. The choice of treating the membrane targets as well as the selection of the bibliographic notes appear appropriate. However, the review only offers an

overview of the situation without specifically discussing the different therapeutic choices available. It would be much more useful if the authors could discuss some of the targets in more depth if not in a generic way as done on page 6.

We are unclear on the area of concern in this comment. Our initial submission includes a subsection titled “current treatment for resistance TNBC” on page 3-4, as well as a summary of the targeted cell surface therapies that are in clinical trial in Table 2. The Table is a comprehensive summary of the available targets, and is referenced in the text.

We hope that the revised version of the manuscript will be acceptable for publication in your journal. If you have any questions or concerns, please do not hesitate to contact me.

Regards,

Marie Catherine Lee, MD FACS
Associate Member, Comprehensive Breast Program
H. Lee Moffitt Cancer Center & Research Institute
12902 Magnolia Drive, Tampa, FL 33612

E: Marie.Lee@moffitt.org

P: 813-745-3512