Reviewer’s report

Title: Association between levels of tumor-infiltrating lymphocytes in different subtypes of primary breast tumors and prognostic outcomes: A meta-analysis

Version: 0 Date: 01 Feb 2020

Reviewer: Roberto Salgado

Reviewer’s report:

The authors have performed a meta-analysis assembling TILs-studies that have been prognostically assessed in different breast cancer subtypes. Methodologically the paper is well designed and the interpretation of the data is correct. They do provide new information of interest to the community, notably in the HER+/ER+ vs HER2-/ER+ space. Therefore, this reviewer supports publication of these results, but only if the following items are taken into consideration:

1. A thorough review of grammatical English by preferably a native English speaker is advised. For example, page 2 bottom line "...tumor subtype was inert to improve..." or page 3, 2nd paragraph "These benefits in Luminal tumor subtype need to be warranted." I know what the authors mean but this is not appropriate English.
2. The term lymphocyte-predominant breast cancer is not used anymore. I would suggest to do an analysis, and assess which cut-off predicts the best benefit to patients in the adjuvant setting. Based on a pooled analysis of 9 phase 3 trials (Loi et al., JCO 2019), the appropriate cut-off identified in TNBC was 30% in the adjuvant setting. Can the authors confirm this in their meta-analysis? Are the cut-offs different in the different subtypes?
4. It is not clear from their article whether the association between high TILs and pCR translated into a global survival gain based on their meta-analysis. It would be good to describe in separate tables the TIL-pCR-OS analysis, and in a separate table the TILs-OS analysis in the adjuvant setting, and this for the different subtypes.
5. The authors need to avoid systematically using just the word "luminal" while is not always clear which luminal-subtype they mean, ER+/HER2+ or always ER+/HER2-.
6. It would be interesting, if the authors have the data, to analyse the prognostic impact in Asian vs non-Asian patients. There's emerging evidence that there are differences between both.
7. Page 11: the reasoning on why ER+ behave prognostically inversely with TILs is debated. The interpretation of the authors is largely speculative and sometimes wrong and is best removed. For example: the sentence "line 239...with a low mutation burden of TILs, which can worsen the tumor response to AI" is wrong and the reference associated with is doesn't make that claim either. Figure 6 should therefore also be removed as this doesn't add anything to the overall conclusion of the paper.
8. Can the authors focus on evaluating whether features of clinicall high-risk ER+ patients, for example those with grade 3, BRCA+, high proliferation-index, etc... do have higher TILs translating this into a higher survival? According to emerging evidence this is probbaly the case, and the authors may have the data to suppor this emerging evidence.

Minor items:
1. In the title I would suggest to replace the word "the elevation" by "levels".

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

No

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited

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