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Dear Dr. Lian-Sheng Ma,
President and Company Editor-in-Chief
Baishideng Publishing Group Inc

RE: Manuscript NO 26596: Tumor infiltrating lymphocytes in triple negative breast cancer receiving neoadjuvant chemotherapy by Castaneda et al.

Thank you for the opportunity to respond to the reviewers on the above referenced manuscript. Enclosed please find our revised manuscript which has taken into account their comments and suggestions. In addition, we have uploaded a copy of the revised manuscript with changes highlighted as a supplemental file.

Our specific responses to the reviewers are as follows:

Reviewer 02460553

- The aim of this study was to determine influence of pre- and post-Neoadjuvant-Chemotherapy (NAC) over Tumor-Infiltrating-Lymphocytes (TIL) in Triple-Negative-Breast-Cancer. The author found some interesting results, like significant associations of TIL with CR and outcomes only in pre-NAC but not post-NAC; however, I have some concerns about this study. 1) The exact inclusion criteria to the cohort, the source(s) of information needed to identify the cohort should be clearly explained. Then explain how the chosen sample size was decided.

  Response: We mentioned about some studies that find similar or different results to our data. However, I think that post-NAC samples are not good for evaluating pathological features because they have confusing features associated to NAC (fibrosis). Inclusion criteria were added to Patients and sample selection (most important Clinical Stage II and III). I added this

sentence (page 6). [We retrospectively reviewed the files of all new BC cases who came to the Instituto Nacional de Enfermedades Neoplasicas between 2005 and 2010, and we selected 98 TNBC cases with Clinical Stage II- III who went to surgery of breast tumor and axilla after receiving NAC].

- How the authors calculated the power of this study? This study seems not to have enough power to detect significant associations due to small sample size, so the significant results seen in the study may purely be due to chance.

  Response: It is a retrospective study and we analyzed all patients with TNBC who came to the institute in a time period. I added this sentence in the discussion (page 12). [Differences among mentioned authors and our findings could be explained by our small population size, analysis of a not representative area in the TMA samples or changes in CD4+ TILs phenotype from effectors to suppressors. Therefore, our results need to be validated in larger series].

- All the results were unadjusted for potential covariates, what are results with adjustment for confounders, normally the covariates have to be adjusted for genetic studies, such as age, sex, other parameters related to your outcomes.

  Response: Our sample size is short and not enough to produce a significant result in multivariate analysis ($p>0.05$).I added this sentences in Results (page 8) [in an univariate analysis. Association between median TIL and pCR remained significant even with adjustment for age].

- The authors should apply a Bonferroni Correction for their analyses. There are at least 4 comparisons for each group (Table 4 and 5). As you know, the more comparisons one performers the more likely they will find differences due to chance.

  Response: We apply a Bonferroni Correction for table 4 and 5 (Page 20-21).

Reviewer 00729478**:** Very interesting, well written

Reviewer 00742121**:**

- The authors should clearly present and discuss those findings in their study, which are original and novel to the field. In particular, the authors mention that Denkert et al. evaluated 1,000 breast cancer samples, whereas in this

paper they evaluated <100; hence, how original is this work and what new evidence does this study bring to the field?

Response: We added weakness, strength and uniqueness of our study in discussion (page 12). [Differences among mentioned authors and our findings could be explained by our small population size, analysis of a not representative area in the TMA samples or changes in CD4+ TILs phenotype from effectors to suppressors. Therefore, our results need to be validated in larger series. Remarkably, our work is the first to our knowledge to evaluate TIL in BC tumors from Latinoamerican women. And, it is the first to compare the evaluation of TIL percentage in full-sections and in TMA sections, as well as to compare the evaluation of TIL levels through percentage analysis and through absolute counting].

- The authors can find all other comments in the manuscript file attached. In particular, the paper should be reviewed by an expert in English and the title should be revised in order to convey the findings of the study.

  Response: Title changed: "Tumor infiltrating lymphocytes in triple negative breast cancer receiving neoadjuvant chemotherapy" (limited to number of words for journal rules).

Reviewer 00742250**:**

This is an interesting study and has a value of publication. Before that, the authors should respond to the reviewer's question.

- Did the authors count absolute stained cells by CD3, CD4, CD8 and FOXP3 in tumor cells? If so, please clarify the description in the text.

  Response*:* Information about absolute count was added to Patients and Methods: Staining and quantification of H&E, CD3, CD4, CD8 and FOXP3 IHC staining (Page 6). [Lymphocyte subsets were calculated through the percentage between lymphocytes/ tumor cells in a 10 percent increment system, and through the absolute count of the lymphocytes in 5 high power fields under 200x- 400x magnification].

- Why did the authors use FOXP3 in the study? The reason should be clarify in the text.

  Response: This information was added to introduction (Page 5). [Recent studies suggest that tumor infiltration by CD8 cytotoxic lymphocytes and absence of FOXP3 immunosuppressive regulatory cells could control tumor growth and carry a better prognosis].

Additionally, we modified next information.

Mistake in previous redaction (page 7): Clinical Stage III was found in 86.7% instead of 84.7%.

We hope that you will find the revisions satisfactory and that our manuscript is now acceptable for publication in the World Journal of Clinical Oncology.

Sincerely,

Carlos Arturo Castaneda Altamirano, M.D., MSc.