Author’s response to reviews

Title: Recent Advances in Triple Negative Breast Cancer Treatment: The Immunotherapy Era

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Version: 1 Date: 19 Mar 2019

Author’s response to reviews:

Dear Editor,

Here it is the point-by-point response letter which accompanies the revised form of the manuscript “Recent Advances in Triple Negative Breast Cancer Treatment: The Immunotherapy Era” (BMED-D-19-00216).

Responses to reviewers’ observations and corresponding changes in the main manuscript are reported hereafter:

Reviewer #1

1) For the general understanding why immunotherapy might be helpful especially in TNBC, the authors should outline in their introduction the well-described prognostic and predictive effects of immune cells especially in TNBC.

Authors’ reply: a paragraph describing prognostic ad predictive role of immune cells in TNBC has been added (lines 51-60, page 3). In addition, references from #7 to #10 have been added to support these arguments.

2) At least for the ICPI used in IMpassion130 (atezolizumab), the predictive relevance of PD-L1, TILs and BRCA mutations was clarified by Emens and coworkers. The authors quote this abstract but they should also comment these important findings.

Authors’ reply: findings from IMpassion130 trial and biomarker analysis by Emens et al. (presented in abstract form at SABCS 2018) have been more accurately reported and commented (lines 104-108, page 4)
3) In their section choosing the right chemotherapy partner the authors mention that nab-paclitaxel was used in IMpassion130 and that there were better agents like anthracyclines, platinum salts and taxanes. However, nab-paclitaxel is a taxane. The authors should correct this confusing contradiction.

Authors’ reply: - Line 191, page 7: the word “other” has been added in order to underline the difference with nab-paclitaxel, avoiding misunderstandings

Reviewer #2:

1) When discussing the results of Impassion130, a more in-depth analysis of the PD-L1 biomarker should be made. It is certainly arguable that the latter would be a robust biomarker for immunotherapy in most of the tumors, but, in the case of this study analysis was done on immune cells of the tumor microenvironment, what is up to now an uncommon and not clearly reliable way to analyze it. Although slightly commented by the authors I would recommend to go more in detail with this crucial point.

Authors’ reply: we agree with these observations moved by reviewer #2. On page 4, we implemented our description of discrepancies in PD-L1 evaluation in breast cancer, also describing other methods including the combined positive score (CPS)

2) Again related to Impassion130, results of the biomarker study communicated at SABCS 2018 (#GS1-04. Emens LA) are extremely interesting and seem to shed light about the potential role of immune biomarkers in TNBC. In this analysis, patients with CD8+ tumors derived clinical benefit only if their tumors were PD-L1 IC+, the same happens with TILs. It would be desirable to mention the results of this study.

Authors’ reply: the interesting evidences provided by Emens et al. have been more accurately described and commented (lines 104-108, page 4, and lines 122-129, page 5), highlighting the role of CD8+ T cells in predicting response to anti-PD-L1 immunotherapy.

3) Results of a biomarker analysis of the neoadjuvant trial Keynote173 trial were also shown at SABCS 2018 (P3-10-09). In this case higher density of pretreatment sTILs and PD-L1 CPS is associated with higher pCR rates. These results should be also mentioned and a discussion about the eventual role of CPS to analyze PD-L1 could be appropriate.

Authors’ reply: recent evidences from KEYNOTE-173 trial have been added and discussed (lines 122-129, page 5)

Lastly, “abbreviations” and “acknowledgements” sections have been added, as required by the Editor.
Kind regards,

Prof. Giuseppe Curigliano MD, PhD