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复旦大学附属肿瘤医院 Fudan University Shanghai Cancer Center
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Review Comments

Reviewer A:

The authors have done an excellent job of a timely review of various therapies for metastatic TNBC, which is difficult to treat with very limited options for patients.

1. It would improve the readability of the manuscript if a figure depicting the targets of chemotherapy and immunotherapy is included.

Reply 1: We have added a figure of the mechanism of action immunotherapy. Please see Figure 1 on page 20. The only mechanism of action discussed for chemotherapy was nab-paclitaxel, and we believed the Figure did not help the manuscript, and we omitted it. If you feel strongly that it would improve the paper, we would add the figure.

2. The tables are informative but a figure with responsive versus non-respoive subgroups and biomarkers will help follow the article better.

Reply 2: We have added a Flowsheet style diagram for responsive groups and biomarkers, please see Figure 2 on page 21.

3. Too many approaches with no significant effect so they may represent it better in a picture rather than table.

Reply 3: Please see Figure 2 to help consolidate the positive biomarkers. We also removed one trial from phase I data (Phase 1Toripalimab) trial, which did not add to the paper give there was no significant effect and it did not add to the paper.

4. Neoadjuvant chemotherapy (NAC) is becoming a standard for debulking for TNBC so disccussing about the NAC will help:

Reply 4: The invitation requested we discuss metastatic treatment only. Given some of the mixed results of PCR rates with immunotherapy and lack of survival data, we thought adding neoadjuvant chemoimmunotherapy in the discussion added more ambiguity and was not helpful to the discussion.

Comment 5: (It's hard to read the article with such a small font or 8 or 9. Better to have 11 or 12 font for the reviewers.)

Reply 5: Font size increased.

Reviewer B:

The authors reviewed the results and the therapeutic effects of immunotherapy in triple negative breast cancer (TNBC) established from the current clinical trials of immune check point inhibitors. It is a very interesting report, and it is important that remarkable clinical effects were observed and the potential role for biomarkers were discussed in these clinical studies. However, this review article also raises some questions that should be further discussed as outlined below in this manuscript:

1. Despite in the interim analysis, the durable clinical responses of Atezolizumab (ref.16) or Pembrolizumab (ref.20) monotherapy observed in responded (CR/PR) groups compared to non-responded (SD/PD) groups.

Reply 1. We discussed long term outcomes of single agent immunotherapy on lines 458-462.

2. Better clinical outcomes were associated with high TMB (>10 mut/Mb) by Pembrolizumab treatment in KEYNOTE-119.

Rely 2: We discussed high TMB starting on 439, and we also added it to our flow sheet for biomarkers on Figure 2 (page 21).

3. Besides PD-L1 positivity, other biomarkers such as high-level TILs, frontline therapy, and TMB were promising for monotherapy responders. (ref. 16,20,21 etc.)

Reply 3: We have added a biomarker section for monotherapy starting on line 436, and added a biomarkers paragraph on 505. We also created a flowsheet on figure 2 to help solidify biomarkers discussion.

4. Durvalumab (SAFIR-02 BREAST trial) was also promising for metastatic TNBC.

Reply 4: We added a paragraph discussing maintenance immunotherapy and the SAFIR-02 Breast trial starting on line 532.

5. The rationale of [Novel targeted therapy combined with immunotherapy] such as the combinations of Ipatasertib, Atezolizumab, and NabPTX (Phase Ib, AKTi trial), niraparib and pembrolizumab, etc.

Reply 5: We discussed the effect and synergy of novel targeted therapy, chemotherapy

and radiation therapy added to immunotherapy starting on line 221.

6. The variety of immune-related adverse events with the checkpoint inhibitors.

Reply 6: Paragraph on side effects starting on line 486.

7. ASCENT trial using Sacituzumab govitecan was updated on metastatic TNBC.

Reply 7: Discussed starting on line 537.

Reviewer C:

This is a comprehensive and well written review of the literature regarding immunotherapy in metastatic triple negative breast cancer. The authors have done a good job in resuming at least all available most relevant studies and put results into context. I have only a minor revision suggestion, as follows:

Regarding Impassion 131, there is no uniform consent over dexamethasone itself being responsible for the trial failure and probably the most reasonable explanation is a combination of several factors, including that is also possible that the mechanism of action of the chemodrug companion itself might be relevant, as also demonstrated by the TONIC trial and considering that nab-paclitxel is not the same as paclitaxel.
Therefore, at page 18-19 lines 418 - 421, the discussion should be further enriched with these elements. The authors can cite this paper when explaining the difference in the mechanism of action between nab pac and pac: Schettini F et al Cancer Treat Rev 2016; 50:129-141, doi: 10.1016/j.ctrv.2016.09.004

Reply 1:

We discussed the mechanism of action of nab-paclitaxel starting on line 466, and discuss in detail the different pharmacokinetics of nab-paclitaxel the paclitaxel chemotherapy.