Peer Review File

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Reviewer Comments

Reviewer A

Comment 1: Reference 17 is a review article, and the manuscript is being used as comparative data. You should use a different reference to prove your point.

Reply 1: Thank you for raising this point. However, we believe that Cogliati V. et al. provide a comprehensive overview of resistance mechanisms and possible therapeutic options post-ET + CDK4/6i to mention in our paper.

Comment 2: BOLERO-6 did not have any patients that received CDK4/6 inhibitor first-line. Thus, you cannot definitively state that this is an option for these patients.

Reply 2: We agree with this suggestion and have excluded this reference from our manuscript.

Reviewer B

I would like to congratulate the authors Dr. Du et al for the submission of this abstract. They gave a good overview of treatment options in ER+/Her2 negative MBC and described the efficacy and toxicity of the HDAC inhibitor well. I would like to see the following though:

Comment 3: A clearer outline of 2nd line, 3rd line (and beyond) of treatment options and the incorporating of mutation analysis. They list all the trials and evidence, but how to apply this to clinical practice. Perhaps adding an algorithm will be helpful.

Reply 3: Thank you for pointing this out. We agree that an oveview would be helpful. Therefore, we have added two figures as a structured overview of treatment options applicable in clinical practice.

Comment 4: I suggest adding a paragraph how the use of adjuvant CDK 4/6i will potentially influence the treatment choices and sequencing at the time of recurrence for MBC patients.

Reply 4: This indeed is an important aspect. We have, accordingly, added a brief paragraph to emphasize this point.

Comment 5: Please discuss and outline the management of "early" recurrence ER+/Her2 negative BC and how treatment choices may be different.

Reply 5: We agree with this and have incorporated your suggestion throughout the manuscript by referring to the EMERALD study by Bardia A. et al.

Comment 6: The ADCs (T-Dxd and Sac. Govitecan) have demonstrated OS benefit in the pre-treated ER/Her low/negative MBC patients. Please elaborate more on the

efficacy and biomarker selection in these patient populations - these are considered HR resistant BC populations and warrants a more detailed review.

Reply 6: We appreciated this suggestion and have further elaborated on this, providing a more detailed overview of recent data on trastuzumab deruxtecan and sacituzumab-

Comment 7: The abstract does not read well - English language can be edited to optimize grammar and flow. Some sentences are too long, and better scientific language should be used ie:
"This is because median progression free survival (mPFS) of subsequent single agent ET like fulvestrant is reduced from 7 months without prior CDK4/6i to 2 months post CDK4/6i progression." This can be written as: "The rational for this treatment preference is due to a reduction in mPFS with single agent ET such as Fulvestrant from 7 to 2 months without prior CDK 4/6i."

There are several examples in the abstract which require rewording and restructuring. Thank you.
Reply 7: Thank you for this suggestion. We re-wrote this section to optimize readability.

Reviewer C

Thank you very much for giving me the opportunity to review the editorial commentary on this highly relevant manuscript. Neven et al. describe the therapy multifaceted therapy landscape of HR+/HER2- metastatic breast cancer after disease progression on CDK 4/6 inhibitors. The authors not only introduce different treatment strategies such as (i) switching CDK 4/6 inhibitor and/or endocrine therapy after disease progression, (ii) the use of targeted therapies such as PI3K, mTOR, AKT and HDAC inhibitors, (iii) the application of antibody-drug conjugates like sacituzumab-govitecan (SG) and trastuzumab-deruxtecan (T-DXd) and (iv) the application of palliative chemotherapy.

Comment 8: However, the authors do not characterize the different therapy options in a stringent way. Although all relevant studies that were presented in the last years and that are conducted at the moment are mentioned, the authors leap between different treatment strategies. The authors highlighted the possibilities to change either the CDK 4/6 inhibitor and/or the endocrine therapy after disease progression and the use of targeted therapies and palliative chemotherapy. However, the emerging role of the antibody-drug-conjugates sacituzumab-govitecan and trastuzumab-deruxtecan has not been addressed properly. SG can be administered in patients with metastatic HR+/HER2- breast cancer following the findings of the TROPiCS-02 study. In particular, the DestinyBreast04 study could demonstrate that most of the formerly HER2-negative tumors can be effectively targeted by T-DXd if the express HER2 on a low level (IHC 1+, IHC2+ without amplified FISH/CISH).

Reply 8: Thanks for bringing up this point. We have provided a more detailed overview of recent data on trastuzumab deruxtecan and sacituzumab-goviteca. (Ref. Modi et al., Mosele et al. and Rugo et al.). (Cfr. Reply 6).

Comment 9: Furthermore, I would like to emphasize the importance of real-world registries like PRAEGNANT, which have the ability to demonstrate the adherence, tolerance, and efficacy of treatment options in a large number of patients that clinical studies could not fully cover. The significance of real-world data will increase in the next years since the variety of emerging treatment options in HR+/HER2- metastatic breast cancer can not be assessed properly in clinical studies.

Reply 9: Agree. We indeed should highlight the added value of real-world data in our paper.

Comment 10: The authors correctly describe the current literature regarding HDAC inhibitor therapy and correctly state that this treatment option is not approved yet in the vast majority of the world. However, they introduce HDAC inhibitors as a potential treatment option after disease progression on a CDK 4/6 inhibitor. Further studies should evaluate the significance of HDAC inhibitors in the treatment of HR+/HER2- metastatic breast cancer.

Reply 10: We fully agree with this statement and so we emphasized the need of future studies on the efficacy and safety of HDAC inhibitors as a potential therapy for patients with HR/HER2- MBC.

Comment 11: Unfortunately, extensive English editing is necessary to make the manuscript more accessible to the reader. Furthermore, I suggest a more stringent and concise way in describing the current therapy landscape first and then construing the findings of the manuscript within the context of the current literature. Moreover, the authors could suggest an algorithm of potential medications after disease progression on CDK4/6 inhibitor therapy.
Reply 11: We have re-viewed our writing in order to allow a more fluent reading.