Peer Review File

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Reviewer A

I consider that it is a topic of interest, the methodology is correct, the discussion is well structured and the conclusions are very clear and concise.
Congratulations.
Reply: I thank the positive opinion of Reviewer A.

Reviewer B

1. Consider to discuss the clinical utility of DESIREE trial for toxicity improvement on side-effects section. I wonder if this could add to the section.
Reply 1: Thank you for the valuable comment. I inserted DESIREE results and two other relevant study results in the safety section. I added to the test:

Changes in the text: "Another method was investigated in the randomized, phase 2 DESIREE trial. The participating 160 patients were randomized to the dose escalation arm (weekly increasing the dose of everolimus from 2.5 mg/day to 10 mg/day) or the conventional 10 mg/day starting dose. The primary end point of the trial was met. The incidence of stomatitis episodes grade ≥2 was significantly lower in escalation arm. There wasn't a significant difference either in other adverse events or in the relative dose intensity in the two arms. Numerically more everolimus discontinuation occurred due to adverse event in the conventional arm and due to disease progression in the escalation arm. These differences were not statistically significant, but they may question the equal efficacy of the escalating dosing. The rate of stomatitis grade ≥2 with gradually increasing everolimus dose was 18.8% in the DESIREE trial. In a study with two different mouth rinses the incidence of grade ≥2 stomatitis was similar (12-18%) and in another trial it was even lower (2%)."

2. Please consider re-write or review title of the "Future perspective" section. The majority of evidence discussed here is published but very little discussed about the future perspective to my view and only ongoing trials mentioned at the end of each paragraph. It would be particularly interesting to understand from Prof Rubovszky's perspective, if sub-titles of this sections could read better such as: how to better position mTOR, limitations of everolimus and how to overcome them, future evidence and what to expect from it.
Reply 2: Thank you for this comment. I changed the title of the section as advised to "Limitations of everolimus treatment and how to overcome them".

3. The review is not focused on CDK 4/6 inhibitors. I wonder if Prof Rubovszky would reconsider if this is this need to be re emphasised or to mention in the introduction, as currently, would suffice?
Reply 3: Thank you for the comment. I completely agree and I intended to emphasize that the standard first-line treatment is the combination of an endocrine drug and CDK4/6 inhibitor and I inserted it in the Introduction and also in the Conclusion section. If the reviewer thinks that it would be better to mention it in another section, too, I will do it eagerly.

4. Statements on lines 233-235 do not seem to belong to the conclusion section and would benefit from a better English level.
Reply 4: Thank you for the comment. I opened a "Strength and limitations" section at the end of "Discussion" and moved here the rephrased sentences.
Changes in the text: "The advantage of this work is that it is based on a review of both a literature database and a clinical trial database. However, it also has limitations, because I chose a single literature database and did not take into account unpublished results or results published only at conferences. It is also a limitation that the literature review was conducted by a single person."

5. Table 1 - G3/4 in BOLERO 4 was intentionally not included?
Reply 5: Thank you very much for your comment. It was unintentional. I inserted the G3/4 side effects of BOLERO 4 trial.

6. Table 1 - please consider adding number of subjects on each arm for the studies
Reply 6: Thank you for your comment, I amended the table accordingly.

7. Table 1 - please consider separate placebo and everolimus in different lines to help making the table more readable
Reply 7: Thank you for the comment, I corrected the table, according to your recommendations.

8. Table 2 - I assume all patients are breast cancer but worth mention?
Reply 8: Thank you for the comment, I corrected the caption of table 2.
Changes in the text: "Post-marketing trials involving more than 200 advanced breast cancer patients with everolimus plus exemestane"

9. Table 2 - MBC amongst other abbreviations missing after the table.
Reply 9: Thank you for the comment, I inserted MBC in abbreviations.