Reviewer’s report

Title: The differential anti-tumour effects of zoledronic acid in breast cancer - evidence for a role of the activin signaling pathway

Version: 2

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Reviewer: Peyman Hadji

Reviewer’s report:

General comments:
This manuscript describes a number of very well performed experiments investigating a potential dual mechanism of action of ZOL on the activin signaling pathway in ER-ve breast cancer cells in vitro and in vivo. The manuscript is clearly structures, well written and discusses conclusively the outcomes of these preclinical studies with regard to clinical reported outcomes with great caution.

Specific comments:
1. With no doubt, the results indicate a potential dual mechanism of action of ZOL on the activin signaling pathway in ER-ve breast cancer cells in vitro and in vivo. The authors suggest that this implies a possible novel anti-proliferative mechanism of action of ZOL involving activin signaling that could contribute to the enhanced anti-tumour effects of the drug. What is still unclear is why neither of the adjuvant BIS studies including ER-ve patients comprised a significant DFS or OS benefit? This has not been discussed in the manuscript, but would be clinically of great interest and should be included into the manuscript. I would be interested how the authors would explain this disparity.

2. The outcome of ZOL not altering proliferation of ER+ve MCF7 and T47D cell lines was somewhat unexpected. Is there any explanation for this and what is the implication with regard to the results of the clinical adjuvant BIS study reports?

3. The same applies to the results on page 7, line 237 were the authors state that Activin A secretion was unaffected by ZOL in MCF7 and MDA-MB-436 cell lines. Was this expected and if not please try to explain your findings.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
'I declare that I have no competing interests'