Reviewer's report

Title: Serum soluble ST2 is a new potential immune-related marker for breast cancer

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Reviewer: Jürgen Radons

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In the manuscript entitled “Serum soluble ST2 is a new potential immune-related marker for breast cancer” the authors analyzed the correlation between serum soluble ST2/IL-33 and VEGF as well as clinicopathological parameters together with the prognostic impact of serum sST2/IL-33 in 150 female breast cancer patients in comparison to 90 healthy individuals. This is an interesting paper which provides evidence for the putative diagnostic role of sST2 in breast cancer. However, there are several concerns that should be addressed.

Major Compulsory Revisions:

1. The manuscript needs the inclusion of cut-off values for any of the serum parameters tested. The authors must declare when a sample was regarded as being sST2/IL-33/VEGF high/low expressed and how the walking cut-offs values were evaluated.

2. The paper lacks any data on the correlation between serum parameters and patient survival. For survival comparisons, Kaplan -Meier together with Cox regression analyses should be included in the manuscript.

3. In the Discussion (4th paragraph, line 4-7) the authors state that “The present study showed that […] disease-free and overall survival rates […] were statistical significantly higher […]” without presenting the data. To strengthen the findings the inclusion of survival data is strictly recommended.

4. There are several contradictory results reported in the literature on serum levels of VEGF in breast cancer patients. While certain studies (including the one presented here) demonstrate elevated VEGF serum levels in cancer patients compared to healthy controls, others do not (e.g. Hodorowicz-Zaniewska et al., Pol. J. Pathol 63, 255, 2012). Moreover, in the latter study VEGF levels did not correlate with clinicopathological factors. These findings argue against a positive correlation of VEGF with breast cancer. Moreover, the composition of the study cohort obviously determines the quality of the outcome measure. The authors are asked to comment on this aspect in the manuscript.

5. It is well known that sST2 is also increased in other pathologies including asthma, cardiopathy etc. Therefore, upregulated sST2 levels might also be the result of mechanisms independent of the malignant process. It is therefore inexplicable why the authors believe that sST2 “may be a new potential
immune-regulated marker in breast cancer.” The conclusion that sST2 might be a promising target in breast cancer therapy is thus too speculative and requires further experimental support.

6. sST2 functions as an antagonistic decoy receptor which serves as a ligand sink by competing for IL-33 with membrane-bound ST2. Therefore, it is not surprising that elevated levels of IL-33 are accompanied by an sST2 upregulation. However, its pathophysiological importance is not addressed in this manuscript. Please discuss it.

7. Gillibert-Duplantier et al. (Ref. 10) already described elevated sST2 serum levels in patients with metastatic but not localized breast cancer. The authors should therefore critically discuss the impact of their own findings.

8. The finding that sST2 levels in breast cancer patients did not correlate with the Her-2 status confirms previous results by Gillibert-Duplantier et al. (Ref. 10). The authors interpretate this finding with “limiting cases or other reasons”. In order to make the article more convincing the authors should discuss possible reasons in the context of the actual literature.

Minor Essential Revisions:

1. Any figure should be supplemented with a detailed legend as given in the instructions for authors. Moreover, the short titles in Fig. 1D+E as well as in Figs. 2A-F need stylistic changes.

2. After inclusion of additional survival data, the association of sST2/IL-33 expression levels with clinicopathological factors should be arranged in the form of a table to make it more comprehensible.

3. In the introduction, a more recent reference on the cellular source of IL-33 and its capacity to induce production of proinflammatory cytokines in pancreatic cancer cells should be mentioned (Schmieder et al., Cytokine 60, 514, 2012).

4. In the Results section the authors state that “Serum levels of sST2 in increasing tumor size [...] were gradually elevated”. Since there is obviously no statistically significant difference in serum sST2 between T1 and T2, this sentence should be rephrased.

5. The sentence “Serum levels of sST2 in these sizes of breast cancer were associated, and [...] needs grammatical correction.

6. Discussion, last sentence: replace IL-27 by IL-33(?)

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published
**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.