Reviewer’s report

Title: Low Annexin A1 expression is predictive for a benefit from induction chemotherapy in oral cancer patients with moderately/poorly pathologic differentiation grade

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Reviewer: Gopalakrishna Iyer

Reviewer’s report:

In this paper Zhu et al examined the use of Annexin A1 as a biomarker of outcomes and response to induction TPF in the context of a clinical trial. The authors should be commended on not only conducted a clinical trial of this nature, but including tissue collection and biomarker profiling as part of the trial protocol, which adds much value to the role of such biomarkers, although I am little curious as to whether they included other biomarkers in their study or plan to validate other biomarkers in the future? The data is interesting and certainly shows that Annexin A1 may be a useful biomarker in head and neck cancers, but needs to be validate in future studies, which I hope this group plan to undertake in the future (although they did not indicate if they were planning to do so).

I have a few issues that need addressing before this paper can be published, although most of them involve re-examination of the data and discussion and hence can be considered minor.

1. This reviewer gets the feeling that the authors have thrown too much statistical methods in this paper, which loses some of the impact of Annexin A1 as a biomarker, and perhaps they should consider trimming some parts out and adding more important data in. This way, the value of Annexin A1 may be better highlighted. Perhaps the authors should define the primary and secondary questions first before plunging into the analyse, where the primary question would be to define the role of annexin expression with regards to overall outcomes and the secondary question would be to define it in the context of induction TPF.

2. Changes in the results section that should be done is listed as below:
   a. In the results section there is a paragraph that reads “Using the Cox model, the patients less than 60-year old, the patients atcN1/cN2 stage, the patients with moderately/poorly pathologic differentiated grade, and the smokers with low Annexin A1 expression had a better DFS andLRFS compared to those with high Annexin A1 expression; the patients at cN1stage or clinical stage III with low Annexin expression had a better OS, DFS,LRFS and DMFS compared to those with high Annexin A1 expression (Figure3)” I feel that this analyses adds little to the data and the model shown is confusing and not intuitive. It can be dropped from the analyses completely.
   b. The statement on multivariate which ends with “because the factor of Annexin
A1 expression by clinical stage interaction was not statistically significant (P=0.231)” makes no sense. A multivariate analyses assumes no interaction between the two anyway. The reviewer is also confused as to why the Cox multivariate model did not include grade when this was shown to be associated with annexin A1 staining to begin with. This should be corrected.

c. The statement “In the patients with well pathologic differentiation grade, there was no significant difference on OS, DFS, LRFS or DMFS between the patientstreated with and without TPF induction chemotherapy, regardless of AnnexinA1 expression. In the patients with moderately/poorly differentiation grade, thepatients with low Annexin A1 expression benefited from TPF induction chemotherapy on OS and DMFS; however, the patients with high Annexin A1 expression did not benefit from TPF induction chemotherapy on OS and DMFS” makes no grammatical sense to me, and should be re-worded

3. With regards to the secondary aim of AnnexinA1 and induction chemo, it makes more sense to re-word it as patients with high AnnexinA1 should NOT undergo TPF or that TPF offers no benefit, especially in preventing systemic disease, rather than the benefits of low Annexin A1?

4. Table 2 has data for local, regional and loco-regional, locoregional should be removed from this

5. Include a separate table for the pathologic and clinical response data, although negative, this is important to visualize.

6. The introduction can be trimmed as the primary objective of this paper is annexina A1, not induction chemotherapy and hence the latter section can be summarized

7. How did the authors arrive at a 50% cutoff for Annexin A1 staining?

8. A diagrammatic representation of patients treated on either arm, and annexin A1 staining results may be useful for visualizing the data?

I feel that the above changes can easily be made and thence the article should be suitable for publication.

**Level of interest:** An article of importance in its field

**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'