Author's response to reviews

Title: Prognostic impact of spliceosomal gene mutations in the myelodysplastic syndrome without ring sideroblasts

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Author's response to reviews: see over
Dear Editor,

Please find electronically appended a revised version of our manuscript, ‘Prognostic impact of spliceosomal gene mutations in the myelodysplastic syndrome without ring sideroblasts’, for reconsideration in BMC Cancer.

We have revised and changed the manuscript according to the reviewer’s comments and suggestions and provided a cover letter giving a point-by-point response to the concerns. Importantly, we revised results, related tables and figures by using IPSS-R instead of IPSS. We believe that the changes made in the manuscript have improved it. Our responses are detailed below. All the authors have reread and approved the revised version of our work. We hope that our manuscript will now be acceptable for publication in BMC Cancer.

Sincerely yours

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Responses to Reviewer comments

Reviewer #1;

1) The title does not reflect the data in the manuscript. It should be retitled “Prognostic impact of spliceosomal gene mutations in non-RARS MDS” (or something like that) as there is a prognostic impact of U2AF1 and SRSF2 mutations seen here and mutations in SF3B1+U2AF1+SRSF2 represented ~25% of MDS patients here.

Response: We retitled our manuscript according to your suggestion as follows: Prognostic impact of spliceosomal gene mutations in the myelodysplastic syndrome without ring sideroblasts. (page 1, line 3-4)

2) There have actually been quite a few studies of the impact of spliceosomal gene mutations in non-RARS MDS, so the parts of the Abstract (last sentence of the Background) and the Introduction which suggest otherwise should be revised (particularly the last sentence of the 2nd to last paragraph in the Introduction).

Response: We revised the parts of 'Abstract' (page 4, line 54-56) and the parts of 'Background' (page 5, line 101-103).

3) The Introduction describes a mechanistic impact of spliceosomal gene mutations which is written far too definitively (Lines 115-118) as the true mechanistic effects of these mutations in the pathophysiology of MDS are not well known now. This section needs to be heavily revised to reflect the uncertain role of these mutations in leukemogenesis. It is also not clear what the authors mean by spliceosomal genes being “tumor suppressors” and this needs to be revised.
Response: We appreciate your comments. Accordingly, we revised the related sentence and clearly described the origin of reference (page 4-5, line 89-96).

4) Table 1 is unnecessary in the main manuscript given the >20 publications which have already reported on the location of spliceosomal gene mutations in these genes.

Response: We removed the Table 1 in main text of manuscripts. And we presented it as a supplementary material.

5) Section of the 1 of the Results can be greatly abbreviated. The mutual exclusivity of spliceosomal gene mutations and the locations of these mutations have been repeatedly described and don't need to be stated in the main text yet again here.

Response: We reduced the section 1 of the Results according to your suggestion (page 8, line 168-178)

6) The Discussion section needs to be greatly abbreviated. It is too long here.

Response: We abbreviated the Discussion section according to your comments.

Reviewer #2;

1) The number of patients included is not large enough to draw the conclusions that the authors have suggested.

Response: We described and inserted the relevant sentence into the Conclusion section to avoid the error of generalization.

2) It is well known that SF3B1 mutations cluster with bone marrow ring sideroblasts and hence in this subgroup it is not surprising to see a low frequency. In addition we and other authors have already demonstrated its lack of prognostic capacity.

Response: We appreciate your suggestion. Accordingly, we inserted comments about the diversity of results of previous researches and current study (page 5, line 101-103 & page 14-15, line 306-312).

3) The methods section contains a large number of technical redundancies, especially details on sequencing of genes and cytogenetic studies, which are already well established and have been published repeatedly.

Response: We abbreviated the Methods section and presented the supplementary method separately.
4) On one hand the authors state that they excluded patients with RS, however in the results they describe patients with RARS. In these studies a central pathological review is critical.

Response: We removed the 3 RARS patients in our study and revised related sentence of manuscript and relevant tables or figures by additional analyses.

5) IPSS-R should be used instead of the IPSS.

Response: We appreciate your suggestion. Accordingly, we revised manuscripts and related tables and figures by using IPSS-R instead of IPSS.

6) Cytogenetic correlates of these mutations should also be looked into.

Response: Detailed and relevant explanation about the cytogenetic correlation of splicing gene mutation are described in section 2 of Result (page 9, line 183-187 & line 196-201; page 10, line 208-212) and Discussion part (page 14, line 295-298)