Author's response to reviews

Title: ADAMTS2 gene dysregulation in T/myeloid mixed phenotype acute leukemia

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

Please find enclosed our revised manuscript (MS: 1694430446143085) entitled “ADAMTS2 gene dysregulation in T/myeloid mixed phenotype acute leukemia” which we are submitting in the hope that it may be found suitable for publication in BMC Cancer.

We would like to thank referees for their helpful suggestions. The manuscript has been revised according to Reviewer comments (in italics) as follows:

Reviewer: 1

1. “...Since there are suggestions that ADAMST2 suppresses tumour growth by the inhibition of angiogenesis (Kumar et al, Cancers, 4, 2012), it is unlikely that deregulation of this gene with overexpression of the protein may have played a role in the pathogenesis of this leukaemia. Authors may comment on this.... " A comment about this topic has been added in the Discussion section (lines 162-165)

2. "... The authors refer to the value of this abnormality for minimal residual disease monitoring by FISH. However, FISH is much less sensitive than multicolour flow cytometry to detect residual leukaemic cells. Therefore, this should be played down and a sentence regarding sensitivity of FISH versus flow cytometry may be pertinent..." A sentence reporting results of immunophenotype analysis at the end of induction and during the follow-up has been added (lines 86-87)

Reviewer: 2

1. “..Figure 1 legend refers to panels (C-D); this should be (B-C)....” Figure 1 legend has been corrected as suggested.

2. “.. Figure 4: as samples were run in triplicate, please include error bars to indicate degree of variability in the assay..” Figure 4 has been modified as suggested.
3. “Case presentation, line 87: How was the “molecular remission” defined? Eg by PCR for clonal TCR rearrangement or flow cytometry? Was this technique also applied at the end of induction?..”

The molecular remission has been defined by the ADAMTS2 gene expression analysis (line 89) and was also performed at the end of induction (line 141).

4. “A paragraph could be included in the discussion to point out that no functional validation has been performed to characterize the leukaemogenic potential of this novel juxtaposition of a TCR locus/enhancer and possibly constitutively activated metalloprotease. It is entirely possible overexpression of ADAMTS2 is of no tumorigenic consequence, and this is simply a passenger mutation...” The text has been modified as suggested (lines 165-167).

5. “The authors might also wish to elaborate/speculate on why overexpression of a protein proposed to be a tumour suppressor (as per citation number 9) might be leukaemogenic in this context. It would be helpful to point this out to readers, that this is contrary to what might be expected based on other published literature. Could the truncated protein for example be functioning as a dominant negative mutation, and suppressing function of the wild-type protein?...” The text has been modified as suggested (lines 162-165).

Thanking you in advance for your kind attention,

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