Reviewer's report

**Title:** Complex NOTCH1 mutations as prognostic impact factors in paediatric T-cell leukaemia.

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**Reviewer:** Claudia Baldus

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Complex NOTCH1 mutations as prognostic impact factors in paediatric T-cell leukaemia.

Marcela Braga Mansur

The authors determined the prognostic impact of NOTCH1 mutation as well as other mutational events in paediatric T-ALL patients. The prognostic significance of NOTCH1 mutations in childhood and adult T-ALL has already been examined in various studies and illustrated different results. In this regard, the current study provides similar conclusions as already reported by others. Mansur et al have additional investigated the prognostic impact of the complex versus point mutations as well as the relevance of other gene mutations.

**Major:**

The authors claim to analyse NOTCH1 mutation in the concert with genes functional associated with the NOTCH1 pathway but they miss to analyze mutations in the FBXW7 gene as important negative regulator of NOTCH1. The mutational analysis of FBXW7 should also be included in the experimental set up.

The authors propose that complex NOTCH1 mutations rather than point mutations are of prognostic significance. However, the authors do not provide any association between the NOTCH1 mutation status (complex vs. point mutation) and other clinical as well as molecular variables (including, age, risk group, CD1a expression)...

The prognostic impact is only related to overall survival, an endpoint that is highly influenced by treatment related or other non-leukemia related events. The authors should provide other endpoints including the CR rate, relapse rate, MRD and DFS to illustrate that the proposed poor outcome is related the recurrence of the leukemia rather than treatment associated events.

The authors will have to be more precise on the multivariable model: how was this constructed, what variables were included in the model, ect. Was expression of CD1a included in the model?

It is difficult to understand why complex mutations should impact differently on outcome than point mutations with respect to treatment response as hypothesis
by the author (page 12). Were the CR rates and the MRD levels different to underline this hypothesis? Is there experimental evidence that would support these findings?

The authors claim (page 12) that SIL-TAL1 is of independent adverse prognostic impact, but since there is no multivariable analyses performed to demonstrated these finding, thus this can not be stated this way!

As in the title the authors conclude at the end of the conclusion that complex NOTCH1 mutations confer a favourable outcome. Based on the small number of cases, the lack of experimental evidence and with no significant impact in the multivariable model this statement needs to be adequately rephrased.

Abstract: in contrast to the conclusion in the text, the authors claim in the final sentence of the abstract that the NOTCH1 mutations should be tested for further treatment strategies. However without a clear prognostic and predictive impact and without targeted therapies available this statement can not be accepted this way.

Minor:
The number of patients for each group has to be indicated in all of the figures.

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.