Peer Review File

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Reviewer A

Comment 1: The authors summarize findings from AALL1331 as reported by Hogan et al regarding efficacy of adding blinatumomab to standard chemo for low-risk B-ALL in first relapse. Overall, blinatumomab fell short of significantly improving DFS and OS for all patients. When site of relapse was considered, patients with isolated BM involvement did indeed benefit while those with IEM or BM+EM disease did not. Patients with CNS relapses are particularly poor responders; however, the authors present summarized data that suggests CAR-T therapy as a beneficial approach for these patients.

This is a well written summary of the key AALL1331 data. I have only a couple minor comments.

Reply 1: We appreciate your kind and thoughtful review of our work.

Comment 2: Line95: It would be helpful to add in the "n=" for blina and chemo groups. Since blina achieved 100% OS for BM+EM patients while not reaching statistical significance, it seems that no therapy could have been found better than chemo alone in this case which points to a lack of adequate numbers of patients or sufficient follow up time to answer this question. Some discussion of the limitations of the study could be a plus.

Reply 2: Thank you for bringing our attention to this point. "n=" have been added for all groups in this section to help strengthen the statistics that are emphasized here. Additionally, a statement addressing the limitations of the study and the lack of adequate patient numbers to derive a statistically significant difference has been included.

Changes in the text: "n=" have been added for all groups in this section, as well as a statement addressing the study limitations, see lines 74-84 on page 4.

Comment 3: Line166: Should "relapsed B-ALL when compared to isolated BM involvement…" be "relapsed EM+ B-ALL when compared to isolated BM involvement…"?

Reply 3: Yes, thank you for identifying that the addition of "EM+" would clarify and further enhance the point that we tried to make in this sentence.

Changes in the text: "EM+" was added to this sentence which is now in line 148 on page 6 in the revised manuscript.

Reviewer B

Comment 1: Congratulations for this nice commentary paper. Many of us were expecting for the results from the second part of the AALL1331 study as we expect blinatumomab to improve treatment results of children after "non-high risk" first relapse of ALL just as it did for high-risk patients.

Just a very few comments and suggestions from my side:

Reply 1: We would like to thank Reviewer B for their review and kind remarks regarding our commentary.

Comment 2: Line 33. "Patients have historically been considered low-risk (LR)…"

These are criteria applied by the Children's Oncology Group (COG), and they somehow differ from those applied by other groups such a BFM-I and IntReALL consortium; please consider to state this.

Reply 2: Thank you for this recommendation to include how risk stratification differs between different collaborative groups. We have added a statement in the text to clarify that these criteria may differ for other groups and that this statement applies for COG trials.

Changes in the text: Please see lines 25-26 in the revised manuscript on page 2 for the clarifying statement on different risk stratification for different consortia.

Comment 3: Line 43. consolidation chemotherapy (is) followed by …

Should we remove "is" within this sentence?

Reply 3: Thank you for identifying this grammatical error. We agree and we have removed is from the sentence.

Changes in the text: We have modified the text as advised and removed "is" from the referenced sentence. Please see page 2, line 35.

Comment 4: Lines 116 to 119. "The authors attributed the lower DFS rate for ICNS relapses to reduced intensity of CNS-directed therapy compared to prior trials with fewer intrathecal doses of chemotherapy given on AALL1331…"

Apart from the number of doses of intrathecal chemotherapy, here you might consider to explain also the possible impact of the lower number of high-dose cytarabine and methotrexate doses. This is in contrast to previous COG trials as stated in the manuscript form Hogan et al, and is also in contrast to other groups' re-induction protocols, such as the F1/F2 in the ALL-REZ BFM 2002 regimen with early introduction of intermediate dose methotrexate and high dose cytarabine.

Reply 4: Thank you for your suggestion to included the changes in the regimen with regard to high-dose cytarabine and methotrexate. We agree that this should be included and we have added this to the list of changes within the approach of AALL1331 that could have contributed to the lower DFS rate observed.

Changes in the text: We have updated lines 100-101 on page 5 to reflect this addition.

Comment 5: Lines 166 to 167."… suggest against the use of blinatumomab in the setting of relapse with extramedullary involvement."

I would recommend to be less imperative or even to omit this statement.

In the study reported by Hogan et al, although the differences were not significant, patients with BM and EM involvement had better DFS and OS. Even patients with isolated EM relapse had a non-significant benefit in terms of OS. Moreover, data presented by Locatelli et al in JAMA 2021 and Leukemia 2022 showed that patients with EM involvement at relapse do better if they receive blinatumomab during consolidation when compared with those treated with standard chemotherapy.

Although blinatumomab has indeed limited access to CNS it probably works to prevent subsequent systemic relapse even in patients with isolated CNS first relapse.

Reply 5: We are appreciative of this comment made by Reviewer B and have omitted this statement from the sentence that is referenced. We agree that there are some settings in which blinatumomab is still beneficial in these patients, including in the reviewers suggestions to prevent systemic relapse, so we believe this change makes our statement less imperative.

Changes in the text: Please see lines 148-149 on page 6 of the revised manuscript to see where this statement has been omitted.

Reviewer C

Different points from the Hogan's manuscript on the findings from AALL1131 are discussed here.

Comment 1: You are just discussing Blinatumomab monotherapy, but not Blinatumomab plus chemotherapy. You should also discuss outcomes for Blinatumomab plus chemotherapy referring manuscripts published previously.

Reply 1: Thank you to Reviewer C for this comment. We had discussed blinatumomab in combination with chemotherapy and its use in consolidation programs briefly in the last paragraph on page 5. We have expanded our discussion of outcomes for Blinatumomab plus chemotherapy as suggested and added in more references to address this.

Changes in the text: Please see addition to the text and references added in lines 128-132 on pages 5-6.

Comment 2: You are just discussing the difference of first and second salvage.

You should discuss the only difference of EM situation at relapse.

Reply 2: The setting of EM relapse is discussed in the third to last paragraph of our manuscript in lines 135-152 on page 6. We believe we have adequately addressed this situation of EM disease at relapse and were unable to find additional references to further emphasize our points.

Changes in the text: No changes to the text as this is already addressed in lines 135-152 on page 6.

Comment 3: Please find further comments in the attached pdf file.

Reply 3: The comments in the attached pdf file are included in the comments above and no further comments were identified in the annotated pdf file. We believe we have adequately addressed Reviewer C's comments above.