

## Peer Review File

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### Reviewer A

This is a nice commentary summarizing current COG risk stratification and the recent retrospective analysis of the COG biology study showing that the EFS And OS of intermediate risk neuroblastoma patients age 12-18 months (stage 4 favorable biology and stage 3 unfavorable biology but MYCN non-amplified) has been maintained despite significant reduction of therapy after 2006.

The commentary might be improved by:

**Comment 1.** A comment on the limitations of the Bender study which might affect the conclusion, such as the fact that only 20/105 in the study cohort were enrolled on therapeutic trials, and therefore had known treatment; the comparison of the 12-18-month intermediate group to an overall group of <3-year-olds; the assumption that those not on study had a high-risk treatment before 2006 and intermediate risk treatment after 2006;

**Reply 1:** We thank reviewer A for his/her suggestion. Accordingly, we add a paragraph in the text highlighting some of the identified limitations.

**Changes in the text:** The following paragraph has been included between lines 134-137 of the new version of the manuscript: *“Nevertheless, the study had some limitations that could affect the conclusions of the study. For example, from the cohort of 105 patients, only 20 received treatment through the enrollment in clinical trials. It is also not clear whether those patients that were not in the trials, received high-risk therapy before 2006 and intermediate-risk therapy after 2006.”*

**Comment 2.** Inclusion of a key reference, Schmidt et al, JCO 2005, first suggesting that this age group of stage 4 MYCN non-amplified patients was more favorable, and formed the basis for the intermediate risk reduced therapy.

**Reply 2:** We apologize Reviewer A for the missing reference, which now has been included in the text.

**Changes in the text:** The new reference 19 has been inserted in line 104 of the re-submitted version of the manuscript.

**Comment 3.** Please clarify comments in lines 157-164. Do the authors mean instead of “Next, the authors compared the outcomes of high-risk patients ( $\leq 2006$ ) of 12-18 months versus the rest of high-risk patients” Rather I think they mean patients age 12-18, months with biologically

favorable MYCN non-amplified disease classified as high-risk patients

**Reply 3:** We thank Reviewer A for detecting this confusing paragraph. Following his/her suggestion, we changed the text accordingly.

**Changes in the text:** Lines 127-128 have been modified. Therefore, the paragraph now reads: *“Next, the authors compared the outcomes of the 12-18 months cohorts with biologically favorable MYCN non-amplified disease (classified as high-risk in  $\leq 2006$ ) versus the rest of high-risk patients.”*

**Comment 4.** Line 162 “no significant different” should read “no significant differences were observed either in ...”

**Reply 4:** We thank the reviewer for detecting this typo, which has been corrected.

**Changes in the text:** The word “different” has been replaced by the word “differences” in line 132 of the new submitted version of the manuscript.

**Comment 5.** The figure is an interesting idea, but the images and color changes hard to understand. Does green mean high risk? If so, please add to legend. Why are there two colors of IV fluid? I think either use better images or explain more clearly in the legend. Figure 1 is not referred to in the text.

**Reply 5:** We apologize for the confusion that the figure may have caused. For a better understanding, we added the missing information in the figure legend. To facilitate the understanding of the figure, green-colored patients are now just those that were between 12-18 months of age, which were assigned to high-risk before 2006 and re-assigned to intermediate-risk after 2006. White-colored patients are those younger than 12 months and red-colored patients are those older than 18 months.

The orange-colored IV fluid icon is to represent the myeloablative chemotherapy. We have also added the reference to Figure 1 in the text (Line 107 of the new version of the manuscript).

**Changes in the text:** The following text edits have been included:

Figure 1: Green-colored patients have been modified.

Line 107: The reference to Figure 1 has been included at the end of the sentence.

Line 212: To clarify why were two IV fluid icon, we add the text (orange fluid IV icon).

Line 213-216: We added the meaning of colored patients.

## **Reviewer B**

**Comment 1:** Mass screening for neuroblastoma, which was performed nation widely in Japan and pilot studies were performed in the North America and European countries, measuring urinary concentration of HVA and VMA, also gave the impact for the “age” as the risk factor. Although the mass screening did not contribute the survival of patients and discontinued, however, the phenomenon of spontaneous regression of tumor which were often observed the neuroblastoma diagnosed less than 1 year old, was also paid attention.

I would recommend for authors to add the comment of mass screening for discussing the relation between the patient age and prognosis of Neuroblastoma in this informative editorial commentary.

**Reply 1:** We thank the Reviewer B for his/her comment. Accordingly, we added a reference to the mentioned mass screening neuroblastoma efforts. However, we apologize that we cannot be more extensive owing to the word and reference limit.

**Changes in the text:** The sentence “*This evidence was also supported by evidence generated from neuroblastoma mass screening programs conducted in Japan, Quebec and North American, and UK*” has been included in line 41-43 of the new version of the manuscript.

**Comment 2:** Minor point. Page 6 L 180 “int”→”into” ?

**Reply 2:** We thank the reviewer for detecting this typo, which now has been corrected.

**Changes in the text:** In line 149 of the new version of the manuscript the word “int” has been replaced by “into”.