Peer Review File
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Reviewer A

The authors conducted a review of preclinical and clinical data on molecules that could serve as new diagnostic and therapeutic targets for neuroblastoma. Several modifications seem necessary.

Reply: I am deeply grateful for the hard work you have put into my manuscript. Your insights and revisions have significantly improved it. I truly appreciate the considerable time and effort you have invested. We concur with all the suggested amendments and hope to effectively implement each improvement, eagerly anticipating your final decision.

1. The overall structure of the targeted therapy section appears to be mixed with preclinical and clinical data. It might be more effective to separate and categorize preclinical and clinical data into distinct sections rather than intermingling them.

Reply 1:

Thank you very much for your comments. Indeed, as you pointed out, our targeted therapy section previously mixed clinical and preclinical data.

Changes in the text:

Considering the abundance and rapid advancement of targeted therapy drugs currently in clinical trials, we have now removed the preclinical data from this section. In the MYCN inhibitor segment, we first refined the introduction of MYCN, highlighting its uniqueness that precludes direct targeted therapy (see page 4, lines 119-123).

In the section on TrK inhibitors, we have reorganized the data, eliminating preclinical studies and incorporating several recent clinical trial outcomes (see page 8, lines 237-242, 246-250).

For the Angiogenesis inhibitors, preclinical studies were also removed, and the clinical research findings have been updated (see pages 8-9, lines 263-275).

A similar approach was taken with mTOR inhibitors, where preclinical research was discarded, and a number of clinical studies have been included (see page 9, lines 286-291).

2. The content related to ESCAT in the targeted therapy section (lines 89-99) seems unrelated to the overall text. If implementing such classification criteria, it would be beneficial to summarize the evidence levels of the molecules discussed in this article in a table.

Reply 2:

Thank you for your insightful suggestions. After careful consideration and review, we also concluded that the section on ESCAT was not contextually relevant.

Changes in the text:

Consequently, we have removed the content related to ESCAT. Following this, we introduced a new segment that provides an overview of targeted therapies, primarily discussing their advantages over traditional radiotherapy and chemotherapy. This serves to effectively set the stage for the subsequent content (see page 4, lines 101-109).

3. It would be advantageous to include a diagram illustrating the total number of papers selected when applying the search terms and how many were excluded.

Reply 3:

Thank you for this suggestion, which I believe will enhance the rigor of my article.

Changes in the text:

I have created a selection flowchart to illustrate the papers that were included and excluded based on the use of specific search terms (see page 17, lines 511-512).

4. There seems to be a potential omission of some clinical papers including following 2 articles: Lorlatinib with or without chemotherapy in ALK-driven refractory/relapsed neuroblastoma: phase 1 trial results. Phase I Study of the Aurora A Kinase Inhibitor Alisertib in Combination With Irinotecan and Temozolomide for Patients With Relapsed or Refractory Neuroblastoma: A NANT (New Approaches to Neuroblastoma Therapy) Trial.

Reply 4:

Thank you for your feedback, which I have taken into consideration and made the necessary revisions.

Changes in the text:

I have incorporated the two articles you mentioned into my paper, specifically focusing on ALK inhibitors (see page 7, lines 223-226). The article on the Phase 1 study of Alisertib is included in the Aurora Kinase section (see page 5, lines 143-147)

5. Although there is substantial research reported on Aurora kinase inhibitors, there is no mention of this in the manuscript. Additional content regarding studies on Aurora kinase inhibitors needs to be added.

Reply 5:

Thank you very much for your valuable advice. Recognizing the importance of aurora kinases in the targeted therapy of neuroblastoma, we have made appropriate revisions.

Changes in the text:

We have compiled and organized clinical studies related to aurora kinases and have now included them in the targeted therapy section (see pages 4-5, lines 128-151).

Thanks very much for taking your time to review this manuscript. I really appreciate all your comments. Your comments will enable us to improve our work.

Reviewer B

The manuscript is reviewing precision medicine applications in neuroblastoma. I like the scope of the manuscript. However, I don't like the structure of the manuscript.

Reply: Thank you very much for your helpful comments regarding this manuscript. We are very pleased that you are giving us the opportunity to submit a revised draft and we appreciate your time and the effort it took you to provide us with your valuable and insightful feedback. We agree with all proposed changes and hope that we were able to implement all suggestions for improvement satisfactorily and look forward to your decision.

1) Subheadings should be well-defined. I recommend to mention clinically approved targeted therapies such as ALK, anti-GD2 etc in a section, pre-clinical studies such as PHOX2B, CTCs, LDH, TMOD etc. in another (separate) section. Because clinically approved targets are very-well studied and their therapeutic effect has been shown in many preclinical and clinical studies. Yet, pre-clinical biomarkers have been examined in few studies and their effectiveness are not very well established. It would be appropriate to list them under candidate biomarkers.

Reply 1):

We wholeheartedly agree with your perspective and have accordingly restructured the sections of the article.

Changes in the text:

We begin with an introduction to targeted therapy and immunotherapy, followed by discussions on preclinical biomarkers and liquid biopsies. In the targeted therapy section, we now only include therapies that have been clinically approved and validated in clinical studies. In the section dealing with MYCN-related targeted therapies, due to the lack of clinical research on BET inhibitors, we have removed this part and replaced it with information on CDK inhibitors, aiming to make this section more comprehensive (see pages 5-6, lines 155-170).

2) In the introduction paragraph, authors mentioned about the risk groups, yet they did not mention about the risk classification. They should have mentioned about the risk factors taking into account in risk stratification and cited most recent paper related to risk stratification. Also, it would be nice to talk about therapy modalities for low-risk, intermediate-risk and high-risk groups. Because in most of the cases, the mentioned targeted therapies/immunotherapies are currently applied to high-risk patients or patients with refractory disease. At least they can provide it as figures. Risk stratification is very useful tool for a clinician to decide on what kind of therapy will be given to each patient.

Reply 2):

Thank you for your constructive comments. We have addressed the previously missing elements in our paper.

Changes in the text:

In the introduction, we have now included details on risk classification and risk factors (see page 2, lines 53-58). Additionally, we have supplemented the document with treatment methods for patients across different risk stratifications (see page 2, lines 58-62 and 64-67). This leads naturally into the subsequent discussion on targeted therapy and immunotherapy, particularly relevant for high-risk neuroblastoma patients who are more challenging to treat.

3) It would be better if authors can write anti-GD2 and ALK sections more detailed and mention about clinical studies and their results (if possible).

Reply 3):

Thank you for your valuable advice. We have expanded on the two sections you mentioned.

Changes in the text:

The immunotherapy section is now divided into anti-GD2 and CAR-T, with a detailed description including an extensive array of clinical studies and their results (see pages 10-11, lines 298-338).For the ALK section, we have made substantial additions, incorporating numerous clinical studies and detailing their findings (see pages 6-7, lines 181-182 and 186-229).

4) In MYCN targeted therapies, it would be nice to mention about Aurora kinase inhibitors targeting AURKA and AURKB.

Reply 4):

Thank you for your valuable feedback. Aurora kinases play an indispensable role in MYCN-related targeted therapies.

Changes in the text:

We have now incorporated clinical studies related to aurora kinases and their findings into our article (see pages 4-5, lines 128-151).

5) ALK and PHOX2B mutations are also highly occurred in familial Neuroblastoma cases as well as in sporadic cases. PTPN11 is another mutated gene, causing Noonan syndrome, increased the risk of neuroblastoma occurrence. It would be nice to mention about PTPN11 in few words in biomarkers section.

Reply 5):

Thank you for your insightful suggestion. We have now included this section in our article.

Changes in the text:

We added relevant studies on the relationship between PTPN11 mutations, Noonan Syndrome, and neuroblastoma into the manuscript (see page 13, lines 408-416).

We appreciate for reviewer's warm work earnestly, and hope that the correction will meet with approval. Your previous constructive comments greatly enriched the current paper. Once again, thank you very much for your comments and suggestions.