ROUND 1

We sincerely appreciate your insightful and thorough review of our manuscript titled "**Clinical outcomes of newly diagnosed primary central nervous system lymphoma treated with Zanubrutinib-based combination therapy**" Your constructive feedback has significantly contributed to the enhancement of our work. We are pleased to submit the revised version of the manuscript, which includes detailed responses to each of your points.

1. It seems that the authors have not performed the stem cells check up in the patients before, applying the autologous stem cell transplantation. Application of stem cell profile at single cell level is required. Besides mentioning the type of stem cell is required. At single cell level.
   Reply: We have integrated the stem cell profile assessment "Stem Cell Assessment and ASCT" into the Patients and Methods section. However, due to challenges posed by the prevailing pandemic situation, some patient samples underwent transplantation procedures at both Guangzhou First People's Hospital and affiliated centers. Consequently, acquiring single-cell transplant data from this subset of patients proved to be a logistical challenge during this pandemic period.

2. In neoplastic disorders, newly diagnosed is also late diagnosis. Since the initiation of the primary event, it takes very long time (approximately 10 years up to the initial medical check-up, including diagnostic period.
   Reply: The limitation of this study regarding the definition of "newly diagnosed" has been discussed in the discussion. "However, limitations exist, it is well-recognized that the journey from the initiation of the oncogenic event to the point of clinical diagnosis is a protracted one, spanning a period of approximately a decade. This extended timeline underscores the intricacies inherent in the development of neoplastic disorders, revealing that the characterization of "newly diagnosed" necessitates a more nuanced understanding—one that acknowledges the substantial span of disease evolution prior to medical recognition.
   Our study particularly emphasizes the significance of adopting novel therapeutic strategies to address the multifaceted nature of PCNSL."

3. Please include the complete spelling of CSF at the initial line here.
   Reply: The complete spelling of CSF has been included at the initial mention as per your request.

4. Circulating lymphoid cells by only 2ml peripheral blood of patient's blood is absolutely non-invasive.
   Reply: We have adjusted the description to highlight the non-invasive nature of cerebrospinal fluid (CSF) liquid biopsy profiling:" Non-invasive cerebrospinal fluid (CSF) liquid biopsy profiling might be a feasible way to evaluate treatment response and tumor burden."

5. Circulating Tumor DNA does not last adequate duration in the bloodstream. Therefore, the achieved results may be challenging.
   Reply: The limitation posed by the transient presence of circulating tumor DNA (ctDNA) in the bloodstream has been discussed in the manuscript's discussion section: "However, the fleeting presence of ctDNA in the bloodstream poses a challenge to the reliability of achieved results."

6. There is no sign of single cell-based analysis.
   Reply: While our study focused on tissue and plasma samples, we understand the potential value of single-cell analysis. However, due to pandemic-related challenges, acquiring single-cell transplant data from a subset of patients was logistically difficult.

7. What is the ID- for the biological status of lymphoma in the target patients? What about proliferative index including Ki-67 or PCNA? What about other proteins including Cyclins D1, E, and B1? These are required in the pre-treatment procedure.
   Reply: Patient IDs, COO subtype, Cyclin D1, and Ki67 results have been incorporated into Table 4, addressing your requirement for pre-treatment procedure information.

8. Upon the provided items, formalin degrades the nature of proteins. Regarding formalin, there is a challenging condition for protein analytical procedures.
   Reply: The tissue specimens collected by our team were submitted to the proficient analysis of the Geneseq company, a leader in genetic diagnostics. Given the logistical constraints posed by transportation and prior epidemic circumstances, the decision was made to employ formalin fixation to stabilize the tissue samples. This facilitated the unification of our approach to testing across the spectrum of samples received by the company.

9. Is there any IHC result available?
   Reply: IHC results for all patients have been added to Table 4.

10. The traced gene or genes are required to be mentioned.
    Reply: We have revised the content to “Within the subset of eight patients possessing alterations in key genes involved in the BCR pathway, such as CD79B and MYD88, the ORR reached 60%.”

11. In hematopoietic disorders, application of cytogenetics study is required.
    Reply: We have included cytogenetics information from the cited paper: “In the Phase I BGB-3111-AU-003 study, which focused on zanubrutinib monotherapy for CLL/SLL, a cohort of 78 patients was assessed for efficacy. This patients group included individuals with high-risk disease features, such as adverse cytogenetics [del(11q), 23.3%; del(17p) and/or TP53 mutation, 19.1%].”

12. The design and categorization of patients was unclear.
    Reply: Patient categorization has been further clarified in Table 4, and we have provided an enhanced explanation of patient treatment in the Patients and Methods section.

13. The methodology of this manuscript is required to be revised.
    Reply: The methodology in the Patients and Methods section has been revised in accordance with your suggestions.

14. The sequencing results are required to be approved by protein expression analysis.
    Reply: Protein expression analysis has been conducted using IHC, and the results for all patients have been added to Table 4.

15. The non-related items to the provided title, is required to be excluded from the text.

Reply: Manuscript title has been revised.

Once again, we are grateful for your time and effort in reviewing our manuscript. We believe that the changes we have made address your concerns and substantially improve the quality of the work. We look forward to your evaluation of the revised manuscript.

Thank you for your continued support and guidance.

Sincerely,

Wenyu Li
Guangdong Provincial People's Hospital Affiliated to Southern Medical University

ROUND 2

Dear Editor,

I would like to express my sincere gratitude to the reviewer and the editorial team for the valuable insights and suggestions on our manuscript titled "Clinical outcomes of newly diagnosed primary central nervous system lymphoma treated with zanubrutinib-based combination therapy" (Manuscript No: 86098). We greatly appreciate the time and effort put into the review process.

We carefully considered the reviewer's comments, which focused on the need for additional analytical approaches, such as pedigree-based analysis, single-cell analysis with high enumeration, relevant molecular-based analysis, and a correlative and sequential-based manner for unmasking the course of evolution in primary central nervous system lymphoma (PCNSL). The reviewer rightfully emphasizes that cancer research benefits from a comprehensive understanding of the disease, and we acknowledge the importance of these suggestions in advancing the field. Given the nature of our data and study design, we are unable to incorporate pedigree-based analysis into this specific study. Our study mainly examines the clinical outcomes of zanubrutinib-based therapy in PCNSL patients. Our study primarily relies on clinical data and outcomes, and we do not have access to single-cell data for the patients included in our cohort.

Despite these limitations, we believe that our study adds significant value to the scientific community by presenting real-world clinical outcomes of zanubrutinib-based combination therapy in PCNSL patients, which is currently lacking in the literature. We have also incorporated a detailed experimental design flow diagram and have undertaken professional language polishing to enhance the clarity and readability of the new version of the manuscript.

We kindly request that the editorial board reconsider our manuscript for publication. We believe that the clinical data presented in our study will contribute to the existing knowledge on PCNSL treatment and potentially guide future research in this field.

Thank you once again for the opportunity to submit our work to the World Journal of Clinical Oncology, and we look forward to your decision.

Sincerely,

Wenyu Li
Guangdong Provincial People's Hospital Affiliated to Southern Medical University