Dear Reviewer,

Thank you for your kind consideration for publication of our manuscript entitled “The synergistic anti-tumor activity of EZH2 inhibitor SHR2554 and HDAC inhibitor chidamide through ORC1 reduction of DNA replication process in diffuse large B cell lymphoma” in Cancers. We deeply appreciate your insightful comments and helpful suggestions. We have made revisions accordingly and responded all the comments point-by-point as follows.

1. In Table 1, can the authors please show that is the cut-off that was used to decide the performance of the inhibitor? IC50>100 um?

   The IC50 value represents the concentration at which a substance exerts half of its maximal enzyme inhibitory effects, which is usually used to determine the performance of the inhibitor. EZH2 inhibitor SHR2554 and EPZ-6438 showed comparable inhibitory effect against wild-type and mutant EZH2 with IC50 ranging from 0.87 to16.80 nM (Paragraph 2, Page 5).

2. Why RNA-seq (NGS) technique was used to investigate the RNA expression? Which platform was used? Which genes were analyzed?

   In order to further illustrate the molecular mechanism of synergistic anti-tumor effects by EZH2 inhibitor and HDAC inhibitor, the RNA-seq analysis was used to analyze the gene expression profile post combination treatment. Sequencing was performed by HiSeq system (Illumina, San Diego, CA, USA) according to the manufacturer’s instructions. The gene ontology (GO) enrichment analyses and gene set enrichment analysis (GSEA) indicated that significant enrichment of DNA replication process was observed after co-administration of EZH2 and HDAC inhibitor. More importantly, DNA replication process related ORC1 expression was decreased in both U2932 and SU-DHL-6 cells. The origin recognition complex (ORC) plays an important role in the initiation of DNA replication. ORC1 is the largest component subunit of ORC protein and determines the biological activity of DNA replication initiation sites and cell proliferation. Thus, the ORC1 was pick up to further illustrate the possible anti-tumor mechanisms of combination treatment. The related information was updated in Paragraph 1, Page 14.

3. The authors used patient-derived lymphoma tissues to create the PDX models. Are there more information available about the characteristics of these DLBCL samples (clinicopathological features)?

   The clinical characteristics of these PDX samples were updated in supplementary Figure 2 according to the comments of reviewer.

   PDX001-EZH2 WT: non-GCB, CD20 (+)，CD3 (-)，CD5 (-)，Bcl-2 (+)，Bcl-6 (+), CD10 (-)，CMYC (30%+)，CYCLIND1 (-)，Ki-67 (80%+)，MUM-1 (+)

PDX002-EZH2 Y641N: GCB, CD20 (+), CD3 (-), CD5 (-), Bcl-2 (+), Bcl-6 (+), CD10 (+), CMYC (80%+), CYCLIND1 (-), Ki67 (90%+), MUM-1 (-)

4. In the GSEA figures. Which are the two phenotypes? Which are the nominal p values?

   The related information was updated according to the comments of reviewer in Figure 4.

5. In the research of Figure 5. The authors performed immunohistochemistry for Ki67. The authors could have marked with other targets, such as apoptotic markers (CASPASE 3, or cleaved PARP), or EZH2. Nevertheless, it may not be feasible to do it now.

   The expressions level of Caspase 3, PARP and H3K27me3 within tumor tissue were analyzed by western blotting in Figure 5d.

6. In Figure 3. I had difficulty understanding the “--” and the numbers such as “18”, “9”, etc…

   According to the comments of reviewer, the figure legend was updated in Figure 3.

7. The datasets, at least the gene expression, could be uploaded to GEO website.

   According to the comments of reviewer, the gene expression datasets is uploaded to GEO website.