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. It is not clear why the authors determined the IC50 of SHR2554 in the various cell line after 6 days of treatment (Fig 1a), while in the rest of the experiments the cells were treated for 72 hours

   According to previous reports, the tumor cells were usually treated with EZH2 inhibitor for 6 days in cell vability assay (Selective inhibition of EZH2 and EZH1 enzymatic activity by a small molecule suppresses MLL-rearranged leukemia, Blood, 2015). But our results indicated that the combination treatment of EZH2 inhibitor and HDAC inhibitor could induced synergistic anti-tumor effect in just 72 hours. Thus, we used different treatment time period in these experiments.

2. Could the authors discuss the high sensitivity of SUDHL2 to SHR2554 compared to the other EZH2WT cell lines ?

   In our study, the EZH2 wild type cell line SU-DHL-2 was sensitive towards EZH2 inhibitor SHR2554 treatment. Similarly, as the novel epigenetic modifications therapeutic approach, the BET bromodomain inhibitor also exhibited the highest sensitive towards ABC-DLBCL type SU-DHL-2 cells. The significant downregulation of MYC related transcripts in SU-DHL-2 cells might account for the highly sensitive towards these epigenetic inhibitor treatment (The BET Bromodomain Inhibitor OTX015 Affects Pathogenetic Pathways in Preclinical B-cell Tumor Models and Synergizes with Targeted Drugs, 2015, Clinical Cancer Research).

3. Figure 5 : Why no H3K27me3 increase was observed in vivo with HBI8000 ?

   The drug metabolism within tumor bearing mice may influence the blood concentration of HBI8000. Meanwhile, the different concentrations of HDAC inhibitor used in vitro and vivo experiment may also influence the expression level of H3K27me3 within tumor bearing mice.

4. In vivo results have to be discussed.

   The Discussion section was updated according to the comment of reviewer (Paragraph 3, Page 15).

5. Minor points :Figure 3 and Figure 5c : too small !

The related figures were updated according to the comment of reviewer.