Author's response to reviews

Title: Anti-tumor effect of bisphosphonate (YM529) on non-small cell lung cancer

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Dear Editor:

We are willing to submit our revised manuscript that has the additional result of western blotting requested by reviewer#1. We hope that our revised manuscript will be accepted in BMC Cancer as an original report.

Major Compulsory Revisions

In order to improve this manuscript, I think authors should demonstrate the inhibition of the prenylation of Ras or Ras related small molecule G-proteins. There are many small G-proteins and other proteins, which are activated after prenylation. Although Ras-MAPK is one of the famous proliferative signals, the upstream of the MAPK signal is not only Ras. There should be or might be Ras-dependent and Ras-independent ERK activation pathways. Although I understand authors show p-ERK1/2 is actually inhibited by YM529, I think authors still demonstrate whether farnesylation as well as geranylgeranylation could be inhibited by YM529 or not. I think it is "essential".

Following reviewer #1's comment, we performed western blotting with other anti-Ras antibody to confirm the prenylation of RAS in YM529 treated cell lines. As expected, the prenylation was observed with YM529 dose dependent manner. We changed following part in RESULTS and DISCUSSION in the text and western blotting result in Figure 2.

P11 line 1. Western blotting analysis showed that anti-Ras antibody recognized a migrating band, indicating that YM529 induced the unprenylation of Ras in a dose-dependent manner. In addition, the phosph-ERK1/2 protein was down-regulated by YM529 treatment. (Fig.4) These results indicated that YM529 inhibited Ras-ERK1/2 pathway.

P12 line 14 Indeed, YM529 induced unprenylation of Ras and down-regulated the phosphorylation of ERK1/2 in NCI-H1819 cell lines despite absence of any effect on ERK1/2 expression.

Minor Essential Revisions
In order to let the readers to better understand their speculation that YM529 is useful for the patients with NSCLC, I recommend authors had better show the growth inhibitory effect against the tumor bearing mice in vivo.

We agree this comment. Further study will be necessary as next step of our study.

Best wishes,

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