

RESPONSE LETTER TO REVIEWERS :

Reviewer 1 :

Points of criticism:

1. The manuscript needs minor linguistic improvement >> As we have a native English speaker in our institution, we have asked her to revise the manuscript,
2. The number of references is not high enough for a review regarding treatment modalities and future directions regarding gastric cancer >> Add more references
3. More details should be given on genetics of gastric cancer and new potent pathways that would lead to modern treatment strategies. >> Add 2 paragraphs in introduction

Reviewer 2 :

1. The authors stated the results of JCOG9912 study in the "1st line treatment" section. The JCOG9912 study is a negative trial which did not show the superiority of irinotecan plus cisplatin to 5-FU alone. On the other hand, SPIRITS trial which is a phase III study comparing S-1 alone with S-1 plus cisplatin showed the superiority of doublet to single agent. If the authors would like to mention the superiority of doublet therapy, the SPIRITS trial is preferred. >> Add results of SPIRITS trial
2. The treatment schedule of SOX regimen is S-1 40 mg /m² bid for 14 days and oaliplatin 100 mg/m² d1 every 3 weeks. >> Totally right. Apologise for the mistake
3. In the "Targeting EGFR1 in advanced gastric cancer" section, nimotuzumab which is a EGFR inhibitor is under investigation by a phase III study in Japan and Korea (NCT01813253). Adding this trial is preferred. >> Add this trial
4. In "Role of angiogenesis" section, a phase III study showed apatinib which is a VEGFR-2 TKI prolong OS compared with BSC in ASCO 2014. The inhibition of VEGFR-2 might be an important treatment strategy for advanced gastric cancer.>> >> Nice comment, Thanks a lot. Add this trial
5. In "Future perspectives" section, the authors stated "Table 1". Where is Table 1?

6. The phase III study, RILOMET-1 was reported at ASCO 2015, and this study was did not meet primary endpoint. In addition, another phase III study including a novel agent, metmab (onartuzumab) showed no survival benefit of onartuzumab for gastric cancer in ASCO 2015.

>> Thanks a lot for your comment. Add this to the article

7. Updated data of KEYNOTE-012 study was reported in ASCO 2015 by Dr. Bang. The median OS was 11.4 months. >> Thanks a lot for your comment. Add this to the article