Nov 15, 2013

Lian-Sheng Ma, MD, PhD
Editor-in-Chief
World Journal of Gastroenterology

Dear Dr. Ma

We deeply appreciate the thoughtful comments of the reviewers and, as suggested, are submitting a revised manuscript, which addresses specific issues brought forth by the reviewers. Below is the letter to the reviewers' comments including our point-by-point replies.

Thank you for your consideration

Title: Personalized cancer targeted therapy in gastric cancer: fitting cancer treatment to different patient genome

Author: Sun Min Lim, Jae Yun Lim, Jae Yong Cho

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5758

Sincerely,

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Response to Reviewers' Comments

We appreciate the thoughtful comments of the Reviewers. We fully agree with the specific comments raised by the Reviewer to improve the scientific value of our study. With all these efforts, we hope to meet all the requirements for publication in World Journal of Gastroenterology.

Comments (Reviewer #1)

The manuscript is useful for basic and clinical research. As understanding the molecular mechanisms in gastric cancer is important for clinical management strategy. But the quality of the figures in the manuscript is poor, especially the figures of microarray, please enhance them. Some of references are quite old, for example, the part of clinical use, please add some newest references.

Replies:

Regarding the quality of the figures, we have revised them to improve the quality.

Regarding the references, we have added four newest references to the manuscript as below.

15 **Tran TN**, Brettingham-Moore K, Duong CP, Mitchell C, Clemons NJ, Phillips WA. Molecular changes in the phosphatidylinositide 3-kinase (PI3K) pathway are common in gastric cancer. *J Surg Oncol* 2013; **108**: 113-120 [PMID: 23813545 doi: 10.1002/jso.23357]

30 **Zang ZJ**, Cutcutache I, Poon SL, et al. Exome sequencing of gastric adenocarcinoma identifies recurrent somatic mutations in cell adhesion and chromatin remodeling genes. *Nat Genet* 2012; **44**: 570-574 [PMID: 22484628 doi: 10.1038/ng.2246]

42 **Wang JL**, Hu Y, Kong X, Wang ZH, Chen HY, Xu J, Fang JY. Candidate microRNA biomarkers in human gastric cancer: a systematic review and validation study. *PloS One* 2013; **8**: e73683 [PMID: 24040025 doi: 10.1371/journal.pone.0073683]

47 **Pietrantonio F**, Braud F, Prat V, Perrone F, Pierotti MA, Gariboldi M, Fanetti G, Biondani P, Bellegrinelli A, Bossi I and Bartolomeo M. A review on biomarkers for prediction of treatment outcome in gastric cancer. *Anticancer Res* 2013; **33**: 1257-1266 [PMID: 23564763]

Comments (Reviewer #2)

The authors reviewed the up to date researches on the ontogenesis of gastric cancer. The manuscript might be helpful to clinicians to pick up a personalized cancer target therapy for gastric cancer patients. In order to do so, the author should include more data on clinical therapies which were designed according to well-known different molecular mechanisms of gastric cancer. The manuscript will be more persuasive if the self cited frequency can decline

Replies:

Regarding the Reviewer's comment on adding more data on clinical therapies according to molecular mechanisms of gastric cancer, we have added three results from recently reported clinical trials. The trials are results regarding Met monoclonal antibody, mTOR inhibitor and VEGFR monoclonal antibody. (Page 5, Line 11-16, Line 17-21, Line 25-27).

Notably, rilotumumab (a monoclonal antibody targeting the Met-HGF axis) yielded superior overall survival rates in a subgroup analysis of a phase II randomized study. Patients with high levels of Met expression were treated with either epirubicin, cisplatin, and capecitabine (ECX) in combination with rilotumumab or ECX alone in the first-line setting (11.1 vs. 5.7 months; HR = 0.29, 95% confidence interval [CI]: 0.11 - 0.76, p = 0.012)[13].

A phase III trial that evaluated supportive care in combination with either everolimus (an inhibitor of mTOR) or placebo for patients with advanced stage gastric cancer yielded negative results, where there was no significant difference in overall survival between the treatment arms (5.4 vs. 4.3 months for the everolimus and placebo groups, respectively)[16].

. Recently, the REGARD Trial reported that ramucirumab (a VEGFR-2 monoclonal antibody)

improved both progression-free survival and overall survival (vs. placebo)[19].

Regarding the self-cited frequency, we have excluded the previous reference number 39 and replaced it with a new reference paper regarding a systematic review on microRNA microarray studies (Page 6, Line 31-34). We also deleted the previous part on 'Reverse-phase protein lysate arrays'.

Recently, miR-21, miR-106b, miR-17, miR-18a and miR-20a were identified as the five most consistently identified miRNAs in screens of gastric cancer. The association between expression level of these miRNAs and clinicopathological features of gastric cancer was significant, and these miRNAs are potential diagnostic and/or prognostic markers that warrant further investigation[42].

Comments (Reviewer #3)

Overall a very good summary of the current state of molecular pathology and targeting in gastric cancer, but little new information. Couple of issues 1. title should reflect the subject matter as being gastric cancer and needs revision 2. There is an overemphasis on the role of molecular markers with regards to targeted drug therapy. Surgery, medical oncology and radiotherapy are part of the continuim of multimodality therapy. Molecular targeting should also include the role of each of these therapies in multimodality therapy. For example, molecular targeting may indicate that any surgery is not beneficial in some types of overexpression, but at the same time, extremely aggressive surgical and chemotherapy including palliative surgery and peritonectomy may be indicated in other tumours expressing other markers. Although the concept is still in its infancy, this ideal represents the holy grail of personalised therapy and should at least be discussed. Reference number 39 refers to an unpublished study (notes that it has been submitted) This data should be

excluded from the manuscript (last half of page 8 and ist half of page 9) as it has not been peer reviewed.

Replies:

Regarding the title concerning the subject matter as being gastric cancer, we have changed the title from “Personalized cancer targeted therapy” to “Personalized cancer targeted therapy in gastric cancer”. We appreciate the Reviewer for the sincere comment.

Regarding the overemphasis on the role of molecular markers and targeted drug therapy, we have added a new session in the conclusion on the role of surgery and radiotherapy in the era of personalized therapy (Page 8, Line 10-12).

Moreover, the roles of personalized surgery and radiotherapy should not be underestimated. Defining a subgroup of patients who benefit from radiotherapy and the potential interactions between patient characteristics and the efficacy of radiotherapy should be further explored in the future.

Regarding the comment on reference number 39, we have deleted the reference and also the part in the manuscript, and added a new reference paper regarding a systematic review on microRNA microarray studies (Page 6, Line 31-34).

Recently, miR-21, miR-106b, miR-17, miR-18a and miR-20a were identified as the five most consistently identified miRNAs in screens of gastric cancer. The association between expression level of these miRNAs and clinicopathological features of gastric cancer was significant, and these miRNAs are potential diagnostic and/or prognostic markers that warrant further investigation[42].