Dear Editor;

Please find the authors' responses to reviewers.

Name of Journal: *World Journal of Gastroenterology*

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Manuscript Type: Review

Title: Targeted therapies in gastric cancer and future perspectives

We would like to thank reviewers for their valuable criticisms. The manuscript and figure has been improved according to the suggestions of reviewers.

Reviewer 1:

Comment: #1. In 3.4. EGFR-Depent Tyrosine Kinase Inhibitors, line 4, the author described Src is involved in EGRC pathways------. What it's mean? It means EGFR pathway?

Authors reply: Src play a central role in progression of cancer. In different cancers the increased activation of Src was demonstrated. The activity of Src protein kinases may be increased in direct or indirect association to receptor dependent tyrosine kinases. Multiple receptor tyrosine kinases might effect the activity of Src kinases. These tyrosine kinases were belong to epidermal growth factor receptor, platelet derived growth factor receptor, fibroblast growth factor receptor, Her2/neu, hepatocyte growth factor receptor. EGFR was associated with Src, both acts in synergistic manner. EGFR activation was one of the activator signals for Src. Therefore; Src was defined in sub-heading of EGFR dependent tyrosine kinases.

Comment: #2. In 3.4. EGFR-Depent Tyrosine Kinase Inhibitors, is AZD0530 sacaratinib or saracatinib?

Authors reply: The word "sacaratinib" in part 3.4. EGFR-Depent Tyrosine Kinase Inhibitors and Table 2 was corrected as saracatinib (AZD0530).

Comment: #3. The authors should add AZD0530, Src, and dacomitinib to Fig. 1

Authors reply: AZD0530, Src, and dacomitinib were added to figure 1.

Comment: #4. In 5.1. Monoclonal Antibodies Blocking HGF-cMet Pathway, the authors described that in chemotherapy alone group, the Met-high subpopulation had poor prognosis and shorter OS compared to MET-low subpopulation. Why in ECX alone group, the subpopulation of patients with low MET staining rate by IHC had poor prognosis?

Authors reply: c-Met proto-oncogenes belong to a family of tyrosine kinase growth factor receptors. Amplification of c-met was evaluated in 128 patients with gastric cancer by using immunohistochemistry and Southern blot hybridization. In 46.1% of patients over-expression of c-*met* was observed. Over-expression of c-met was correlated significantly with depth of tumor invasion and lymph node metastasis. The survival rate of patients with over-expression of c-met had poorer survival compared to patients with no c-met over-expression (Ref: Cancer 1999;85:1894–902).

In the study the patients with high c-met staining and receiving ECX had poor prognosis compared to c-met low patients. There was mistake in the mentioned sentence, the low c-met should be high c-met.

In 5.1. Monoclonal Antibodies Blocking HGF-cMet Pathway part: the patients with low (< 50%) was corrected as high (> 50%). The correct sentence was as follows "In ECX alone group, the sub population of patients with high (>50%) MET staining rate by IHC had poor prognosis [93]. "

Comment: #5. The authors should add crizotinib to Fig. 1.

Authors reply: Crizotinib was added to figure 1.

Comment: #6. In 7.5. Insulin Like Growth Factor Inhibitors, there was no explanation about ganitumab.

Authors reply: The ganitumab was tested in phase 1 trial in 3 patients with gastric cancer. In this phase 1 study, the response rate of patients with gastric cancer did not indicated in detailed. Therefore, in patients with gastric cancer the available data about ganitumab was limited. The further studies of ganitumab related to activity against gastric cancer are awaited.

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