Editorial Office World Journal of Gastroenterology

RE: Revision of **18945**

Column: Topic highlight

Title:

Changing strategies for target therapy in gastric cancer

Dear Editor-in-chief

Thank you very much for providing us with an opportunity to improve our manuscript. We have carefully read all the comments made by the reviewers and revised the manuscript according to their suggestions. We believe that we have responded to all the comments and now the manuscript has been satisfactorily improved. I would appreciate your proceeding with the publication.

Sincerely yours,

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Reviewer(s)' Comments to Author:

1. Since the therapy targeting HER2 holds a predominant position, it's better to introduce it first. The paragraph transition between "introduction" and "Anti-angiogenesis" is not smooth.

Answer> Thank you for your opinion. We changed the order of contents, and introduced the therapy targeting HER2 first.

2. In the first sentence of the paragraph "Anti-angiogenesis" "In addition to angiogenesis and vascular permeability, VEGF-mediated signaling is known to contribute to tumorigenesis, tumor migration and metastasis", the authors haven't emphasized the function of anti-angiogenesis. Therefore, the subheading is not suitable, or they need to add some information.

Answer> Thank you for your opinion. We modified our manuscript as below:

Angiogenesis is a multistep process of new vasculature formation from the pre-existing blood vessel. The vascular endothelial growth factor (VEGF)-mediated signaling is known to play an essential role in the angiogenesis and vascular permeability. In addition to these roles, it also contributes to the tumorigenesis, tumor

migration and metastasis.

3. There is a spelling mistake, receptor tysosine kinases (RTKs) shoule be receptor tyrosine kinases (RTKs).

Answer> Thank you for your kind comment. We made a correction the spelling mistake.

4. When writing "Agents targeting ERBB family receptors", it's essential to describe the connection between ERBB family receptors and tumorigenesis, tumor migration and metastasis.

Answer> Thank you for your opinion. We modified our manuscript as below:

The results of activation of ERBB signaling pathway range from the tumorigenesis such as cell division and migration to differentiation and apoptosis, depending on cellular context. ERBB receptors are associated with development of various types of cancer by undergoing their alteration with several mechanisms. The best known example of the alteration is amplification of ERBB2 in a subset of breast cancers as well as in gastric, ovarian, and salivary cancers. In non small cell lung cancers (NSCLC), mutations in the tyrosine-kinase domain of EGFR have been found in a subset of patients. For the implication of the tumorigenesis, ERBB receptors have been

the candidates as targets for anti-cancer therapy. The ERBB receptors-targeted agents are summarized in table 1.

5. The authors have discussed the mechanisms of acquired resistance to trastuzumab in gastric cancer. They need to add content about occurrence rate of resistance.

Answer> Thank you for your opinion. We agree with your opinion. However, to the best of our knowledge, no study has reported the accurate occurrence rate of resistance. Therefore, we modified our manuscript as below:

Despite the proven efficacy of trastuzumab in the treatment of HER2-overexpressing gastric cancer, 12% of patients treated with chemotherapy plus trastuzumab were refractory to the therapy, and disease progression was eventually documented in 7 months from the initiation of the therapy, suggesting presence of primary resistance and development of acquired resistance against the antibody.

We have highlighted all of those revisions in the updated version of the manuscript.

Thank you.