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Title: ***Precision medicine in gastric cancer***

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ANSWERS TO REVIEWERS

Reviewer 1 (code: 02541859)

- There are roles of endoscopy and surgery including eradication of H. pylori infection in the management of gastric cancer. It would be great if you could touch on those particularly in conclusion.

- The authors added, in conclusion, the part concerning the eradication of *H. pylori* infection and the role of endoscopy and surgery in gastric cancer management.

The authors thank for the suggestions and excellent judgment regarding the scientific quality of the manuscript.

Reviewer 2 (code: 02993121)

- In epidemiology should be summarize as a figure for easy understanding.

- The authors added Figure 1 that summarizes the epidemiology of gastric cancer.

- More information in H. pylori and gastric cancer

- The authors added more information about the role of *H. pylori* in gastric cancer in the introduction and conclusion of the manuscript.

- Proper and new investigations

- The authors, in the manuscript, have described proper investigations, all relating to terminated clinical trials that have led to results and even clinical trials that are still under investigation. Also, other new investigations have been added in the section "Biomarkers

for targeted therapy", paragraph "EGFR signaling pathway", related to the use of trastuzumab emtansine, pyrotinib, nimotuzumab and, in the paragraph "PARP signaling pathway".

– More review for surgical treatments. AI and gastric cancer eg. robot surgery.

- The authors added more references on surgical treatments and also comments on robotic surgery in the paragraph "Biomarkers for targeted therapy" and conclusion.

The authors thank for the suggestions and good judgment regarding the scientific quality of the manuscript.

Reviewer 3 (code 02904061)

- *Update the data about the incidence and mortality rate of gastric cancer in the "EPIDEMIOLOGY OF GC" part.*

- The authors have updated the data on the incidence and mortality of gastric cancer according to the Global Cancer Statistic of 2018.

- When discuss the EBV-positive tumors in "MOLECULAR CHARACTERIZATION OF GC" part, the term "PDL-1","PDL-2" should be corrected as "PD-L1" and "PD-L2".

- The authors corrected the terms PDL-1 and PDL-2 with PD-L1 and PD-L2 in each section of the manuscript.

- In the end of page 10, the description "gefitinib and erlotinib, have shown efficacy in EGFR-amplified tumors." and "Mutations of EGFR confer resistance to these drugs" are inappropriate. These two drugs have been approved as standard first-line therapy for EGFR sensitive mutation patients in non-small cell lung cancer.

- In response to the comment on the phrase "Mutations of EGFR confer resistance to these drugs", as inappropriate, the authors report that these drugs, gefitinib, and erlotinib, first-generation TKI inhibitors, while showing good results with an improved progression-free survival (PFS), compared to standard chemotherapy in advanced NSLC patients, cause resistance after about 9-14 months from treatment due to a T790M EGFR mutation. This mutation increases the ATP binding affinity but decreases the binding affinity to drugs, thus reducing the power of any ATP competitor [**Yun CH**, Mengwasser KE, Toms AV,

Woo MS, Greulich H, Wong KK, Meyerson M, Eck MJ. *Proc Natl Acad Sci USA*. 2008; **105**: 2070–2075]. This mechanism is one of the most common among those involved in acquired resistance, having been highlighted in more than 50% of patients treated with first-generation TKI (erlotinib or gefitinib) [**Takeda M**, Nakagawa K. *Inter J Mol Sci* 2019, **20**: 146].

Instead, two references were added relating to the sentence "Mutations of EGFR confer resistance to these drugs".

- The paragraphing of each part is not clear enough which is easy to make confusion. For example, in page 9, the description of ACRG classification system was mixed with the description of subtype "CIN", which is one part of TCGA classification system.

- The final part of the paragraph "Molecular characterization of GC" describes the differences between the two classifications for which the subgroups of both classifications are present (TCGA, ACRG).

- The same problem exists in page 11. 5.In the section of "Biomarkers for diagnosis and prediction", the discussion should focus on gastric cancer. For example, in page 11, the predictive value of TP53 mutation in GC should be mentioned but not just describe its significance in human tumors. In the section discussing target therapy, the clinical evidence is relative insufficient. As a review, the demonstration of the advances should be more comprehensive.

- As for the GC, there is no well-established clinical significance between the TP53 status and the outcome of the patients. Recent studies have integrated the mutational status of TP53 and other genetic alterations to define subpopulations of GC to identify clinical relevance. This part was added in the paragraph "TP53 signaling pathway".

- For example, for the EGFR signal pathway, TDM-1 is an important agent for anti-HER2 therapy. Although the clinical trial in gastric cancer (GATSBY) was failed, it should be mentioned. Pyrotinib is an oral tyrosine kinase inhibitor targeting both EGFR and HER-2 receptors. A phase I study of pyrotinib in patients with HER2-positive advanced gastric cancer is recruiting. Two phase II clinical trials for Nimotuzumab, which is the first humanized EGFR monoclonal antibody, has been published.

- The authors mentioned the clinical trial GATSBY, the studies with pyrotinib and the two clinical studies with nimotuzumab in the paragraph "EGFR signaling pathway" and in Table 1.

-Beyond the signal pathway mentioned in this paper, the exploration of parp inhibitor in gastric cancer is ongoing, which is also a promising agent.

- The authors added a paragraph on PARP inhibitors in the section "Biomarkers for targeted therapy". The relative clinical trials were added in Table 1.

- Increase more context about the outlook and expectations of target therapy in Gastric cancer in the conclusion part.

- The authors described the outlook and expectations of targeted therapy in the conclusion of the manuscript.

- The language need to be more concise.

- The authors believe that the language is concise. In the treatment of molecular markers as targets of precision therapies, to each description of a clinical study mentioned corresponds to the results.

The authors thank for the suggestions and good judgment regarding the scientific quality of the manuscript.

Reviewer 4 (code: 02941657)

- On the part of conclusion, the author should add the author's opinion or suggestion on which group of population or stage who should been tested for each target biomarkers. In case of non operable treatment, how the target can be precisely tested.

The authors have expanded the conclusion by pointing out which groups of patients with GC can benefit from targeted therapy. In the case of non-resectable patients, the target will always be tested on biopsy.

The authors thank for the suggestions and good judgment regarding the scientific quality of the manuscript.