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Review Comments-reviewer A

- 1) First, the title needs to indicate HER2- advanced or metastatic GC patients, efficacy and safety, and the clinical research design of this study, i.e., a retrospective cohort study.

Answer: We have modified our title to “Anti-PD-1 plus anti-angiogenesis combined with chemotherapy in patients with HER2-negative advanced or metastatic gastric cancer: a multi-institutional retrospective study” as advised.

- 2) Second, the abstract needs some revisions. The background did not explain why the Anti-PD-1 + anti-angiogenesis + chemotherapy is potentially safe and effective, the clinical needs for this research focus, and what the knowledge gap is on this research focus. The methods need to describe the inclusion of subjects, the assessment of baseline clinical factors, follow up, and outcome measurements of efficacy and safety. The results need to first briefly summarize the clinical characteristics of the study sample and the safety outcomes should also be reported. The conclusion could be more detailed for the clinical implications of the findings.

Answer: We have modified our text as advised (see Page 2, line 38-40, 46-47, Page 3, line 58, Page 7, line 214-215)

- 3) Third, in the introduction of the main text, the authors need to further explain why “there is still lack of sufficient evidence about efficacy and safety”. I suggest the authors to have detailed comments on the limitations and knowledge gaps of prior studies to indicate the clinical needs for the current analysis. An important concern is the safety of the Anti-PD-1 + anti-angiogenesis + chemotherapy, the authors need a detailed review on this and explain why the combination of the three is safe.

Answer: We have modified our text as advised (see Page 4, line 110-111, 114-115, 117-118).

- 4) Fourth, in the methodology of the main text, please describe the clinical research design, sample size estimation, efficacy outcomes, and detailed procedures of follow up. In statistics, please specify the analysis for “Exploratory analysis of the association between clinical response and PD-L1 expression, TMB, or TIME was conducted”, ensure $P < 0.05$ is two-sided, and the descriptive statistics of the baseline clinical characteristics.

Answer: We have modified our text as advised (see Page 5, line 131, 133-137, 141, and Page 7, line 193).

- 5) Finally, please consider to cite the below related papers: 1. Chen KB, Wu ZW, Huang Y, Kang MX, Lin LL, Jiang SS, Zhang H, Huang YJ, Chen L. Successful outcome of neoadjuvant PD-1 blockade, VEGFR-2 inhibitor plus chemotherapy for potentially unresectable esophagogastric junctional squamous cell carcinoma: a case report. *Transl Cancer Res* 2022;11(9):3329-3336. doi: 10.21037/tcr-22-789. 2. Mi L, Ji X, Ji J. Prognostic biomarker in advanced gastric cancer. *Transl Gastrointest Cancer* 2016;5(1):16-29. doi: 10.3978/j.issn.2224-4778.2016.01.02. 3. Yang

D, Hendifar A, Lenz C, Togawa K, Lenz F, Lurje G, Pohl A, Winder T, Ning Y, Groshen S, Lenz H. Survival of metastatic gastric cancer: Significance of age, sex and race/ethnicity. *J Gastrointest Oncol.* 2011;2(2):77-84. DOI:10.3978/j.issn.2078-6891.2010.025.

Answers: Thank you so much for your valuable suggestions. We have cited another related paper: Li S, Yu W, Xie F, Luo H, Liu Z, Lv W, Shi D, Yu D, Gao P, Chen C, Wei M, Zhou W, Wang J, Zhao Z, Dai X, Xu Q, Zhang X, Huang M, Huang K, Wang J, Li J, Sheng L, Liu L. Neoadjuvant therapy with immune checkpoint blockade, antiangiogenesis, and chemotherapy for locally advanced gastric cancer. *Nat Commun.* 2023 Jan 3;14(1):8. doi: 10.1038/s41467-022-35431-x.

Review Comments-reviewer B

1. Ethical Statement

a) We suggest to remove relevant regulatory.

Suggested wording: The study was approved by the Ethics Committee of Gusu School of Nanjing Medical University (No. K-2021-016-H01) and conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines.

b) In the main text, the statement should be the same as the footnote, please revise.

c) Version of the Declaration of Helsinki should be added.

Suggested wording: and conducted in accordance with the Declaration of Helsinki (as revised in 2013) and the International Conference on Harmonization Good Clinical Practice guidelines.

Answer: Thank you for your suggestions. We have revised the manuscript accordingly (See Page 5, line 141-145, Page 13, line 402-405).

2. Patient Source

Please also indicate the patient source in the method. Which hospital did the patient come from?

Answer: Thank you for your suggestions. We have revised the manuscript accordingly (See Page 5, line 132-134).

3. Figure 2

The figure 2 you sent to us is different from the one in the main text, please confirm which is correct.

Main text:

Answer: Sorry. This one is correct and we have put the Figure 2-revised in the file.

The figure you sent:

4. Figure 3

Please explain the meaning of “*” in the legend.

Answer: Thank you for your suggestions. We have revised the manuscript accordingly (See Page 21, line 538).

5. Figure 4

Please explain the meaning of “*, **” in the legend.

Answer: Thank you for your suggestions. We have revised the manuscript accordingly (See Page 22, line 546-547).

6. Figure S6

Please provide the scale bar in the figure or magnification for figure S6C in the legend.

Answer: Thank you for your suggestions. We have revised the manuscript accordingly (See Page 38, line 44).

7. References/Citations

a) Please double-check if more studies should be cited as you mentioned “studies”.
OR use “study” rather than “studies”.

Answer: Thank you for your suggestions. We have revised the manuscript accordingly (See Page 11, line 326,328)

b) Please double-check if citations should be added as you mentioned “studies”.
*Please note that the references should be cited in order of their appearance in the text. If the studies are not included in the reference list, please also update the current version.

Answer: Thank you for your suggestions. Here, previous studies means reference 24,25,26,27 that have been cited in the following context.