Format for ANSWERING REVIEWERS

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Dear Editor,

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Title: Tumor progression-dependent angiogenesis in gastric cancer and its potential application

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Name of Journal: *World Journal of Gastroenterology Oncology*

Manuscript ID: 46230

Reviewers' comments:

Thank you for the insightful review and excellent suggestions from the anonymous reviewers of the manuscript ID:46230, entitled " Tumor progression-dependent angiogenesis in gastric cancer and its potential application ". The revisions requested by the reviewers are now complete. The reviewer's criticisms, suggestions and comments have been addressed and the manuscript revised accordingly. The changes are indicated by the lines/page numbers and colored font. We hope that you and the reviewer will be satisfied with the revised manuscript. Moreover, the article has been revised by NPG Language Editing. Thanks again for your valuable suggestions. I look forward to your favorable reply.

Reviewer #1: This review article overviews the tumor microenvironment and angiogenesis-related molecules. It is well written and comprehensive. Table 1 may be re-checked in terms of targets of anti-angiogenic drugs.

Author Response 1:

Thanks for your suggestion. I have modified and re-checked in the terms of targets of anti-angiogenic drugs in the Table 1. (line 1, page 20- line 21, page 21)

Reviewer #2: This is a comprehensive review. However, some issues have to be addressed:

1). It has been suggested that the anti-angiogenesis strategy can be ineffective due to the metabolism change and stemness of malignant cells lacking oxygen supply in various tumors. Various clinical trials have not shown a statistically significant improvement in survival regarding this strategy. The author seems to have merely written the good and promising aspects while neglecting the obstacles in improving this strategy. Thus this could be a biased review and even misleading.

Author Response 2-1

Thanks for your suggestion. I have modified Table 1 section and added phase III clinical trials sentence in the Part II and Table 2 section. (line 1, page 20) (line 2, page 22) (line 18, page 24) (line 22, page 26) (line 22, page 27).

Indeed, Due to the metabolic changes and stemness of malignant cells lacking oxygen supply in various tumors, tumors appear to escape antiangiogenic therapy within a short time owing to the manipulation of alternative pathways [1], vasculogenic imitation [2] and recruitment of bone marrow-derived cells [3, 4] Various clinical trials have not shown a statistically significant extension of survival outcomes. Thus, most of the antiangiogenesis strategy can be ineffective. In phase III clinical trials, only ramucirumab (anti-VEGFR) and apatinib (VEGFR-TKI) have reported to improve ORR and prolong OS and PFS outcomes when used as a 2nd-line regimen combined with chemotherapy treatment in advanced GC. Moreover, there are some limitations in this study. This review only included phase III clinical trials published in English. Previous studies have found that the combination of antiangiogenic agents with chemotherapy may be beneficial for advanced GC in OS, but potential publication bias should be considered when construing these results. To reduce possible publication bias, we tried to search in multiple databases. Nevertheless, some restrictions were present in this systemic review and statistical analysis (e.g., meta-analysis)[5, 6] such as the small size of included studies, multiple drugs implemented and the high heterogeneity between different studies. Therefore, a larger cohort size, more standardized research and high statistical quality should be implemented in future studies to identify patients who would most likely benefit from antiangiogenic treatment. Thus, this review will provide basic (tumor angiogenesis) and clinical (antiangiogenic drugs) research for the survey of the management of GC treatments.

2). The author cited lots of literature, while came up with few of his/her own comments/points.

Author Response 2-2

Thanks for your suggestion. I have added my own comments/points sentence in the Part VI and Part V section. (line 16, page 31) (line 10, page 33) (line 26, page 33) (line 1, page 34) (line 11, page 34) (line 16, page 34).

Although several phase III clinical trials have reported positive results, the tumor develops several ways of escaping treatment and rapidly activating angiogenic pathways in GC. This may partly fail to translate to a survival benefit of antiangiogenic drugs in management of GC treatments. Therefore, the GC patients should be selected, and angiogenic factors should be detected before the administration of antiangiogenic drugs. Individual angiogenic profiling according to an individual's genetic background remain a problem that need to be addressed.

3). Some somehow irrelevant parts (e.g., cell-cell adhesion, which is actually the major process in EMT/MET) could be removed.

Author Response 2-3

Thanks for your suggestion. I have removed this sentence (e.g., cell-cell adhesion) in the Table 1 and the Part I section.

Sincerely,

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