

Format for ANSWERING REVIEWERS



March 21, 2015

Dear Editor,

We appreciate the opportunity to reply to the thoughtful review on our manuscript. Please find enclosed the edited manuscript in Word format (file name: 16551-edited.doc), which was revised according to the reviewers' suggestions.

Title: Chemotherapy beyond second-line in advanced gastric cancer

Author: Sung Min Kim, Se Hoon Park

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 16551

The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated including Core Tip and Keywords.
2. Revision has been made according to the suggestions of the reviewer: See next pages...
3. English has been reviewed and corrected by a professional English Editing Service.
4. Overlapping and/or similar sentences have been checked by CrossCheck, and revised the manuscript accordingly. Please note that the majority of the potential overlapping text are derived from the reference articles, or from the author's previous publications.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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(1) Reviewer one:

This is a well written systematic review and meta-analysis paper concerning the impact of third-and subsequent lines of chemotherapy on survival and quality of life in patients with advanced gastric cancer. The authors give the extensive overview about the present outlook of the studies related to prospective phase III trials in the second-line treatment of gastric cancer and consider the importance to offer further chemotherapy for advanced gastric cancer. The authors have reviewed and analyzed a sufficient amount of literature (31 references). The review is supplied with one Table and one Figure. However, it would be useful to discuss also the influence of genetic factors and molecular characteristics of advanced gastric cancer on improvement of chemotherapy of cancer (e. g. The Cancer Genome Atlas Network authors. Comprehensive Molecular Characterization of Gastric Adenocarcinoma. Online July 23, 2014. DOI:10.1038/nature13480).

-> Thanks for an encouraging comment. We added description of TCGA gastric adenocarcinoma project as "In addition, researchers have focused their efforts on defining specific predictive factors of responsiveness to certain types of chemotherapy and targeted therapy. The Cancer Genome Atlas (TCGA) research network, for example, reported a comprehensive molecular evaluation of 295 gastric adenocarcinomas [28], and proposed four distinct molecular subtypes: (1) tumors positive for Epstein-Barr virus, (2) microsatellite unstable tumors, (3) genomically stable tumors, and (4) tumors with chromosomal instability."

(2) Reviewer two:

The authors performed a literature review of the current status of chemotherapy beyond 2nd line in treatment of advanced gastric cancer. Personally, I believe that most of the drugs that are used as 3rd line or below are probably new drugs undergoing phase I/II studies so this is very subjected to institutional research etc. Perhaps the focus of the article could be on 2nd line therapy or beyond and this may be more useful for the average reader.

-> You are absolutely true and we cannot agree more. However, please consider that this article reviews available evidences and literature to date. Mere listing of new drugs on early phase development may seem too redundant as we believe most of them would be proved to be inactive.

(3) Unpublished data are best not used as these have not been subjected to peer-review and the accuracy of data is not known.

-> Thanks for the thoughtful comment. We decided to remove the unnecessary description of our unpublished data including Figure 1.

4) For Targeted therapy, I believe some institutions are using as 1st or 2nd line so perhaps these should be discussed under a separate heading

-> There may be institutions where targeted therapy is used as first or second-line setting. However, you may agree the practice is based solely on anecdotal reasons. Considering the main focus of the present article is on chemotherapy beyond second-line, and we based only evidences available, it seems inappropriate to describe first-line use of targeted therapy in patients with gastric cancer.

(5) English language needs editing

-> English has been reviewed and corrected by a professional English Editing Service.

(6) Reviewer three:

This review entitles "Chemotherapy beyond second-line in advanced gastric cancer" is well-written and

comprehensive review about this subject. I have one comment – I feel that discussion is a little redundant. Please shorten the discussion.

-> Thanks to your comment, we revised and condensed the discussion.