

March 18, 2015



Dear Editor,

Please find enclosed the edited manuscript in Word format contained in two files named 17099-edited(clean copy).doc and 17099-edited(marked copy).doc

Title: Second-line treatments for advanced gastric cancer: Interpreting outcomes by network meta-analysis

Authors: Brigitta Badiani, Dario Maratea, Andrea Messori

Name of Journal: *World Journal of Clinical Oncology*

ESPS Manuscript NO: 17099

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

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers; please refer to our detailed response describe in the table below.

3 References and typesetting were corrected

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

Sincerely yours,

A handwritten signature in grey ink, appearing to read 'AM'.

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POINT-BY-POINT RESPONSE TO REVIEWERS

1) REVIEWER 2446471

POINT 1: In this network meta-analysis study, the author investigated 21 direct or indirect comparisons of overall survival of total of 2298 advanced gastric cancer patients. The result shows that there are statistically significant differences in OS between paclitaxel vs BSC and ramucirumab +paclitaxel vs BSC groups, indicating that both paclitaxel and ramucirumab +paclitaxel determine a significant prolongation in survival in comparison with BSC. This has significance for the second-line drugs treatment of gastric cancer.

AUTHORS' RESPONSE: We confirm that the comments by this reviewer reflect the main message conveyed by our study.

POINT 2: The manuscript could be enhanced if the author could give more detailed patients information and included it into the analysis such as the races and age of the patients in each study.

AUTHORS' RESPONSE: This additional information on included patients has been incorporated in our revised paper.

POINT 3: The legend of Figure 3 indicates that there are 8 ranks, however, only see rank 1 to 7 was shown. Please check for consistence.

AUTHORS' RESPONSE: Thank you very much for identifying this error that we have corrected..

2) REVIEWER 68472

POINT 1: The authors evaluate second-line treatment modalities for advanced gastric cancer using a Bayesian network meta-analysis. They included 21 direct or indirect comparisons in the meta-analysis. The difference in OS between paclitaxel vs BSC and ramucirumab + paclitaxel vs BSC was statistically significant, while the other comparisons showed no statistical difference. They concluded that both paclitaxel and ramucirumab+paclitaxel are associated with a significant prolongation in survival in comparison with BSC.

AUTHORS' RESPONSE: We confirm that the comments by this reviewer reflect the main message conveyed by our study.

POINT 2 (Specific comments): Overall, the presentation of the topic is a little confused.

AUTHORS' RESPONSE: We agree that several points of our overall presentation required some improvement, particularly in the description of the methods.

POINT 3 (Specific comments): The English language should be improved.

AUTHORS' RESPONSE: We have checked the quality of the language and we have improved it by revising several sentences.

POINT 4 (Specific comments): The chemotherapy regimens were not uniform in all patients and studies that can be a confusing issue.

AUTHORS' RESPONSE: We have mentioned this point in the Discussion of the revised paper.

POINT 5 (Specific comments): The significance values should be added in table 1, Figure 2.

AUTHORS' RESPONSE: This correction has been made as indicated by the Reviewer.

Point 6 (Specific comments): Further prospective randomized studies are needed to establish the clear-cut clinical impact of the second line treatment regimens.

AUTHORS' RESPONSE: We have mentioned this point in our revised Discussion.

3) REVIEWER 111771

POINT 1: The paper is about an interesting topic. The methods are sound, although the authors should consider to add the quality assessment of each trial, as recommended by Cochrane guidelines.

AUTHORS' RESPONSE: We have added a new section in which we describe the tool we used for this purpose and we present the results generated from the analysis of the individual studies.

POINT 2: Reference 11 is mentioned in the text but I cannot see it.

AUTHORS' RESPONSE: We apologise for this error. The erroneous citation to reference 11 has been corrected by citing the pertinent reference (i.e. Reference 7)

4) REVIEWER 2936069

POINT#1: Authors of this article carried out a Bayesian network meta-analysis to evaluate second-line treatments for advance gastric cancer, but the design of the relevant idea has been published by Plos one(2014.9).

AUTHORS' RESPONSE: We checked on PubMed all meta-analyses recently published in PLoS One and we presumed that the article to which the reviewer wanted to make reference is the following: Iacovelli R, Pietrantonio F, Farcomeni A, Maggi C, Palazzo A, et al. (2014) Chemotherapy or Targeted Therapy as Second-Line Treatment of Advanced Gastric Cancer. A Systematic Review and Meta-Analysis of Published Studies. PLoS ONE 9(9): e108940. doi:10.1371/journal.pone.0108940.

As pointed out by Goggins (Goggins A. Repeated meta-analyses are both worthy and to be encouraged. BMJ 2013;347:f5508), by Mohler (Moher D. The problem of duplicate systematic reviews. BMJ 2013;347:f5040), and, to a lesser degree, by Siontis et al. (Siontis KC Hernandez-Boussard T, Ioannidis JPA. Overlapping meta-analyses on the same topic: survey of published studies. BMJ 2013;347:f4501), publishing more than one meta-analysis on the same topic is perfectly acceptable (and even useful) particularly when one or more of the following criteria are met:

- a) when the time intervals covered by the new vs the previous meta-analysis are different; in this case, our meta-analysis was updated as of February 2015 while the study by Iacovelli was updated until February 2014
- b) when the number of included studies is different: in this case, our meta-analysis included 7 randomized controlled studies (RCT) while the one by Iacovelli included 5 RCTs.
- c) when the number of studies focused on an innovative treatment is different; in this case, our meta-analysis included two RCTs focused on ramucirumab while the one by Iacovelli included only one RCT focused on ramucirumab.
- d) when the type of meta-analysis is different; in this case, our meta-analysis was an

“all-in-one” network meta-analysis (aimed at evaluating all combinations of direct and indirect comparisons) while the meta-analysis by Iacovelli was a traditional pairwise meta-analysis (in which all active treatments were compared vs best supportive care, and no comparison between active agents was made).

- e) when the end-point is different; in this case, our meta-analysis was based on an absolute outcome measure (duration of survival) while the one by Iacovelli was based only on a relative outcome measure (hazard ratio); this importance of this distinction has been emphasised by King et al. (King NB, Harper S, Young ME. Use of relative and absolute effect measures in reporting health inequalities: structured review. BMJ 2012; 345: e5774).

In our view, the above six points represent a convincing reason why our meta-analysis can be of interest despite the previous publication of the article by Iacovelli et al.

POINT#2: This article was rejected because of Lack of innovation.

AUTHORS' RESPONSE: It is quite unusual that a reviewer does not make a simple recommendation on whether an article should be accepted, revised or rejected, but directly states which editorial decision has been made.

POINT#3: The authors used only one search engine (PubMed), while the PRISMA guideline (see for details <http://ijphjournal.it/article/view/5768>) states a systematic review and meta-analysis require at least two databases.

AUTHORS' RESPONSE: This observation is correct. We added a second search engine (EMBASE) to our literature search. However, no further studies that met the inclusion criteria of our analysis were identified.

POINT#4: A quality assessment is missing. Authors can use the Newcastle-Ottawa scale to assess the methodological quality of studies included in this meta,

AUTHORS' RESPONSE: This observation is correct. We have employed a scale for assessing the methodological quality of the studies included in our analysis.

POINT#5: in addition , the quality assessment must be used for a sensitivity analysis, dividing the studies which included in this meta into good and low quality studies.

AUTHORS' RESPONSE: Dividing the studies included a meta-analysis into good and low quality studies for the purpose of conducting a sensitivity analysis can be useful particular when a certain number of studies are classified in the first category and a similar number of other studies are classified in the second category. In the case of our analysis, all clinical studies fell in a single category. For this reason, the sensitivity analysis was not carried out.

POINT#6: This article need a grat deal of language polishing.

AUTHORS' RESPONSE: We have improved the quality of the language.

5) REVIEWER 67544

No comments

6) REVIEWER 3002166

No comments