Dr. Xue-Jiao Wang
Science Editor
World Journal of Gastroenterology

April 16, 2018

RE: Manuscript 38796 "New therapeutic options opened by the molecular classification of gastric cancer" by Chivu-Economescu M. et al.

Dear Dr. Xue-Jiao Wang,

Thank you and the reviewers for the careful evaluation of the above referenced manuscript. We are very grateful for your comments and suggestions, which were valuable in improving the quality of our manuscript. We have considered them carefully and addressed them in full in the revised manuscript. All the changes made in the revised manuscript are highlighted and explained in an itemized, point-by-point response to the **Reviewers Comments** (see enclosed).

We updated Table 1 according to Guidelines and Requirements for Manuscript Revision and the Format, however we think that the table is difficult to follow in this form without any inside lines or color shadow.

We did not add a language verification certificate because both reviewers said "language is perfectly correct" (R1) and "the language is correct" (R2).

We hope that the revised manuscript is now acceptable for publication in World Journal of Gastroenterology.

We look forward to hearing from you.

Sincerely,

Mihaela Chivu-Economescu.

Response to Reviewers Comments (shown in italics):

Reviewer #1:

Comments:
I have noticed one editorial mistake - line 6 from the bottom of the page 6. "…. genetic alteration CAN BE MAY HAVE..... (can be or may have) ".

Response: We are very grateful for your comments to our manuscript. We also thank you for the observation. The text was properly corrected (page 7, highlighted).

Reviewer #2:

We thank you for your comments and suggestions to our manuscript.
"…there are some points that should be addressed before publication. 1. I have not found in the manuscript the literature about the peritoneal spread of stomach cancer which occurs very often and affects the way of treatment. I'm suggesting the literature below. M. Kanda and Y. Kodera, "Molecular mechanisms of peritoneal dissemination in gastric cancer," World J. Gastroenterol., vol. 22, no. 30, pp. 6829–6840, Aug. 2016. 2. I have not found in the manuscript the literature/information about signet ring adenocacinoma which is very resistant to all therapies and only early surgery gives a chance to cure. I suggest literature below. T. Voron, M. Messager, A. Duhamel, J. Lefevre, J. Y. Mabrut, D. Goere, B. Meunier, C. Brigand, A. Hamy, O. Glehen, C. Mariette, and F. Paye, "Is signet-ring cell carcinoma a specific entity among gastric cancers?," Gastric Cancer, vol. 19, no. 4, pp. 1027–1040, 2016. 3. I have not found in the manuscript the literature/information about early onset gastric cancers, where is postulated that it is the best model of gastric cancerogenesis/ molecular changes leading to cancer, and the best model for testing the treatment options.I suggest literature below. M. Skierucha, A. N. Milne, G. J. A. Offerhaus, W. P. Polkowski, R. Maciejewski, and R. Sitarz, "Molecular alterations in gastric cancer with special reference to the early-onset subtype.," World J. Gastroenterol., vol. 22, no. 8, pp. 2460–2474, Feb. 2016. I support publication of the presented article in the WJG. Thank you for your choice me as a reviewer."

Response: Thank you for your comments and appreciations. We have referred to literatures and papers and included information about early onset gastric cancer, peritoneal dissemination and signet ring adenocarcinoma as suggested inside of the genomic stable gastric carcinoma, due to their diffuse type and CDH1 mutations. We integrated the new data in two paragraphs at page 8 and 24 (highlighted):

"E-cadherin, which is encoded by the CDH1 gene, is an adhesion molecule widely involved in carcinogenesis. E-cadherin deficiency has been linked to early tumor initiation in a large proportion of diffuse GC like signet ring adenocarcinoma, which is very resisting to all therapies, and hereditary diffuse GC, both with very poor survival[25, 26]." (page 8)

*"*This form of cancer includes early-onset gastric carcinoma's and, due its association with some early triggers that impair genome stability, could be considered the best model of gastric

cancerogenesis and the best model for testing the new treatment options, in the pressing need for new therapeutic for diffuse GC[81]. One key finding was that the MSS/EMT subtype showed a higher recurrence rate with peritoneal seeding, and very poor survival compared to other subtypes. EMT is an important mechanism in tissue fibrosis that is characterized by the loss of cell–cell adhesion. Various studies have indicated transforming growth factor (TGF)-b1, secreted by gastric cancer cells and cancer-associated fibroblasts (CAFs), as common initiator of EMT[82, 83]. Saito H et al[84] successfully used tranilast, an inhibitor of TGF-b/Smad pathway to inhibit interactions between cancer cells and stroma, preventing fibrous tumor establishment represented by peritoneal dissemination". (page 24)