

Fredensborg, November 17, 2013

Jin-Lei Wang, Director; Editorial Office  
World Journal of Gastroenterology  
Baishideng Publishing Group Co., Limited

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name 131117-5495-edited). As requested in your e-mail dated November 4, 2013 all the changes made are highlighted in the manuscript.

**Title:**The role of HER2 in gastric cancer: Biological and pharmacological aspects

**Author:** Jan Trøst Jørgensen

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 5495

Thank you very much for the review comments. The manuscript has now been improved according to the suggestions by reviewers. Below please find my reply to issues raised by the three reviewers.

**Reviewer code: ? (Date reviewed:2013-09-22 18:58)**

**Comment 1:** *“The Title and abstract are clear and accurate. Regarding figure 3: The testing algorithm for HER2 status in gastric cancer is controversial because in the TOGA trial virtually everyone had both tests done. The author points this out in the text, but does not mention the controversy (ie some have advocated a different algorithm than is depicted in Fig 3 that includes reflex FISH testing on all non-positive IHC results). At a minimum, this should be addressed, and consideration should be given to including a figure depicting the other algorithm.”*

**Answer to Comment 1:** *It is a very relevant point to address as the testing algorithm for HER2 status in gastric cancer is not as clear as we know it from breast cancer. An additional figure (Figure 4) has been added showing the algorithm suggested by US FDA. Further, the discussion of reflex FISH testing on all non-positive IHC results has also been added on page 10.*

**Reviewer code: 00057485**

**Comment 1:** *“Jorgensen provides a review of HER2 directed treatments undergoing active study in the setting of gastric cancer. The review is detailed, well rounded and clear. The author has strong mastery of describing the scientific methods, clinical trials and future drugs in development. I would suggest (for the ready not familiar with HER2) some basic diagrams cell membrane drug interaction.”*

**Answer to Comment 1:** *The suggestion about diagrams showing the drug-receptor/pathway interaction is excellent and we have tried to draw a couple using power point, but unfortunately without success. Instead I have made a short table (Table 3), which gives a brief overview of the compounds and their targets.*

**Reviewer code: 00208526**

**Comment 1:** *“The Role of HER2 in Gastric Cancer- Biological and Pharmacological Aspects This review focuses on the status of HER2 in gastric and gastroesophageal junction (GEJ) cancer. The authors do a really good job of relaying*

important information about HER2 in these types of cancers. In particular, the authors focus on the following topics: 1) HER2 screening 2) Variability of HER2 overexpression 3) HER2 and Lauren histological classification 4) The ToGA trial 5) HER2 and prognosis 6) Potential HER2 targeted drugs that can be used clinically Strengths: The article represents viewpoints fairly and lacks biased opinions. The authors also summarize a broad range of studies that have been conducted to examine HER2 and its implication in gastric and GEJ cancers. Overall, the review stays focused on important research without going into unnecessary detail. Weaknesses/ minor concerns: 1. Weak abstract: the abstract fails to tell the reader about the main focus of the article, which is to discuss the current status of HER2 in gastric and GEJ cancer and future directions."

**Answer to Comment 1:** Minor changes have been made to the abstract emphasizing the main focus of the article. Further, a short "Core Tip" has been included on page 3.

**Comment 2:** "Review contains an excessive amount of information about the ToGA trial"

**Answer to Comment 2:** Some few sentences have been deleted in order to make the paragraph shorter. However, one of the other reviewers asked for an expansion of the discussion of HER2 testing algorithm, so altogether the status is more or less status quo.

**Comments 3:** "Some of the figures are somewhat vague a. Figure 3 has a typo (FISH -; not FISH ÷) b. Table 2 needs footnote for N; it is also presented twice (once on page 28 and again on page 29)."

**Answer to Comment 3:** The above described deficiencies have been corrected.

**Comments 4:** "Poor sentence structure and several grammatical errors/typos within the review. Some Examples: a. "Examples of a positive HER2 status in gastric cancer by IHC and FISH are shown Figure 1." b. "In table 1 is shown the interpretation..." c. A large interstudy variation of the prevalence of HER2 overexpression in gastric cancer is seen." d. "This survey also looked at HER2 amplification, however, here the number of patients were somewhat lower. The prevalence estimate was here based on 1,597 patients..." e. "A number of studies has shown..." f. "...was found to be statistical significantly higher..." g. "The ToGA trial must be regarded as a landmark in the treatment of gastric cancer, not only did the study show that trastuzumab is effective in treating HER2 overexpressing gastric cancer but it also gave us important information on the pathophysiological characteristics of the disease."

**Answer to Comment 4:** The different linguistic issues have been resolved.

**Reviewer code: 00505438**

**Comment 1:** "This is an interesting paper reviewing the role of HER 2 in gastric cancer. However this paper spends a large amount of time summarising previous publications, without really giving new information or performing any true analysis of data. Similar systematic review was performed and published by Chua and Merrett Clinico-pathologic factors associated with HER2-positive gastric cancer and its impact on survival outcomes--a systematic review. *Int J Cancer*. 2012 Jun 15;130(12):2845-56 is not referenced."

**Answer to Comment 1:** The literature study by Chua and Merrett (*Int J Cancer* 2012 Jun 15; 130 812:2845-56) has now been included as a reference and is briefly discussed on page 10 (ref. 33). The reason why I might have missed it is that it seems to have been published after the study by Jørgensen and Hersom (*J Cancer* 2012; 3: 137-44).

**Review Comment 2:** "The association between HER 2 overexpression and prognosis in intestinal type gastric cancers is only mentioned obliquely and should be emphasised."

**Answer to Comment 2:** The discussion on the association between the intestinal subtype and prognosis and HER2 has been further emphasized on page 10.

**Review Comment 3:** "The details on different drugs are perhaps too detailed for this journal."

**Answer to Comment 3:** *I think the development of trastuzumab for treatment of gastric cancer was a landmark as it was the first targeted compound to show efficacy in this disease. In my opinion it is very positive to see that a number of new follow-up compounds are now under development. Based on searches in different databases, including ClinicalTrials.gov, I have given an up-to-date status on where we are with these compounds and would like to keep this part of the manuscript as it is.*

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

Best regards,

Jan Trøst Jørgensen, M.Sc. Pharm., Ph.D.  
Director of the Dx-Rx Institute