

Format for ANSWERING REVIEWERS

Invited review article (ID = 02494908)

September 7, 2013



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4885-review.doc).

Title: Anti-angiogenic therapies for metastatic colorectal cancer: current and future perspectives

Author: Inês Marques, António Araújo, Ramon Andrade de Mello

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 4885

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 reviewer

We would like to thank you for your consideration of our manuscript and the reviewers for their insightful comments. We have made a number of changes to the manuscript based on the reviewer's suggestions. These changes are highlighted with the text highlight color function in the revised manuscript.

Reviewer 1

We included in section "*Angiogenesis and CRC – molecular mechanisms*" a description of novel angiogenesis targets, namely FGF (lines 218 - 233), Ang-2 (lines 201 - 217) and EGF (lines 234 - 256).

As you suggested, we added a brief description of sorafenib (lines 620 - 628) and the main clinical trials which are already completed (RESPECT and FOSCO trails – lines 629 - 659) and clinical trials that remain in progress (Table 2).

We also added a new section (i.e., "*Double Monoclonal Antibody Therapy*") in order to emphasize negative results related to anti-EGFR agents and bevacizumab combination (lines 407 - 438).

In original manuscript we had mentioned the need for cost benefit analysis (lines 739 - 741). In fact, there are few studies in this area but only related to few countries. For this reason, we think that those studies are not relevant enough to be explored in detail in the manuscript.

We added a brief section “*Management of liver metastasis*” (lines 440 – 466) to describe the current criteria for choice of treatment strategy according to metastatic disease (metastasis readily resectable; metastatic disease initially unresectable; unresectable metastasis).

We apologize for multiple typos and grammatical errors in the manuscript. We have corrected all indicated misspellings and carefully checked the manuscript.

Reviewer 2

The introduction was reformulated in order to highlight the advanced disease as well as the need for new therapies (lines 81 - 90).

We added in section “*Angiogenesis and CRC – molecular mechanisms*” a description of EGFR (lines 234 - 256) for the purpose to help the understanding the role of anti-EGFR therapies in cancer, as you suggested. Also in that section, we differentiated tumoral and physiological angiogenesis before describing the molecular mechanisms of angiogenesis (lines 98 - 112).

As you suggested, we added clinical trials that are still in progress using anti-EGFR and bevacizumab (table 2).

We completed figure 1 with other pathways now mentioned on “*Angiogenesis and CRC – molecular mechanisms*”, their interactions and the positions of the anti-angiogenic therapies.

We apologize for multiple typos and grammatical errors in the manuscript. We have corrected all indicated misspellings and carefully checked the manuscript.

3 References and typesetting were corrected

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

Sincerely yours,



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