Format for ANSWERING REVIEWERS

December 26, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6030-review.doc).

Title: Which strategy after the first line therapy in the advanced colorectal cancer?

Author: Coinu Andrea, Petrelli Fausto, Borgonovo Karen Francesca, Cabiddu Mary, Ghilardi Mara, Lonati Veronica, Barni Sandro

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6030

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

1 English language and grammar has been revised

2 Revision has been made according to the suggestions of the reviewer

Reviewer #1: *This is an interesting and well written review on the medical treatment of metastatic colorectal cancer. There are some minor flaws Section: second line treatment Line 12 "Therefore" better than "So".*

As suggested, we extensively reviewed english language and grammar

Line 27 and the two following paragraphs: "toxicity" please give details, in brief, i.e. which complications, side effects and toxicity rate after sequential chemotherapy compared with combined one, to support the statement that the first is superior. The authors just mention 3-4 grade diarrhea. Are there other complications worth to be mentioned?

We have further clarified why, in terms of side effects, as emerged by CAIRO and FOCUS trials, a sequential strategy of single agents rather than an upfront combination treatment, could be suggested in a proportion of patients, to obtain a similar OS with less initial toxicity (especially diarrhea, nausea and vomiting, lethargy)

Section: Anti-VEGF Line 23 "1445" pts in the BRiTE study Please check the no. of patients in the three groups, as the sum of 253, 531 and 642 is not 1445, but 1426. Maybe some pts were not considered, but it should be said and explained why.

We have highlighted that the difference between patients considered in the BriTE study (N=1445) and the sum of patients included in the mentioned three groups is given by patients (N=19) who received post-progression treatment with bevacizumab only, who were excluded.

References Ref 23 please give just the initials of the first name of the authors, as in the other references.

We have corrected the above-mentioned reference

Reviewer #2: *It is a very interesting review summarizing second line therapies for patients with metastatic colorectal cancer. It needs extensive editing before it becomes acceptable for publishing in this journal*
As suggested, we extensively reviewed english language and grammar

Reviewer #3: *Thank you for the opportunity to review this work. Overall it is a nice review of the second line (adjuvant) therapy for colorectal cancer. A few comments/questions:*

1. Although it is fairly well written, it could benefit greatly from someone review it for language and grammar.
As suggested, we extensively reviewed english language and grammar
2. Please clarify further on this need to have an entire strategy laid out from the beginning. The way this is written, I think I understand, but I am not so sure I agree. You need to have knowledge of the treatment options available, but you have no idea what is exactly going to take place and need to have the ability to react and change plans. Furthermore, you need to see how the patient responds to different regimens and what works and what does not affect disease progression.
We have accepted your valuable suggestion to clarify the need to be ready to change treatment strategy planned by the beginning of the first line therapy on the basis of response to treatment and toxicities experienced by the patient

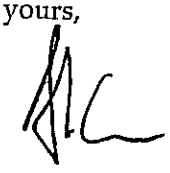
3. Throughout the manuscript you have statements like this... "In second or further lines the influence of subsequent therapies is less pronounced so that an OS benefit is more likely to be demonstrated" IF the influence is LESS pronounced, why would an OS benefit be MORE likely to be demonstrated?
We have tried to explain better the influence of post-progression survival (PPS) on OS, that, according to recent findings, in first line phase III trials, would be more associated with PPS than PFS. This confirms the increasing relevance of second-lines and beyond on the overall treatment strategy.

4.You frequently talk about dual therapy and its effect may be more pronounced than monotherapy--however you fail to mention the significant risk of increased complications and cost.
We further specified toxicities that affected combination regimens in Cairo and FOCUS trial compared the sequential use of active single agents. In the CAIRO trial, the XELIRI regimen was affected by a higher 3-4 grade diarrhoea rate, and almost half of the patients starting with this combination did not receive second-line chemotherapy. Moreover, in the FOCUS trial, grade 3-4 lethargy was noted in 13% of patients receiving 5FU/LV, compared with 20-21% of patients receiving combination chemotherapy. Furthermore, the rates of neutropenia (9% versus 19-28%), and nausea and vomiting (4% versus 9-10%) were lower among patients receiving 5FU/LV
5. Speaking of cost, many of these secondary and tertiary drugs are extremely expensive and more maybe 1-3 months OS improvement. While statistically significant, the clinical and overall health cost benefit is extremely controversial and you fail to adequately address this
We have not addressed the issue regarding costs of new regimen containing biologic agents, because, even if this aspect has big relevance and is very actual, the aim of the article was to perform an overview of second line therapeutic options for patients affected by advanced colorectal cancer, showing the main data supporting their use, without a cost-effectiveness analysis.

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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