Reviewer’s report

Title: Bevacizumab with 5-fluorouracil, leucovorin, and oxaliplatin versus bevacizumab with capecitabine and oxaliplatin for metastatic colorectal carcinoma: results of a large registry-based cohort analysis

Version: 2
Date: 11 February 2014
Reviewer: Pilar Garcia-Alfonso

Reviewer’s report:

When assessing the work, please consider the following points:

1. Is the question posed by the authors well defined?
Yes, the objective is well defined although I do not agree with the selection of patients. The authors have selected patients whom received 6 cycles of treatment and as such we do not know if the tolerance towards the first three months of treatment has been worse and thus lead to the suspension of the treatment in one cohort more than in the other.

2. Are the methods appropriate and well described?
Yes, they are

3. Are the data sound?
The data is sound because the results are in accordance with the data published in the bibliography.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Yes the manuscript adheres to the relevant standards.

5. Are the discussion and conclusions well balanced and adequately supported by the data?
Yes but I believe that in the discussion the authors must consider that they have only evaluated patients whom received 6 cycles or more.
The author must reference this point: the percentage of patients who have kras mutational status determined, is not well balanced, it is much lower in the XELOX arm. A proper comparison cannot be done of these cohorts by kras mutational status.

6. Are limitations of the work clearly stated?
Yes but emphasizing the points mentioned above.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
Yes, the bibliography is adequate.

8. Do the title and abstract accurately convey what has been found?
   Yes, they are adequate

9. Is the writing acceptable?
   Yes it is

In reviewing the revised manuscript, please consider whether the authors have answered your points sufficiently well to allow their manuscript to be published. As before, we would like you to divide your comments into the following three categories:

- Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)
- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
- Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

In my opinion the article must be included in the third category which is Major Compulsory Revisions. I am attaching the article with the corrections.

The points that the authors must correct are the following:
Page 2 - Total number of included patients regardless treatment, should be mentioned
Page 3 - It seems a typo mistake, should it be FOLFOX instead of FOLFIRI?
Page 5 - The inclusion of patients that have received 6 cycles apart from selecting the best patients makes the adequate comparison between the two cohorts difficult (for example more treatments because of toxicity have been suspended in one cohort than in another cohort in the first three months). I suggest the evaluation of the data including patients whom have received a 3-month treatment like in the TML study.
Page 7 - It has been reported that a major benefit of bevacizumab occurs in patients who have surgery of primary tumor. It would be important to know this actor as the poor prognosis of synchronous metastases may be associated with this factor.
Page 7 - The percentage of patients who have kras mutational status determined, is not well balanced, it is much lower in the XELOX arm. A proper comparison cannot be done of these cohorts by kras mutational status. The author must reference this point.

MORE REVIEWS
•The phrase that is near reference nº 5 is not understood : suggest revision (error because of missing word?)
• The last phrase of the background: "Our results suggest that the outcomes with these regimens are similar in the clinical practice." – I would eliminate it from the background, it should be in the discussions or conclusions.

• Disbalance in the PD and an elevated number of unknown PS: the number of patients with unknown PS is elevated.

  . Disbalance in primary metastatic table 1: they could condition the obtained results. It is a register not a random practice and as such these disbalances would be expected.

• Error in table 1: it should say PRIMARILY METASTATIC instead of PRIMARY.

  . Specify the percentage of patients inside the cohort of FOLFOX that received FOLFOX-4 and 6 or 7.

• Describe the percentage of patients with hepatic metastases like the unique metastatic location and the ones who underwent metastatic surgery both in lung and peritoneum.

• Favourable toxicity stands out in bevacizumab regarding VTE: 0.8% in total, excessively low in comparison to the more recent phases III 4-9% aprox, ask if they included incidental phenomenon (TEP, visceral, mesenteric thrombosis, etc) in this evaluation or only the symptomatic events. And also the HTA, perforation…the authors give a reasonable explanation to what they are communicating.

• The OS in XELOX-BEVA 30 months is noteworthy: I think they should better the discussion between this discovery and the stratification with k-ras.

Once you have done this, there are also some questions for you to answer, including one that asks your advice on publication. Please remember that since we have no space constraints, we will publish all work deemed by peer review to be coherent and scientifically sound, providing it does not substantially duplicate work that the authors have published elsewhere or is such a trivial study that it does not deserve publication at all at this stage. Further guidance on these points follows.

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are issues with the authorship or contributions towards the manuscript, such as the unacknowledged involvement of a medical writer.

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BMC Cancer has a policy of publishing all scientifically sound research whatever its level of interest. However if you choose one of the first three categories below, we may ask the authors if they would like the manuscript considered instead for the more selective journal BMC Medicine.

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- An article whose findings are important to those with closely related research interests
- An article of limited interest
- An article of insufficient interest to warrant publication in a scientific/medical journal

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An article whose findings are important to those with closely related research interests

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Statistical review
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Is it essential that this manuscript be seen by an expert statistician?
If you feel that the manuscript needs to be seen by a statistician, but are unable
to assess it yourself then please could you suggest alternative experts in your confidential comments to the editors.

- Yes, and I have assessed the statistics in my report.
- Yes, but I do not feel adequately qualified to assess the statistics.
- No, the manuscript does not need to be seen by a statistician.

Yes, and I have assessed the statistics in my report.

Declaration of competing interests

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If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I do not have any conflict of interests but I would like to mention that I have participated in the advisory dept. of ROCHE, Sanofi and Merk.

What next?

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Based on your assessment of the validity of the manuscript, what do you advise
should be the next step?
- Accept without revision
- Accept after discretionary revisions (which the authors can choose to ignore)
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