Reviewer’s report

Title: Capecitabine and oxaliplatin combined with bevacizumab are safe and efficacious for treating patients with metastatic colorectal cancer aged 75 years and older

Version: 2
Date: 2 April 2015
Reviewer: Michael Montemurro

Reviewer’s report:

Patients with Colorectal Cancer are frequently elderly and mostly excluded in CRC trials. Thus, your efforts to investigate this population are very welcome.

Unfortunately the following information are missing:
- Number of patients screened (and main reasons for not being eligible)
- Geriatric scale(s) (Performance Status is probably not sufficient in this population)
- Response rate was assessed locally (and not by blinded central review)
  ( -PK data )

Major Compulsory Revisions
1) How was neuropathy/neurotox assessed? Maybe you could briefly state or provide in an appendix what algorithms you have used to manage drug-toxicities, especially regarding neurotoxicity
2) Give reasons for trial termination in more detail. You say n=14 patients stopped treatment due to AE, please specify further.
3a) Please comment on your strategy to treat until progression. Many colleagues would treat over 6 months and then stop.
3b) Put your strategy into context of point 1 and 2
3c) Neuropathy G3 is defined as „severe symptoms; limiting self care ADL“.
   14% of your patients experienced this „endpoint“ , which to me seems unacceptable in a palliative setting. Please comment in detail. Was your strategy of dose reductions well chosen?
4) What formula did you use for estimations of CrCl? What are the age corrected reference values?
5) Text/Discussion – Modify:
   - OS in general populations today is >30months (FIRE, CALBG)
   - I miss a discussion on Pharmacokinetic, especially of capecitabine, in general and in the elderly. Is CrCl the only determining factor for toxicity? Differences
between populations US vs Europe vs Asia. Role of nutrition? Gender? BMI? And, of course age?

- Please discuss the role of PS and age in CRC (ARCAD data (Lieu et al ESMO 2013) and older data (Folprecht et al Ann Oncol 2004))

Minor Essential Revisions

- Please give number of patients screened (or state reasons for unavailability)
- You state: „we recommend more rigorous measurements of baseline values of the cerebrovascular system …:“ Could you please outline your (future) strategy? Is there any evidence or published data to support a more „rigorous measurement“? Please comment
- Did you measure cholesterol, triglycerids or glucose? Many reports appearing about capecitabine leading to important increases in the before values. Please comment.
- Please discuss cardiovasc/thromboembolic risk of BEV in more detail esp as 1/36 of your patients had a lethal intracerebral bleeding.
- Delete or replace ref 14 – In my view technical advances in pancreatic cancer surgery do not explain increasing age of a population
- Is there any large, randomised trial on QOL Cap vs 5FU? If yes, please cite. If not please give a more balanced view on selecting capecitabine vs 5FU.

Discretionary Revisions

- Language might benefit from review
- Personally, I would not discuss stop/go strategies (ref 27) in conjunction with your data
- Personally, I would review the selection of references

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
'I declare that I have no competing interests'