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

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Reviewer: Efrat Dotan

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Overall:
This is an interesting phase II study evaluating the tolerance and efficacy of XELOX+Bevacizumab regimen in the front line setting for patients >75yo with untreated mCRC. The study is limited by it’s small sample size. In addition, data is available in the literature evaluating this regimen in older patients (Feliu et al. BJC 2014). This study is reporting similar data on specific population of older Asian patients. This should be clearly stated in the introduction/abstract. Additional shortcomings of the paper are listed below:

Major:
1. As a study evaluating treatment of older cancer patient a geriatric assessment would have been of high value to learn about factors that are specific to the older patient population which could affect treatment outcome. Since this data is difficult to obtain retrospectively, it would be interesting to have more information regarding the patient’s co-morbidity index, BMI, and other factors associated with Performance status. (similar to the analysis done with the CCr)
2. The authors fail to discuss additional papers evaluating treatment of older patients with mCRC. These include the AVEX study – which evaluated cape+bev vs. cape alone – interestingly this study showed a very similar OS (20.7m) to the one reported in this study, which raises the question regarding the benefit of adding oxaliplatin. Another study that should be discussed is the FOCUS2 study which compared 5FU/CAPE +/- oxalplatin and did not show any significant benefit to the addition of oxaliplatin. These studies should be included in the discussion and the question regarding the benefit of oxaliplatin should be raised.
3. The authors report TTF of 7 months. This outcome measure is not clear, and is not defined in the methods. It is not clear what is the difference between TTF and PFS. Is the meaning to time until treatment discontinuation? Furthermore, it is clear that most patients were not able to stay on XELOX+bev for the full study period (median 5 cycles). There is no information in the paper regarding what patients got after they were taken off oxaliplatin, this is important when evaluating efficacy.
4. The rates of AEs reported in the study are quite high (neuropathy of 13.9%, is higher than seen in other studies). This may be related to the small sample size in which even small number of patients would result in high percentage of the
total. However, the authors fail to describe what method was used to evaluated toxicity in the study in the method section. This is important to evaluate this in relation to other studies.

Minor:
1. Abstract: missing data regarding the number of patients on the study, and some information regarding the patient’s characteristics.
2. Introduction: Page #7 line #7 – there is newer data from the recent CALGB 80405 study of longer overall survival of mCRC patients. Line #16 wrong reference for the XELOX study.
3. Methods: Please include how many centers participated in the study. As noted above – definition of TTF and the tools used to assess toxicity should be included.
4. Results: The use of acronym CCr for the analysis of toxicity – please clarify if this is creatinine clearance or baseline creatinine?
5. Discussion:
   a. The AVEX study is included in the references and listed under a few of the sentences regarding prior studies with XELOX – this is incorrect since the study did not include oxaliplatin.
   b. The authors use the term “survival benefit of XELOX” multiple times throughout the article. This seems in appropriate since the study did not compare XELOX to any other regimen. Furthermore, as noted above, the results from the AVEX study (phase III RCT trial) are not much different, which raises a question regarding the benefit of oxaliplatin.
   c. Page #17 line #4 – the authors state that oxaliplatin can be given without a central venous port. This is not correct, there is a risk of extravasation with oxaliplatin and at least in our institution we give it with a central access.
6. Table 3: This table is not clear – it most likely should be a table with the rates of response. However in includes treatment cycles and dose intensity. The section of the treatment cycles is very vague, is that what patients got after the stopped oxaliplatin? The dose intensity does not make sense – it seems that the dose intensity of bev was 1.0, yet above that 10 patients received XELOX alone and 2 patients received capcitabine alone.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I have no competing interests.