Reviewer’s report

**Title:** Bevacizumab plus FOLFIRI or FOLFOX as third and further line treatment in metastatic colorectal cancer patients: a retrospective study.

**Version:** 2  **Date:** 24 December 2008

**Reviewer:** Bruce Giantonio

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Bevacizumab plus FOLFIRI or FOLFOX as third and further line treatment in metastatic colorectal cancer patients: a retrospective study.

Liever, A, et al

The authors have analyzed outcome data from 31 consecutively treated patients with metastatic colorectal cancer who were treated at two institutions with bevacizumab combined with either folfox or foliri, following progression on a fluoropyrimidine and oxaliplatin and/or irinotecan. They report a 32.2% objective response rate, a PFS of 13.6 months and OS of 17.8 months.

These findings are impressive, and as such raise very important questions about the nature of this analysis.

1. What defined a line of therapy?
2. How was progression on first-line and second-line therapy defined?
3. Was there central review of the first-line and second-line scans to verify progression?
4. What is the breakdown of regimens that constitute a line of therapy for each patient?
   a. This is especially important for patients who received more than two lines of therapy before entering the study.
5. Were patients previously treated with bevacizumab excluded?
6. The title says the study was for patients treated in third line or further, yet there are data from a patient in the study who were treated second line, why is that?
7. How do the authors explain a disease control rate of 55% in the ‘later’ line group that is statistically significant when compared to the 25% disease control rate in the fourth line group. Without doing the statistical testing myself, I don’t see how with only 10 patients in each group, we can claim the additional three patients with disease control achieve a level of statistical significance, and I suspect there is great overlap of confidence intervals (moreover, the text states these numbers come from table 2, but not all the groups mentioned are listed in table 2)
8. How do the authors explain the results in comparison to the outcome data for secondline FOLFOX4 from E3200 (Giantonio, et al) in which overall response for
the bevacizumab + FOLFOX was 22%, OS was 12.9 months, and PFS was 7.2 months—all numbers considerably less yet from a much larger study in less pretreated patients.

9. There should be overall toxicity data.

10. In patients who had been treated with oxaliplatin, how much oxaliplatin were they subsequently able to receive?

11. The subgroup comparisons should be done with confidence intervals and not p-values.

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**

I have no competing interests to declare