Reviewer’s report

Title: Angiogenesis-related protein expression in bevacizumab-treated metastatic colorectal cancer: NOTCH1 is detrimental to overall survival

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Reviewer: Bruce Giantonio

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The authors report a retrospective study of 105 cases of metastatic CRC treated at a single institution with chemotherapy + bevacizumab for which tissue was available (either met or primary) for biomarker analysis. The markers evaluated were: VEGFR 1, 2, and 3; PlGF1; NOTCH1 and DLL4. These markers were determined using IHC, and were evaluated for association with metastatic patterns of spread, and outcomes (RR, PFS, OS). PFS and OS were defined from start of bevacizumab therapy. Of note 70.5% received bevacizumab with first-line therapy and the remainder received it with 2nd to 4th line therapy.

The authors conclude from their findings that: “High expression levels of VEGFR1 and VEGFR3 were associated with a higher rate of lung metastasis. VEGFR3 expression was also associated with liver metastasis. NOTCH1 expression was associated with an increased risk of lymph node metastasis and a worse overall survival.”

Major Compulsory Revisions

1. In the background section the authors discuss the need for biomarkers for angiogenesis (line 87), suggesting that their underlying hypothesis is that the markers being evaluated may serve a predictive function for anti-angiogenic therapy in CRC. A larger study from China (Chu, D et al, Clin Cancer Res; 17(17); 1–9, 2011) clearly establishes a prognostic function for NOTCH1 (that may be related to P65 expression). The present paper, to a lesser degree, simple recapitulates that work. But it does not provide any evidence that NOTCH1 may serve a predictive function for bevacizumab, as the design of the study (everyone got bevacizumab) does not allow one to distinguish the marker as being predictive from being prognostic.

2. The background section contains too much detail on colorectal cancer in general, and not enough information on the NOTCH pathway in particular, and the mountain of data that already exists on VEGFRs and PlGF expression and outcome to bevacizumab therapy

3. line 115: states they used both versions of RECIST 1.0 and 1.1. The citation is for version 1.1, and given that some of the cases were from a few years preceding the publication of version 1.1, we assume that there was a centralized response assessment done explicitly for this study; that should be verified.

4. line 116 determining PFS and OS from time of bevacizumab therapy is also
problematic, as approximately 30% got it later than first line, and the outcomes are going to be affected by the variation. Having said that, it is surprising that the PFS and OS data are as robust, and consistent with what is seen with first-line therapy. The outcomes are best evaluated by line of therapy.

5. line 222 states that bevacizumab as first line therapy was associated with higher response, which given the design of the study is taken to mean in comparison to bevacizumab used with later-line therapy. But this is misleading and likely a function of the line of therapy and in dependent of the bevacizumab, as response rates are generally lower with later line therapy; e.g. If the univariate and multivariate analyses looked at "chemotherapy", first-line versus other lines, there is likely to be the same association with response.

Minor Essential Revisions

1. foot note for table 7 has typo: CIR: hazard ratio. should be HR: hazard ratio

Level of interest: An article of limited interest

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.