Reviewer's report

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

Version: 1 Date: 22 February 2015

Reviewer: Weijing Sun

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Major Compulsory Revisions:
1) Are all these 105 patients had metastatic disease at the treatment with bevacizumab? Not clear: -193 ‘By the time of diagnosis, 72.8% of patients had stage IV, the liver being the most common site of metastasis.’ How many of them had synchronous vs. metachronous lesions?
2) By the time of exposing to bevacizumab, were any (if yes, how many) patients were treated with bevacizumab as ‘adjuvant setting’?
3) More detailed data (from this study) are needed to support the statement (on line -307) ‘In our cohort, while higher expression of membrane and cytoplasmic VEGFR3 was associated with lung metastasis, lower expression was associated with liver metastasis. Increased NOTCH1 expression was associated with lymph node metastasis which is in line with previously reported data on NOTCH1 as a predictor of lymph node metastasis’.
4) The authors need to supply info regarding the correlation the expression of VEGFRs/NOTCH1 receptor and the outcome in those mCRC patients treated without bevacizumab?

Minor Essential Revisions:
1) “Bevacizumab was administered as the first, second, third, and even the fourth line of therapy, with the majority of case (70.5%) using it as the first-line.” – these info should be supplied in the table 1 in details (70.5%– 74 pts/105? Combination with? Number of patients had bevacizumab as 2nd, 3rd or 4th line, and the combination of chemotherapy regimen(s).
2) On the line -219 ‘Response rates were analyzed in 95 patients since ten patients were not presented with detectable disease prior to bevacizumab treatment.’ Are these patients had bevacizumab as adjuvant therapy or without measurable disease?
3) Table 2 - Retarding Objective Response (N=95, see #4)-- Need clarifications:
   a. Grade 1+2: n=74 and grade 3: n= 9 with total of 84 patients, how about the rests;
   b. Chemotherapy: FOLFIRI: n=37; FOLFOX n=31 with a total of 68 pts, how about the rest 27 (~1/3 of the all patients)? Bevacizumab was given alone or with 5-FU?
4) A clarification is needed for this statement in the discussion (at line 269) –‘Of note, in patients who used bevacizumab in the first-line therapy (68 patients in this analysis) the objective response rate was 59%.) –there were 70.5% patients with bevacizumab therapy as the first-line; were the rest 6 not detectable?

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

**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 any conflict interests.