Reviewer #1

The authors showed that the ratio of free VEGF to total VEGF serum and BV plasma concentrations for predicting the response to BV plus oxaliplatin-based chemotherapy could be a promising biomarker of response to BV. The study is well-written and designed.

Comment: 1. Histologically confirmed mCRCs were included in this study. The tumor differentiation (low or high grade) may also influence the treatment effect and VEGF concentration. If the authors can categorize the tumor differentiation, this maybe more helpful to choose patients for different treatment regimen.

We categorized tumor differentiation of our patients. Nevertheless, we did not observe an influence with respect to serum levels of VEGF, suggesting the lack of role for tumor differentiation in the selection of patients. Anyway, we insert tumor differentiation in ***Table I. "Clinical characteristics of patients"***

Tumor differentiation	
G1-G2	12/20
G3	8/20

Comment: 2. Besides endothelial cells, tumor cell itself can also produce VEGF. Have the authors see difference of tumor size decrease and low VEGF? Angio 2 is mainly produced by endothelial cells, maybe that is the reason there is no change in its concentration. The authors may add these in the discussion.

We did not observe a correlation between tumor size decrease and low VEGF and Angio 2 serum levels.

Reviewer #2

Although the study has been done in a small subset of patents treated with chemotherapy plus bevacizumab in firsts and second-line therapy and it's exploratory it's interesting because shows that patients with response to therapy are those with a higher decrease of free VEGF (not bound to bevacizumab). I have only minor comments

1. In patients and methods it should be stated when the authors performed radiological evaluation of response

We inserted it.

Response to treatment was evaluated between the 4th and the 5th cycle according to the Response Evaluation Criteria in Solid Tumors (RECIST) definition 1.1[22].

2. Figure 4 does not reflect well changes in free VEGF and total VEGF (it should be modified)

Thank to the reviewer. We modified the picture taking into account how free and total VEGF change.

3. there were 4 cases in adjuvant treated with FOLFOX alone (as a control arm). It should be state when the second evaluation was placed in patients and methods.

We specified in the section Patients and Methods the timing of the second evaluation.

To exclude that the associated chemotherapeutic regimen could affect VEGF and Ang-2 levels, four patients in adjuvant treatment were included as a control arm.

Reviewer #3

We modified the text following all comments provided by the reviewer