ANSWERING REVIEWERS

March 12th, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 16253-review.doc).

Title: Bevacizumab plus XELOX as first-line treatment of metastatic colorectal cancer: the OBELIX study.

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The manuscript has been improved according to the suggestions of reviewers:

REVIEWER 1

(1) There 's no information about the average doses of chemotherapy received and about bevacizumab monotherapy continued after chemotherapy per patient. Indeed, the fact of continuing the XELOX bevacizumab schedule followed by monotherapy bevacizumab until disease progression is not a standard treatment and these data are important. we don't have any data about the later lines of treatment: TML strategy ? anti-EGFR therapy?

We agree with reviewer 1 and therefore have included in the manuscript the information reported in Table 6.1-2 of the statistical report of the study, which is attached below.

Table 6.1-2: *Treatment exposure (Safety population)*

Number of cycles performed*	(N=197)		
	Bevacizumab	Capecitabine	Oxaliplatin
N	197	197	197
Mean	9.16	5.94	5.85
SD	7.27	2.69	2.62
25th percentile	3.00	3.00	3.00
Median	8.00	7.00	7.00
75th percentile	12.00	8.00	8.00
Min	1	1	1
Max	39	13	13

	(N=197)					
	Bevacizumab		Capecitabine		Oxaliplatin	
	N	%	N	%	N	%
Number of patients without any dose modification/interruption	44	22.34	68	34.52	58	29.44
Number of patients with at least a cycle with a dose modification/interruption	153	77.66	129	65.48	139	70.56
Number of patients with at least a cycle with a dose modification/interruption due to AE	98	49.75	98	49.75	90	45.69
Number of patients with at least a cycle with a dose modification/interruption due to refusal	3	1.52	-	-	-	-
Number of patients with at least a cycle with a dose modification/interruption due to non-compliance	6	3.05	7	3.55	1	0.51

"Results" section, *page 11, lines 12-15:*
Patients underwent 9.2±7.3 cycles of bevacizumab, 5.9±2.7 cycles of capecitabine and 5.9±2.6 cycles of oxaliplatin. The number of patients without any dose modification or interruption was 44 (22.3%), 68 (34,5%) and 58 (29,4%) for bevacizumab, capecitabine and oxaliplatin, respectively.

Regarding bevacizumab monotherapy and later lines of treatment, we have no data on single patients treated with bevacizumab monotherapy until PD, after bevacizumab/XELOX. OS is affected by treatment after first progression, but unfortunately no data are available about the later lines of chemotherapy, as in this study second-line therapies were at the investigator's discretion according to local guidelines, and thus were not recorded in the study's CRF. In Italy, during the study period (Februry 2008–November 2009), patients treated in first-line with fluoropyrimidine and oxaliplatin plus bevacizumab received mostly second-line therapy with fluoropyrimidine plus irinotecan, whereas the use of bevacizumab beyond progression was not allowed, nor the use of FOLFIRI plus aflibercept. Therefore, we can assume that patients enrolled in the present study did not receive anti-VEGF therapy beyond PD (TML strategy).[13] In the same period, patients with K-RAS wt (exon 2, codon 12 and 13) tumors were treated with FOLFIRI plus cetuximab in second line or with cetuximab or panitumumab monotherapy in third line. Unfortunately, the total number of patients with K-RAS wt tumor is unknown and consequently also the number of patients hypothetically treated with anti-EGFR antibody.
Following the reviewer's comment, we have now included this information in the "Discussion" section, *page 14, lines 19-28 and page 15, lines 1-3*.

(2) minor criticism the discussion is a bit short on the therapeutic approach in 1st line
Following the reviewer's comment, we added the following information on therapeutic approach in the first line of the "Discussion", *page 14, lines 3-8:*
In patients with mCRC, chemotherapy is recommended to reduce symptoms and prolong survival. Various combinations of chemotherapy and biological drugs are available for first-line treatment depending on patients' features, disease characteristics and aim of therapy. The combination of chemotherapy with targeted agents as bevacizumab in molecularly unselected populations, and anti-EGFR cetuximab and panitumumab in RAS wt patients significantly prolonged survival in phase III randomized trials.

REVIEWER 2

1. The authors only provided the 95% CI of each outcome, please add the P value as well.
This is a single arm study and the comparison group are historical controls. Within a historical comparison, the p-value is not reported and conclusions are based on the estimation of PFS, OS, TOR, DOR, TTF and on its confidence interval.
As no formal statistical hypothesis was defined *a priori* , it is not possible to calculate a p-value.
We report the p-value for K-RAS and B-RAF analysis and for QoL analysis. We have also added the Log-rank test p-value in subgroup analysis for clinical prognostic factors (*page 12, lines 17, 19*): considering PFS: Log-rank test p-value=0.527; considering OS: Log-rank test p-value=0.149. The non-uniform distribution of patients in the three groups should be considered when evaluating these results.

2. Please add some contents to introduce the included drugs in the passage of "Treatment".
Following the reviewer's suggestion, we modified the text by adding the following sentence (*page 8, lines 26-29)*: the planned treatment schedule was oral 5-fluorouracil pro-drug capecitabine in combination with oxaliplatin plus the humanized anti-VEGF antibody bevacizumab. After signing the informed consent, eligible patients received 21-day cycles according to the following scheme.

3. In the passage of "Treatment" the authors mentioned "Second line chemotherapy was at the investigator's discretion", it remains suspicious whether this will affect the results of this study.
We agree with reviewer 2 to give more details on second-line therapy: as also reviewer 1 has made the same observation, we have already included the related information by modifying the "Discussion" section, *page 14, lines 20-29 and page 15, lines 1-3*: [...]unfortunately no data are available about later lines of chemotherapy, as in this study second-line therapies were at the investigator's discretion according to local guidelines, and thus they were not recorded in the study's CRF. In Italy, during the study period (Februry 2008–November 2009), patients treated in first-line with fluoropyrimidine and oxaliplatin plus bevacizumab received mostly second-line therapy with fluoropyrimidine plus irinotecan, whereas the use of bevacizumab beyond progression was not allowed, nor the use of FOLFIRI plus aflibercept. Therefore, we can assume that patients enrolled in the present study did not receive anti-VEGF therapy beyond PD (TML strategy).[13] In the same period, patients with K-RAS wt (exon 2, codon 12 and 13) tumors were treated with FOLFIRI plus cetuximab in second line or with cetuximab or panitumumab monotherapy in third line. Unfortunately, the total number of patients with K-RAS wt tumors is unknown and consequently also the number of patients hypothetically treated with anti-EGFR antibody.

4. **The limitation of this manuscript is the lack of control group. The authors compared all results with previous studies, however, it would be more reasonable to compare a control group with conventional treatments in Italy.**
We agree with the reviewer on the limitations represented by the lack of a control group and the comparison with historical controls. Therefore, we modified the text as follows:
page 15, lines 4-9: Main limitations of the present study were the lack of randomization and blinding, but since this was intended to be a confirmatory study, randomization and blinding would have been beyond the requirements of the study. Moreover, although the bevacizumab/XELOX combination has proven its efficacy in treating CRC patients, treatment prognostic markers are still needed. Further investigation is also warranted for selecting the optimal treatment duration and the role of

bevacizumab in selected patients groups.
We also agree that it would be more correct to compare our results with conventional treatments in Italy. Unfortunately, to our knowledge there are no published data about the outcome of conventional treatments in Italy in this setting. Therefore, we have provided this information in the "Discussion" section (*page 14, lines 23-29*) and have also specified that the aim of the OBELIX study was to confirm previous efficacy and safety data of XELOX plus Bevacizumab, in the setting of Italian population (*page 15, lines 4-6)*.

5. The total number of "Site of metastases" in table 1 is not 197 or 205. The authors should check these numbers.
We understand the point made by reviewer 2, but after a careful revision of Table 1, we can conclude that the numbers reported are correct. In fact, Table 1 reports the baseline characteristics, of the ITT population of 197 patients. As some patients have more than 1 site of metastasis (as reported in table 1 "N of metastases for each patient), the total number is higher than 197, being 359 distributed as follows: liver 150, lung 70, lymph nodes 27, peritoneum 14, other 98.

Thank you again for publishing our manuscript in the World Journal of Gastroenterology.

Yours sincerely,

Lorenzo Antonuzzo

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