Author's response to reviews

Title: Biweekly cetuximab in combination with FOLFOX-4 in the first-line treatment of wild-type KRAS metastatic colorectal cancer: final results of a phase II, open-label, clinical trial (OPTIMIX-ACROSS Study)

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Author's response to reviews: see over
Dear Editor,

Please find enclosed the revised version of the manuscript entitled "Biweekly cetuximab in combination with FOLFOX-4 in the first-line treatment of wild-type KRAS metastatic colorectal cancer: final results of a phase II, open-label, clinical trial (OPTIMIX-ACROSS Study)". We would like to thank the two reviewers for their constructive work in order to improve the manuscript. Their considerations have been taken into account and included in the revised version. A detailed response to all questions raised by the reviewers is included in the "Point-by-Point response to the reviewer’s comments".

We will be very pleased if you find the revised version of the manuscript suitable for publication in BMC Cancer.

Thank you very much in advance.

Sincerely,

Lluis Cirera
POINT BY POINT RESPONSE TO THE REVIEWER’S COMMENTS:

Reviewer 1:

Q1.1. Why author decrease the cetuximab by hematological toxicity? since cetuximab is rarely associated with hematological toxicity

1.1. It should be clarified that, according to the study protocol, after the identification of a haematological toxicity the relative dose of cetuximab was reduced to ½ and administered weekly until the end of the toxicity episode. However, this does not mean that the total dose of cetuximab has been reduced, since the total original dose was administered biweekly. In order to avoid this confusion, the sentence “Haematology toxicity leading to chemotherapy delays was the main reason of cetuximab dosing reduction” included in the original text was deleted in this corrected version since it does not reflect accurately the procedures.
**Reviewer 2:**

**Major essential revisions**

**Q2.1.** The major point that authors have to elucidate is that a sample size of 98 patients was calculated to detect a 95% confidence interval (CI) for the ORR of 50-70%, assuming an estimated rate of 60% according to previous studies and on the basis of anticipated loss to follow-up of 10% of patients. The above sample size was based one-arm or two-arms sample size estimation? Additionally, the intention to treat population (ITT) included all patients that received at least one dose of the four drugs and had at least one radiological assessment at 8 weeks. If the patients just received one dose of the four drugs could be considered as a candidate for the evaluation of ORR?

2.1. The sample size calculation was based in one arm sample design.

The definition of the intention to treat population was reworded in this version to avoid confusion: “The intention to treat population (ITT) included all patients that received at least one dose of the combination chemotherapy (four drugs) and had at least one radiological assessment at 8 weeks.” (see page 6).

The ITT population is the recommended population for the calculation of endpoints in oncology clinical trials by the FDA (see “Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics” at [http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071590.pdf](http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071590.pdf)).

**Q2.2.** There were 16 patients received prior chemotherapy in the current study, what was the regimen used should be present in the text.

2.2. We have added the regimen details of these 16 patients with prior chemotherapy in the revised version of Table 1.

**Q2.3.** For mCRC treatment, the median OS was actually over 24 months and the current study was only based a median follow-up of 17.8 months. Apparently, the relatively shorter follow-up time was another limitation for further interpretations.

2.3. The primary end-point of our study was ORR. PFS and OS were secondary end-points. In this context, we do not feel that the median follow-up is a limitation for interpretation, also taking into account that our OS is consistent with the median OS reported for standard weekly cetuximab in combination with FOLFOX-4.
Q2.4. From the data from OPUS study, the combination of FOLFOX4 and cetuximab for mCRC, only a better ORR and PFS but no OS advantage was found. Why did authors try to conduct the study design? Moreover, the issue regarding weekly vs. biweekly cetuximab administration for mCRC is actually approved and widely accepted.

2.4. Firstly, we should specified that we have conducted this trial because we felt that FOLFOX + cetuximab was a very good combination. In fact, during the last ASCO Annual Meeting (2014); results of a very important trial, the CALGB/SWOG 80405 (abstract LBA3), were communicated. These results confirm that the FOLFOX + cetuximab combination is as good as other combinations such as FOLFIRI + cetuximab.

Secondly, and more important, biweekly schedule is a very convenient schedule for patients and institutions.

To our knowledge, and as it is reflected in the product information sheet available at the EMA webpage, cetuximab (erbitux) should be administered as a weekly schedule. See in the Product Information Sheet: “In all indications, Erbitux is administered once a week”. Although some institutions use the biweekly schedule (based on the pharmacokinetic profile of cetuximab described by Tabernero et al.), at the present time biweekly schedule is not yet accepted in many institutions.

The main objective of our study was to confirm the same efficacy and safety profile for weekly and biweekly cetuximab administrations.

Q2.5. In the Results section, authors must provide the detailed information about how many cycles of regimen was administrated to the studied patients and the definition of relative dose intensity (RDI).

2.5. We have included in this revised version of the manuscript the information regarding the cumulative dose, dose intensity and relative dose intensity (see “Treatment exposure” section in page 8). The definition of relative dose intensity was also included in the Methods Section (see page 6).

Q2.6. The relatively high incidence of 31 patients (39.4%) had at least one cetuximab dose reduction, if it would affect the clinical outcome? Furthermore, the most common adverse events grade 3 or 4 were neutropenia (32.3%) and diarrhoea (13.1%). The AE was prominently different from previous reports; especially the constipation was the major GI AE.

2.6. In the OPUS trial, 86% of patients who received cetuximab had a RDI ≥80%. In our study, eighty-two patients (82.8%) received relative dose intensity (RDI) of cetuximab ≥80%. In this context, it does not seem to us that cetuximab dose reduction affect the clinical outcome.

On other hand, when we reviewed the OPUS Trial toxicity profile, we observed that OPUS Trial toxicity was in order with the one we have reported here. In the Opus Trial, neutropenia grade 3/4 was described in 30% of patients, while in our study was described in a similar proportion
of patients (32%). Diarrhoea grade 3/4 was described in the OPUS trial in 8% of patients and in our study it was observed in 13% of patients.

**Minor Essential Revisions:**

**Q2.7.** In Table 1, authors have to look up their data again, Prior therapy, n (%) Chemotherapy 9 (56.3%); Chemotherapy and radiotherapy 7 (43.8%); Surgery 48 (48.5%). Also uniform UK and missing data.

**2.7.** Proportions of prior therapy in Table 1 has been recalculated in this version in relation with total number of patients (N=99). “Missing data” and “Unknown” categories were uniform to “Unknown”.

**Q2.8.** Please correct the typo, this phase II study was design with... (designed)

**2.8.** The typo mentioned by the reviewer has been corrected in this text version.