Author’s response to reviews

Title: First-line single-agent regorafenib in frail patients with metastatic colorectal cancer: A pilot phase II study of the Spanish Cooperative Group for the Treatment of Digestive Tumours (TTD)

Authors:

Alfredo Carrato (Acarrato@telefonica.net)
Manuel Benavides (manuel.benavides.sspa@juntadeandalucia.es)
Bartomeu Massutí (bmassutis@seom.org)
Reyes Ferreiro-Monteagudo (reyes-ferreiro@hotmail.com)
Pilar García Alfonso (pgarcaalfonso@gmail.com)
Esther Falcó (efalco@hsl.es)
Margarita Reboredo (margareboredo@hotmail.com)
Maria Teresa Cano (maytecano79@hotmail.com)
Javier Gallego (j.gallegoplazas@gmail.com)
José Mª Viéitez (josemarievieitez@yahoo.es)
Laura Layos (llayos@iconcologia.net)
Antonieta Salud (asaluds@hotmail.com)
Eduardo POLO (eduardopolomarques@hotmail.com)
Emma Dotor (edotor@cst.cat)
Gema Durán-Ogalla (gemaduo@hotmail.com)
Mercedes Rodriguez-Garrote (mercedes3110@yahoo.es)
Aitana Calvo (aitanacalvo@hotmail.com)
Enrique Grande (egrande@mdanderson.es)
Enrique Aranda (earandaa@seom.org)
Author’s response to reviews:

Dear Editor,

We appreciate the constructive comments highlighted by the reviewers and you and we have proceeded accordingly.

We hope that the points addressed are viewed as satisfactory responses to the doubts and clarifications presented by the reviewers.

Next, we describe the changes made, point-by-point, and the response to each of the reviewers.

Editor Comments:

1. Please incorporate the "Key message" section into the main manuscript, this is not a standard section in Research articles.

The Key Message section has been deleted. All the information in this section is in the Results section of the main manuscript.

2. Please move the Declaration of interest information to the Competing Interests section in the Declarations.

The Declaration of interest has been deleted as that information was already in the Competing Interests section in the Declarations.

3. The trial registration included in the manuscript (EudraCT (2013-002124-17) https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-002124-17/ES) appears to refer to a trial on eyes, is this the correct number? Please amend the trial number to the correct trial.

The correct EudraCT number is 2013-000236-94 and trial registration dated April 9th, 2013 (https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-000236-94/ES). The text has been amended accordingly.
4. Please include the ethics approval reference number in the Ethics approval and consent to participate, if applicable.

The reference numbers of the Regional Clinical Research Ethics Committee of the Community of Madrid is Acta 5/2013. This information has been included in the text.

5. Please note, the role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should be declared in the Funding section.

All mentions of the Spanish Cooperative Group for the Treatment of Digestive Tumours (TTD) group have been deleted and limited to the Funding section. The text has been amended accordingly.

Reviewer 1 (Eric Chen):

1. Forty-seven patients were enrolled in the study. It is not clear how many patients were screened.

A total of 55 patients were screened and eight of them were screening failure. This information has been included in the text.

2. Authors claimed that patients who participated in this study were frail or unfit for chemotherapy (lines 140-141), yet

a. 64% patients were of ECOG 0-1

Frailty criteria defining frail or unfit for chemotherapy patients is shown in table 1. Patients should have one or more of the three criteria (a, b, c) listed. Likewise, in the discussion section, it is recognized that there is an absence of standardized frailty definition. Therefore, according to the frailty criteria used in this study some patients might be seen as fit patients for chemotherapy under others' criteria. Even so, 64% patients with ECOG ≤ 1 is not a surprise result considering that an ECOG performance status ≤ 2 was an inclusion criterion.

b. 19/47 patients received subsequent chemotherapy, some as many as 6 lines.

Regarding the subsequent post-study antineoplastic treatment, in the manuscript is shown the total number of treatment lines received by the patients (i.e. from 1 [regorafenib being the first one] to 6 lines) and not the total number of treatment lines received after regorafenib for the patients (i.e. from 1 [the second line] to 5 [the sixth line]). This mistaken has been amended,
leaving only the total number of treatment lines received after regorafenib. Only two patients received more than 2 lines after regorafenib, one patient received 3 single-agent treatments and the other one received 5 single-agent treatments.

3. Response assessment was based on investigator assessment, and there was no central review. This might have contributed to the PFS at 6 months of 45%.

Thanks for your comment. A central review would have enhanced the quality of the results. This fact has been included in the text in the results section.

4. The median time to treatment failure was only 2.1 months, quite different from median time to progression of 5.6 months. The difference should be explained and discussed fully.

The main reason for the difference from the time to treatment failure and time to progression is that almost half of patients (N=21; 45%) discontinued treatment due to disease progression or death (N=18 and 3, respectively). The remaining 26 patients discontinued treatment for other reasons: intercurrent disease/AE not related to the treatment in four patients (8.5%), decision of the patient/investigator in 11 patients (23%), and toxicity in 11 patients (23%). In addition, most of the patients that discontinued treatment for other reasons reported disease progression and/or death after treatment discontinuation; only eight patients did not. The reasons for treatment discontinuation have been included in the text.

5. The effect of post-progression treatment on overall survival was not discussed.

Thanks for your suggestion. New text commenting this issue has been added in the discussion section.

6. The incidence of grade 3/4 AEs is high and according to authors, these grade 3/4 AEs mainly occurred in the 1st cycle. It is not clear how these events affected quality of life of these patients.

Excellent observation. Quality of life was not assessed in this study. This limitation has been included in the text.

7. Authors argued for further investigation of regorafenib in this patient population, despite the fact that the primary endpoint was not met, and significant toxicities.
The study data does not reject the null hypothesis being PFS rate lower than 35%. Considering the results of other single agent studies in frail patients we think that our results are interesting. The text has been amended accordingly to your suggestions.

Reviewer 2 (Mei-Chin Hsieh, Ph.D.)

1. The main issue with this study is the small sample size. Because results generated from small sample size studies are usually neither stable nor reliable, a concrete conclusion cannot be made at. However, authors were aware of this issue and addressed it in their study limitation. I suggest changing the "phase II" in the study title to the "pilot phase II."

Phase II has been replaced by pilot phase II through the manuscript. The text has been amended accordingly.

2. It is not clear whether the advanced stage of colorectal cancer was identified at the same time the cancer diagnosed or the colon cancer patients later progressed or developed metastases to distant site(s). In the methods, it mentioned patients with microscopically confirmed advanced colorectal adenocarcinoma who were not amenable to curative surgery and were not previously treated for advanced disease. However in the results section, authors described other patients as having surgery and receiving previous adjuvant chemotherapy.

Table 2 shows that 30 patients (64%) had metastases at the time of the cancer diagnosis. The remaining 17 patients relapsed or developed metastases after a time frame from the primary cancer diagnosis. Thus, seven of the patients that progressed or developed metastases after the cancer diagnosis, had adjuvant chemotherapy prior to the identification of metastatic disease.

Regarding surgery prior to first-line regorafenib treatment, no major surgery within 28 days prior to the initiation of study treatment was allowed. However, prior surgery with curative intent (17 patients) or palliative surgery for metastatic colorectal cancer (14 patients) was allowed. Thus, 31 patients with curative or palliative surgery but without prior chemotherapy for metastatic disease were included in the study.

This has been clarified in the text.

3. In the Results section (line 218) complete response was achieved by one patient with a partial response observed in two patients. Did all of these subjects receive the full dose 160mg/day over
the 3+1 week schedule OR did any receive the reduced dose? If so, it would be helpful to indicate that for clarity.

The dose reduction, dose delays and relative dose intensity for patients with complete and partial response have been included in the text.

4. Other minor issues includes:

a. Remove the repeated words "colorectal cancer" from the first sentence of abstract.

The text has been amended accordingly.

b. Proper use of abbreviations: abbreviated words should spelled out for the first time with the corresponding abbreviation in parenthesis, e.g. progression-free survival (PRS) rate.

The text has been amended accordingly.

c. Remove "percent" after 5% from the second sentence under "Safety and post-study treatments".

The text has been amended accordingly.

d. Tables and figure: Tables 2 and 3 should be cited with the mention of relevant statistical results and not at the end of the paragraph. Figure 1 was not mentioned in the results at all.

The text has been amended accordingly.

e. Suggest to carefully read through the paper and fix other glitches before resubmission.

The text has been amended accordingly.