Author's response to reviews

Title: Phase II clinical trial of sorafenib plus interferon-alpha treatment for patients with metastatic renal cell carcinoma in Japan

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Author's response to reviews: see over
Dear Dr. Dafne Solera:

Thank you very much for the e-mail of 2nd April, 2015, along with the comments from the reviewers. We have read the comments carefully, added some data, and have corrected the manuscript accordingly. The following alterations have been made:

For reviewer #1, Dr. Pablo P Maroto:

Q1: To your attention: This paper Phase II clinical trial of sorafenib plus interferon-alpha treatment for patients with metastatic renal cell carcinoma in Japan exposes the results of a phase II clinical trial combining interferon plus sorafenib. Results are well explained, although it is only a phase II trial, so conclusions should be less confident and no recommendation could be stated from this trial that the combination should be a first line in metastatic renal cell carcinoma.

A: According to the comments of reviewer #1, we have changed our conclusions to “Our data have demonstrated that sorafenib plus IFN-α treatment is safe and effective for untreated mRCC patients.” in the ABSTRACT on page 5, lines 75 to 76. We have also changed our conclusions to “Our results have clearly demonstrated that sorafenib plus IFN-α treatment is safe and effective for untreated mRCC patients.” in the CONCLUSIONS on page 17, lines 272 to 274.

Q2: Some recommendations: I would not explain about the patients considered as wrong inclusions, simply I would exclude them and I would not speculate about results. In addition, it should be explained why the patients in Japan go better with immunotherapy than in other countries. Finally, terms like excellent, should be avoided.

A: To explain why the patients in Japan go better with immunotherapy than in other countries, we have added a sentence, “Since the beginning of the cytokine era in Japan, many urologists have tended to treat patients with even very small metastatic lesions (less than 1 cm), and this may be one reason for the good prognosis of mRCC patients..."
with cytokine therapy in Japan.” in the Discussion on page 15, lines 254 to 257. According to the comments of reviewer #1, we have changed the term “excellent” to “good” in the ABSTRACT on page 7, line 107, in the RESULTS on page 12, line 184, in the DISCUSSION on page 13, line 203.

Q3: Regarding the discussion, there are no much data about the combination of immunotherapy and TK inhibitors, and this is one of the strengths of this manuscript. I would suggest to review data about combinations in the discussion, may be through a table summarizing the data available. Besides, review of phase I and II trials with Sorafenib plus immunotherapy should be contemplated.

A: Thank you for your important questions. According to the comments of reviewer #1, we have made Table 4 summarizing the data available, and added some discussions, “So far, all [8-10, 20] but one study [21] has demonstrated the effectiveness of IFN-α when combined with molecular targeted drugs (Table 4). The exception (a randomized phase II study which compared sorafenib alone with a combination of sorafenib and very low dose [0.5 million U twice daily] IFN-α) revealed no advantage for patients in the combination arm, indicating that the selected dose of IFN-α was suboptimal (Table 4).” in the DISCUSSION on page 13, lines 212 to 216, and “Taken together, these findings indicate that sorafenib, in the absence of IFN-α, cannot induce the immune response, and thus, IFN-α may have prolonged the CR in the several reported cases (6%) of the Rapsody study [13] and in the one case (2.4%) of our study (Table 4).” in the DISCUSSION on page 14, lines 229 to 232.

Q4: More data about the statistical design should be added.

A: According to the comments of reviewer #1, we have added data about the statistical design. Two sentences, “The primary endpoint was the proportion of patients who achieved an objective response. Point of estimation of objective response and 95% confidence interval were calculated.” in the PATIENTS and METHODS on page 9, lines 149 to 151.

Q5: Finally, at least in Europe, Sorafenib is not anymore a first line therapy for patients with metastatic Renal Cell Cancer. It should be described why authors could or not still considered Sorafenib for first line.

A: Thank you for your important question. To answer to the question of reviewer #1, we have added e few sentences, “Taken together, these findings indicate that sorafenib, in
the absence of IFN-α, cannot induce the immune response, and thus, IFN-α may have prolonged the CR in the several reported cases (6%) of the Rapsody study [13] and in the one case (2.4%) of our study (Table 4). To overcome the rarity of CR by molecular targeted therapy [4], sorafenib plus IFN-α could be useful, although sorafenib itself is not basically recommended as first line treatment.” in the DISCUSSION on page 14, lines 229 to 234.

For reviewer #2, Dr. Vsevolod MATVEEV:
The manuscript of Masatoshi et al. is an original multicenter prospective study assessing the efficacy of combination of Sorafenib 400 mg b.d. + low doses of INF-alpha (3 dosages of 3 million U per week for 2 weeks) as a first line treatment of metastatic RCC. While both agents had demonstrated modest response rate in several randomized studies, the potential benefit of combining of two drugs is studied insufficiently as well as toxicity profile of this combination.

Q1: Although, authors have demonstrated improved PFS and OS for the whole cohort of 42 patients, the distribution of patients according to MSKCC risk group is not clear. Absence of patients with poor and intermediate MSKCC prognosis may partly explain the improved clinical outcome and question the advantage of combination.
A: According to the comments of reviewer #2, we have added MSKCC prognostic risk in the Table 1, and added a sentence, “Twelve, 28, and 2 patients revealed Favorable, Intermediate, and Poor in MSKCC prognostic risk score, respectively.” in the RESULTS on page 11, lines 167-169, to show the distribution of mRCC patients in this study.

Q2: Combination of sorafenib and INF-alpha was associated with common for both drugs adverse events. Despite the fact that the study did not show any significant difference in adverse events when compared with patients in phase II study of sorafenib alone in Japan , 45% of patients in the current study had to discontinue treatment due to side effects, which is significantly higher than in studies where Sorafenib was used as a single agent. The rate of discontinuation of Sorafenib due to toxicity in TARGET trial was only 10% (1).
A: Thank you for your important questions. To respond to the question of reviewer #2, we have made Table 4 comparing our results with the data of previous studies, and added some discussions, “In our study, a high incidence of patients (42.9%) receiving sorafenib plus IFN-α discontinued treatments due to adverse events (Table 4). Although
the incidence of discontinuation was a little higher than other studies (Table 4), the dose reduction rate of the combination therapy was almost compatible with other studies (Table 4). Regarding this point, as we performed this study as an investigator-initiated clinical trial, but not sponsor-initiated clinical trial, more investigators might have treated patients in the style of daily medical practice, resulting in early exchange of molecular targeted drugs. Indeed, a recent post-marketing clinical trial of sorafenib in Japan also demonstrated that a high incidence (40%) of patients discontinued sorafenib, and started other molecular targeted drugs [24].” in the DISCUSSION on page 14, line 237 to page 15, line 246.

Q3: Recent randomized phase II trial failed to show any advantage of combining the two drugs in terms of survival (2) in mRCC patients, although the doses of INF-alpha were different from the regimen used by authors. Until the benefit of combination of sorafenib with INF-alpha is not proved in phase III randomized trials it should not be recommended as a treatment option for untreated mRCC patients outside clinical trials.

A: According to the comments of reviewer #2, we have changed our conclusions to “Our data have demonstrated that sorafenib plus IFN-α treatment is safe and effective for untreated mRCC patients.” in the ABSTRACT on page 5, lines 75 to 76. We have also changed our conclusions to “Our results have clearly demonstrated that sorafenib plus IFN-α treatment is safe and effective for untreated mRCC patients.” in the CONCLUSIONS on page 17, lines 272 to 274.

For reviewer #3, Dr. Sebastiano Buti:
The work by Eto M et al. is well written, generally clear and of interest in the field of metastatic renal cell carcinoma treatment.

Minor Essential Revisions.

Q1: In the abstract, Results, lines 70-73: these sentences are not clear when read before the following full text of the manuscript.

A: According to the comments of reviewer #3, we have changed them to “Rate of Response to the combined therapy of sorafenib plus IFN-α was 26.2% (11/42) (CR 1, PR 10). The median PFS was 10.1 months (95% CI, 6.4 to 18.5 months), and the median OS has not been reached yet. The combined therapy increased neither the incidence of adverse effects (AE) nor the incidence of unexpected AE.” in the ABSTRACT on page 4, lines 69-73.
Q2: Only IFN-alpha tolerant patients were enrolled in this trial: this could be a cause of bias. To comment in the discussion section.
A: According to the comments of reviewer #3, we have added a sentence, “The fact that only IFN-α-tolerant patients were registered to this trial could also be a cause of bias.” In the DISCUSSION on page 16, lines 263 to 264.

Q3: Background page 6, lines 92-93: to add also the development of resistance as limitation of new agents
A: According to the comments of reviewer #3, we have added “the development of resistance [6],” in BACKGROUND on page 6, line 93.

Q4: Page 8, lines 119-121: to better clarify why the authors specify the possible adjuvant IFN therapy...It is not a standard!! How many patients received this therapy?
A: Thank you for your important questions. As reviewer #3 pointed out, it is not a standard now. However, some urologists in Japan performed adjuvant IFN-α therapy after radical nephrectomy at the era of cytokine therapy. That is why we described about adjuvant IFN therapy. However, only one patient had received adjuvant IFN-α therapy in this study.

Q5: Page 8, lines 123-124: to clarify what means “could tolerate IFN treatment”....grade 3 toxicity? At discretion of clinician?
A: Thank you for your important questions. In this study, 2 patients were excluded due to more than grade 3 toxicity of IFN-α monotherapy before the combination therapy. However, the judge of this discontinuation was done at discretion of clinician. So, as mentioned at Q2 of reviewer #3, we have also added a sentence, “The fact that only IFN-α-tolerant patients were registered to this trial could also be a cause of bias.” In the DISCUSSION on page 16, lines 263 to 264.

Q6: Page 9, line 151: to specify that 12.4% of response rate was in patient after failed at least 1 prior cytokine cointaining therapy in the Akaza study.
A: According to the comments of reviewer #3, we have changed the part to “based on the response to sorafenib monotherapy after at least 1 prior cytokine containing therapy in Japan (12.4%) [17].” in BACKGROUND on page 9, line 152 to 154.
Q7: Page 11, lines 167-168: high rates of adverse events and patient's request as reasons for treatment discontinuation: this data should be discussed in the discussion section.

A: According to the comments of reviewer #3, we have made Table 4 comparing our results with the data of previous studies, and added some discussions. “In our study, a high incidence of patients (42.9%) receiving sorafenib plus IFN-α discontinued treatments due to adverse events (Table 4). Although the incidence of discontinuation was a little higher than other studies (Table 4), the dose reduction rate of the combination therapy was almost compatible with other studies (Table 4). Regarding this point, as we performed this study as an investigator-initiated clinical trial, but not sponsor-initiated clinical trial, more investigators might have treated patients in the style of daily medical practice, resulting in early exchange of molecular targeted drugs. Indeed, a recent post-marketing clinical trial of sorafenib in Japan also demonstrated that a high incidence (40%) of patients discontinued sorafenib, and started other molecular targeted drugs [24].” in the DISCUSSION on page 14, line 237 to page 15, line 246, as mentioned at Q2 of reviewer #2.

Q8: Page 12, toxicity: to add mood depression rate (patients treated with IFN!, it is a relevant toxicity to report).

A: According to the comments of reviewer #3, we have added a sentence, “Depression (related with IFN-α) was observed in 4 patients (9.5%).” In the RESULTS on page 12, line 192.

Q9: Page 13, line 197: the response rate 26% is inferior (not compatible) compared to response rate of Bracarda study.

A: Thank you for your important questions. We have changed the sentence to “Although the response rate (26.2%) was slightly lower than previous data [13], and the median PFS was longer in our study (10.1 months) than the previous study [13].” in the DISCUSSION on page 13, lines 201 to 203.

Q10: Page 13, lines 207-208: to add and comment the work of Melichar et al. Ann Oncol 2008 (subanalysys of AVOREN trial for patients that received bevacizumab and reduced doses of IFN-alpha).

A: According to the comments of reviewer #3, we have added Melichar’s manuscript as a reference, and modified the sentence to “So far, all [8-10, 20] but one study [21] have demonstrated the effectiveness of IFN-α when combined with molecular targeted drugs (Table 4).” in the DISCUSSION on page 13, lines 212-213.
Q11: Page 14 line 226: yes but to specify that in the Bracarda study the complete responses were only in the arm with 9 MUI x 3 of IFN.
A: Thank you for your important questions. However, reviewer #3 may have misunderstood the results of Bracarda study, because 3 CRs were observed only in the arm with 3MUI x 5 of IFN. Anyway, we have modified the sentence to “Taken together, these findings indicate that sorafenib, in the absence of IFN-α, cannot induce the immune response, and thus, IFN-α may have prolonged the CR in the several reported cases (6%) of the Rapsody study [13] and in the one case (2.4%) of our study (Table 4).” in the DISCUSSION on page 14, lines 229-232.

Q12: Figure 2; to add two horizontal lines at 20% and -30% points (do discriminate stable disease from response and progression)
A: According to the comments of reviewer #3, we have added two horizontal lines at 20% and -30% points in Figure 2. Although 14 patients showed more than 30% decrease in Figure 2, confirmed response was not observed in 3 patients. Thus, objective response rate was 26.2% (11/42).

Major Compulsory Revisions
Q1: Page 12, lines 179-180: the OS was excellent but it may be strongly influenced by treatments administered after protocol drugs. To add in the discussion that also the post-treatment is a relevant potential factor that influenced the good OS.
A: According to the comments of reviewer #3, we have added a sentence, “Alternatively, the post-treatment after this study may be a potential factor that influenced the good OS, although we have not examined it.” in the DISCUSSION on page 13, lines 206-207.

Q2: Page 13, lines 200-202: To add in the discussion that also the distribution of prognostic factors could be a relevant potential factor that influenced the good OS. The patient distribution according to motzer score or Heng score schould be added to the results section.
A: According to the comments of reviewer #3, we have added MSKCC prognostic risk in the Table 1, and added a sentence, “Twelve, 28, and 2 patients revealed Favorable, Intermediate, and Poor in MSKCC prognostic risk score, respectively.” in the RESULTS on page 11, lines 167-169, to show the distribution of mRCC patients in this
study, as mentioned at Q1 of reviewer #2.

**Q3:** Page 15, line 250: a study comparing sorafenib alone versus a combination of sorafenib with an optimal dose of IFN-α would be not ethical because the standard globally accepted first line is sunitinib or pazopanib or bevacizumab + interferon, not sorafenib.

A: According to the comments of reviewer #3, we have changed the sentence to “Therefore, a prospective randomized trial comparing sunitinib or pazopanib versus a combination of sorafenib with an optimal dose of IFN-α will be needed to evaluate the efficacy of sorafenib plus IFN-α as first line treatment for mRCC patients.” in the DISCUSSION on page 16, lines 264 to 267.

**Q4:** Page 16, line 259: the word “may” should be changed in “could” and to add “in the future” at the end of the sentence.

A: Thank you for your important comments. However, according to the comments of reviewers #1 and #2, we have already changed the sentence to “Our results have clearly demonstrated that sorafenib plus IFN-α treatment is safe and effective for untreated mRCC patients.” In the CONCLUSIONS on page 17, lines 272 to 274.

**Q5:** Table 1: to add prognostic score (MSKCC or Heng or both). To add subsequent treatments.

A: According to the comments of reviewer #3, we have added MSKCC prognostic risk in the Table 1 to show the distribution of mRCC patients in this study, as mentioned above. However, as the subsequent treatments’ analysis was not included in this study, it was impossible for us to add the data, unfortunately.

We would like to thank both you and the reviewers for helping us improve our manuscript. We hope that the revised manuscript is now suitable for publication in BMC Cancer.

Best Wishes,

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