Author's response to reviews

Title: Randomized phase II study of pemetrexed/cisplatin with or without axitinib for non-squamous non-small-cell lung cancer

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

Re: Resubmission of the manuscript MS 7183263401163512

On behalf of all authors, I would like to resubmit our manuscript titled “Randomized phase II study of pemetrexed/cisplatin with or without axitinib for non-squamous non-small-cell lung cancer” to be reconsidered for publication in *BMC Cancer* as an original research article. We thank referees for their comments and suggestions. We have listed below our point by point response to referees’ comments and the revisions that were made in the revised manuscript. We have added names of all institutional review boards and independent ethics committees under Appendix, per editorial request. We believe that we have addressed referees’ comments satisfactorily and revised the manuscript appropriately. We hope that the manuscript is now acceptable for publication in *BMC Cancer*.

Thank you for your consideration and we look forward to your response.

Sincerely yours,

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**Response to referees’ comments**

Referee #1

**Comments:** This is a well written paper explaining clearly the results of a 3 arm randomized phase II study exploring the addition of 2 different dosing schedules of axitinib to the standard cisplatinumpPemetrexed regimen in non-squamous NSCLC. The methods applied seem adequate and the data (although negative) seems sound. The manuscript clearly adheres to relevant standards and the discussion and conclusions are well balanced. The literature seems well cited as well.

**Response:** We thank the referee for his nice comments.
Belani et al conducted another study with an inhibitor of VEGFR in combination with Cis-Pem as first line treatment in advanced NSCLC (non squamous). This study failed to reach its primary endpoint i.e. PFS assessed by investigators, despite significant improvement of the response rate in the two groups receiving axitinib.

**Discretionary revision 1:** Despite the negative results, one of the interesting data is the better PFS and OS observed in the three groups of patients than in the landmark study of Scagliotti et al. (almost + 3 and +5 months respectively). These differences were quoted by the authors and were judged important enough as to be developed in the first chapter of their discussion. They suggested different reasons of which the presence of better prognostic factors in the population studied and also the possible influence of subsequent treatments. Data on post discontinuation therapies were nevertheless not shown but could perhaps be given as they were in the study of Scagliotti et al.

**Response:** We agree with the referee that follow-up therapy post-discontinuation would affect OS, as we stated in our original manuscript (page 11-12): “Another possible explanation for longer survival in the control arm may be due to the subsequent therapies, especially EGFR inhibitors in patients with tumors that harbor EGFR mutations [16, 17] and crizotinib in ALK-positive NSCLC [18]”. Although the percentage of patients who received any subsequent follow-up systemic therapy, including EGFR inhibitors, in our study was not too different from that of the landmark study by Scagliotti et al (J Clin Oncol 2008;26:3543-51) (47% and 52.6%, respectively), no data on specific mutations in EGFR or ALK, which might have identified individuals who could have benefited specifically from these follow-up therapy, were available in either study. As suggested by the referee, we have revised our original statement and added a phrase regarding post-study therapy on in the revised manuscript (page 12) as “Although the percentage of patients in this study who received any follow-up systemic therapy post-study, including EGFR inhibitors, was not too different from that reported for patients who received pemetrexed/cisplatin in the previous phase III trial [10] (47% compared with 52.6%, respectively), no data were available in either study to identify individuals with genomic mutations in **EGFR** or **ALK**, who would have benefited from the specific molecularly-targeted follow-up therapy”. 

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**Note:** The above text has been revised to correct errors and improve clarity.
Discretionary revision 2: If we look at the survival curves, we can see that the group of patients who received axitinib continuously had a better survival between the 6th and the 10 or 12 months suggesting three explanations: an imbalance in post-discontinuation therapies between the groups (cfr previous point), a real activity of adding this VEGFR inhibitor continuously to chemotherapy, or an imbalance in the per protocol treatment. Indeed, as written in the section “Study design and treatment”, the dose of axitinib could be reduced according to the side effects but also increased if the tolerance was good (except if development of hypertension). Data or comments according to the number of patients who received more axitinib were unfortunately not shared. Authors could give comments on these points.

Response: It is true that OS for arm I appears to be longer than arm II or III between 6 and 10 months per Figure 2b. However, the overall curve shows hazard ratio of 1.05, and so we conclude that there is really no statistical difference.

Discretionary revision 3: Another concern is the design of the study. When almost in all the other studies with anti-VEGF agents, these agents were maintained after chemotherapy, this was not the case in the present study. What is the rationale behind this decision?

Response: In this study, patients received single-agent axitinib maintenance therapy after chemotherapy, as indicated under Patients and Methods in the original manuscript (page 7): “Patients randomized to arms I and II who completed four to six cycles of axitinib plus pemetrexed/cisplatin and had stable disease or better continued to receive single-agent axitinib maintenance therapy until disease progression, unacceptable toxicity, or withdrawal of patient consent.” To make this point clearer, we added the following sentence under Results in the revised manuscript (page 10): “Following combination treatment, 58% of patients in arm I and 50% in arm II received single-agent axitinib maintenance therapy”.

Major compulsory revision
None

Minor Essential revision
None

Referee #3

Belani et al are presenting a randomised phase II study assessing the effectiveness in adding axitinib to cisplatin-pemetrexed in non-squamous NSCLC. The study cannot demonstrate an
additional value of axitinib to conventional chemotherapy for PFS, its primary endpoint. This is in agreement with a recent meta-analysis on the role of oral antiangiogenic agents showing an increase in response rate without survival improvement by adding those agents to chemotherapy (Eur J Clin Pharmacol 2013; 69(2):151-9).

**Major compulsory revisions**

1. The authors are presenting data obtained at different time-point. If all patients completed follow-up on May 18, 2012 then it can be suggested that PFS and safety also can be obtained at this date. Further, if duration of response is available on December 21, 2011, I do not understand why the authors are presenting PFS data obtained 9 months before.

**Response:** After the database lock (May 18, 2012), only OS, duration of response among responders, number of deaths, and serious AEs were updated. Since the results of efficacy endpoints were generally comparable between the analyses using different data cutoff dates (e.g., median PFS from the first analysis was 8.0, 8.1, and 7.1 months in arm I, II and III, respectively, compared with 8.0, 7.9, and 7.1 months from the second analysis; similar results were obtained for OS), we presented the most up-to-date results for each endpoint in the original manuscript. However, to address the referee’s concern, we modified the sentence in the original manuscript on page 8 that “OS, duration of tumor response, number of deaths, and serious AEs are based on the most recent data at the time of final database lock on May 18, 2012, after all subjects had completed the follow-up period” to “The final analysis for OS, duration of tumor response among responders, number of deaths, and serious AEs was conducted after the database lock on May 18, 2012. For each endpoint, the most-up-to-date results are presented in this manuscript.” in the revised manuscript (page 9). In addition, we added a sentence that “It should be noted that median PFS in each arm were very similar between the two analyses” in the same section.

2. The primary endpoint is PFS. Can the authors precise if the follow-up post chemotherapy was similar in the three arms, also for the axitinib maintenance period?

**Response:** Yes, the percentage of patients who received any follow-up systemic therapy was generally similar between the three arms (62% in arm I, 53% in arm II, and 47% in arm III). As indicated in the original manuscript (page 7), no crossover between different treatment arms was allowed, and the percentage of patients who received >6 cycles of axitinib was similar between arm I and II.
3. In the statistical analysis, it is unclear why the authors are suggesting that “The emphasis of the final analysis was not on hypothesis testing”. I suggest suppressing this confusing sentence. The primary endpoint on which are based the statistical considerations is the subject of the final analysis and secondary objectives have only exploratory value. With the same idea, p values are not for reference only at least for the primary endpoint.

**Response:** Since this was a phase II study, our primary aim was to estimate hazard ratio and confidence intervals for PFS between axitinib-containing arms and pemetrexed/cisplatin control arm. However, the referee’s point is well taken. We have deleted the sentence in question in the revised manuscript, as suggested.

4. As the authors are presenting statistical comparisons for response rate and MDASI, they also have presenting p value for toxicity comparisons among the 3 arms.

**Response:** According to the study protocol, the safety was to be assessed by summarizing all treatment-emergent adverse events and laboratory, biochemical, and hematologic parameters, graded by maximum Common Terminology Criteria for adverse events (CTCAE). In this study, it was not intended to compare safety between the 3 treatment arms by a formal statistical testing.

5. Figure 1: which was the reason for study termination by the sponsor in 34 cases?

**Response:** The study was terminated in 34 patients at the end of the study. It should be noted that none of these patients were receiving active treatment and all were being followed for OS only at termination.

**Minor essential revisions**

1. The editorial independence from the sponsor has to be explicated.

**Response:** Mariko Nagashima is a professional medical writer at Engage Scientific Solutions, a medical publications agency that has been contracted by Pfizer to assist with publications on axitinib. This agency strictly adheres to publication and authorship guidelines recommended by ICMJE (http://www.icmje.org/) and GPP (http://www.gpp-guidelines.org). As such, her non-author contributions to this manuscript and source of funding are clearly stated in the acknowledgments section.

This article was written entirely, from concept to submission, under the direction of the authors. Ms. Nagashima provided writing and editorial assistance to facilitate development of a manuscript that reflects the authors’ opinions, and is medically accurate, readable, and in compliance with current regulatory requirements. Given that the authors are solely responsible
for the content and interpretations included in the manuscript without input from any commercial source, we believe that this original article is scientifically and medically rigorous and unbiased and that the editorial and peer review process should be able to judge the manuscript on its merits.

2. References 4 and 5 are inappropriate when meta-analyses on antiangiogenic agents have been published (one for oral antiangiogenic agents and two for bevacizumab).

Response: We appreciate the referee’s suggestion to cite a paper on meta-analyses. We have replaced reference 4 with the paper on meta-analyses (Xiao et al., Eur J Clin Pharmacol 2013;69:151-9) suggested by the referee in the revised manuscript (page 4). The reference 5 (a review published in 2012) was retained as we believe it provides useful information, covering several multi-targeted antiangiogenic agents.

3. Can the authors specify if patients with recurrent NSCLC are eligible if not amenable to a curative treatment?

Response: Yes, patients with recurrent NSCLC were eligible for the study whether the disease was amenable to a curative or not, as indicated in the original manuscript under Patients and Methods (page 5) and in Table 1. Prior systemic therapy was not permitted, as described in the manuscript.

4. It is unclear if patients in the phase I lead-in are included in the analysis of the randomized phase II.

Response: A non-randomized phase I lead-in (n = 10) evaluated the pharmacokinetics and safety of axitinib given continuously with pemetrexed and cisplatin administered once every 21 days, as described in the original manuscript under Patients and Methods (page 6). The safety data in these patients were analyzed separately from the patients enrolled in the randomized phase II study, but the results were not included in the manuscript. To make this point clearer, we have added a clause “and the results from only the randomized phase II portion were presented here” following the sentence “Safety was analyzed in patients who received at least one dose of study drug” on page 9 in the revised manuscript.

5. The dose adaptation plan must be available, at least in an appendix.
Response: In the original manuscript, we provided dose adaptation plan for axitinib as well as pemetrexed and cisplatin under Patients and Methods (page 6). However, as suggested by the referee, we have inserted more details in the revised manuscript (page 6-7).

6. How many chemotherapy cycles were planned? 4 or 6?
Response: Up to 6 cycles of chemotherapy was planned as indicated in the original manuscript under Patients and Methods on page 6 (page 7 in the revised manuscript): “Pemetrexed 500 mg/m2 and cisplatin 75 mg/m2 were administered intravenously on day 1 of each of up to six 21-day cycles”.

7. Dates of first and last inclusion have to be provided.
Response: We have inserted this piece of information under Results on page 9 in the revised manuscript per referee’s suggestion.

8. More information on the dose intensity in each arms are needed
Response: As suggested by the referee, we have provided the dose intensity for axitinib, pemetrexed, and cisplatin in each arm under Results on page 10 in the revised manuscript.

9. The authors are presenting the investigator-assessed data. Will it say that data were centrally revised? If yes, did it a significant discrepancy between investigator and central assessments?
Response: In this phase II study, tumor responses were assessed only by investigators, and not by an independent review committee, as indicated in the manuscript (under Patients and methods section on page 6; under Results on page 10; and Table 2 caption).

10. As there is no statistical difference, we cannot conclude that the HR for PFS is favoring axitinib when comparing arms I and III (page 9).
Response: In the current comparison of PFS between arm I vs. III, a HR below 1 would indicate reduction in hazard rate to favor axitinib whereas HR above 1 would indicate reduction to favor pem/cis. Since P value was 0.36, we made a statement in the original manuscript (page) that “The hazard ratio (95% CI) was 0.89 (0.56–1.42; P = 0.36) for arm I versus arm III, favoring axitinib, without reaching a statistically significant difference”. However, to avoid any misunderstanding, we have deleted the phrase “favoring axitinib, without reaching a statistically significant difference” in the revised manuscript (page 10), as pointed out by the referee.
11. Table 2: what means “indeterminate”

**Response:** The word “indeterminate” is defined in this study as patients who did not have evaluable baseline scan or no post-randomization scan or those who had stable disease for <8 weeks. We have added this definition in a footnote to Table 2 in the revised manuscript.

**Editorial request:**

Please update your ethics statement to include the name of the ethics committee that approved your study.

**Response:** The names of all institutional review boards and independent ethics committees are provided in Appendix in the revised manuscript, as requested.