Author's response to reviews

Title: Phase II study of two dose schedules of C.E.R.A. (Continuous Erythropoietin Receptor Activator) in anemic patients with advanced non-small cell lung cancer (NSCLC) receiving chemotherapy

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Author's response to reviews: see over
Phase II study of two dose schedules of C.E.R.A. (Continuous Erythropoietin Receptor Activator) in anemic patients with advanced non-small cell lung cancer (NSCLC) receiving chemotherapy

By Vera Hirsh, John Glaspy, Paul Mainwaring, Christian Manegold, Rodryg Ramlau and Joseph E Eid

The authors would like to thank the reviewers for their useful and interesting comments. Please find below our point by point response to each of the reviewers comments. We have also amended the manuscript accordingly, with all changes highlighted in yellow so that they can be seen easily.

Referee 1 (Professor R Pirker)

General

The papers reports on a randomized phase II dose-finding study of CERA for the treatment of anemia in patients with advanced non-small cell lung cancer (stages IIIB & IV). The trial evaluated CERA administered either weekly or 3-weekly and at each schedule with 3 different doses. The authors found a dose-dependent effect of CERA on the increase of Hb levels at both schedules and on the proportion of patients achieving a hematopoietic response.

CERA was well tolerated. The findings are of clinical relevance. The data are well and thoroughly presented and the paper is well written.

Discretionary revisions (which the author can choose to ignore)

1. The authors should specify IIIB which most probably refers to “wet” IIIB only.
   
   The study did not restrict entry to patients with “wet” stage IIIB NSCLC only. Between 17 and 38% of patients (depending on treatment group) had received prior radiotherapy before entering the study but no patients received radiotherapy during the study.
2. Background: The authors mention chemotherapy as part of the management of stage III-IV NSCLC. They might mention that radiotherapy is added to chemotherapy in patients with stage III (N2-3). Alternatively, they might specify stage III as “wet stage IIIB” where no radiotherapy is added. *We have made this change to the introduction as suggested by the referee (first paragraph of the “Background” section).*

3. Exclusion criteria: malignancy of the CNS: “brain metastasis” might be more appropriate. *

*This refers to page 8, paragraph 2 of the manuscript. We have made this change to the manuscript as suggested by the referee.*

4. Study design: “.. where patients received CERA over a 12 week-treatment period…” change to “… where patients were planned to receive CERA over a …”.

*This refers to page 9, paragraph 1, line 2. We have made this change recommended by the referee.*

5. Page 9: what does appropriate clinical intervention refer to?

*This comment refers to page 9, end of second paragraph. We have amended the text to explain the types of clinical intervention that were considered as follows: “If the Hb level was >14 g/dL, patients were evaluated for appropriate clinical intervention (for example, phlebotomy or use of fluids if hydration was considered necessary).”*
Referee 2 (Dr A Mancuso)

General

I read your paper entitled ‘Phase II study of two dose schedules of C.E.R.A. (Continuous Erythropoietin Receptor Activator) in anemic patients with advanced non-small cell lung cancer (NSCLC) receiving chemotherapy’, assessing efficacy and safety of different dose schedules of C.E.R.A. As you mentioned, higher dose schedules could give more information in terms of both efficacy and safety. Quality of written English is good and the paper is important mostly for those with closely related research interests.

However, I am unable to decide on acceptance until you have responded to the major compulsory revisions.

Major compulsory revision

1. Overall, the paper is interesting but not of immediate comprehension. A more schematic description is suggested.
   We agree that the design of the trial is quite complex and we attempted to address this by including Figure 1, which describes the randomization of patients to the individual treatment groups and the flow of patients through the study. Because of the referee’s concerns, we have attempted to simplify Figure 1 and we have also modified the text to include additional headings. We believe that the study design is more easily understood now.

2. In the Abstract Results (page 3): it is not understandable which is the best dose between the 6 ones used.
   This was a phase II trial designed to assess 6 doses of C.E.R.A. according to two dose schedules. The doses used were based on an earlier phase I study of patients with multiple myeloma who were selected to be sensitive to ESA therapy based on low endogenous erythropoietin levels. The current study provides information that C.E.R.A. has activity in anemic patients with stage IIIIB/IV NSCLC. Dose-dependent increases in Hb were observed when the change from baseline during week 5 to week 13 was assessed with the
C.E.R.A. doses used (maximum 2.1 µg/kg QW and 6.3 µg/kg Q3W). The best dose in the current study, in terms of improvement in Hb parameters, was the 6.3 µg/kg Q3W dose, but it is likely that more substantial erythropoietic benefits would be observed with higher doses of C.E.R.A. Because of the reviewer’s concerns, we have modified the abstract so that it is more obvious that the 6.3 µg/kg Q3W dose provided the best efficacy in the study, but additional studies are required to determine the optimal dose of C.E.R.A. in these patients:
“There were dose-dependent increases in Hb responses. C.E.R.A. appeared to be more effective when the same dose over time was given Q3W than QW, with a suggestion that C.E.R.A. 6.3 µg/kg Q3W provided the best efficacy in this study. However, further dose-finding studies using higher doses and permitting dose escalation are required to determine the optimal C.E.R.A. dose regimen in cancer patients receiving chemotherapy.”
Statistical analysis should be reported. Finally, more simple description of the results is suggested.
The abstract has been modified to take into account this comment. We have simplified the description of the results and added a description of the primary efficacy parameter and a definition of the hematopoietic response rate as follows:
“Primary endpoint was average Hb level between baseline and end of initial treatment (defined as last Hb measurement before dose reduction or transfusion, or the value at week 13). Hematopoietic response (defined as Hb increase ≥2 g/dL determined in two measurements within a 10-day interval or achievement of Hb ≥12 g/dL with no blood transfusion in the previous 28 days) was also measured.”

3. Page 9, Line 18: explain the meaning of “appropriate clinical intervention”.
   Please see comment 5 from Referee 1.
4. Page 13, Lines 13–18: explain the reason of investigator withdrawal and of the site error.

One patient was withdrawn from the 0.7 µg/kg QW group at the discretion of the investigator. However, the reason for this withdrawal is unknown. One patient was withdrawn from the 6.3 µg/kg Q3W group by the investigator because he was started on third-line treatment (gefitinib) and the investigator erroneously thought the patient had to be withdrawn. This was listed as a site error. A summary of this has been added to page 14, paragraph 2.

5. Page 13, Line 22: give a reason of a so high number of protocol violations.

Overall, 44 and 36 patients in the QW and Q3W groups, respectively, were excluded from the per-protocol (PP) population, the most common reason being the need for blood transfusion during treatment in 39 (89%) and 28 (78%) patients, respectively. Some patients were excluded from the PP population for more than one reason. Acute infection or inflammatory disease (CRP >50 mg/L) led to the exclusion of 6 patients in the QW cohort and 8 patients in the Q3W cohort. Three patients from the Q3W cohort were excluded because they received blood transfusion in the 4 weeks before study entry, while one patient in the Q3W cohort was excluded because inclusion criteria were not met. This information has been added to page 15 of the revised manuscript.

Patients who received blood transfusions during the study were not really protocol violations per se (as the purpose of this study was dose finding), rather they were excluded from the PP population so that true effect of C.E.R.A. on Hb levels could be determined without the compounding effect of blood transfusions. All efficacy parameters were determined in both the ITT and PP populations with results following largely similar trends in the two populations.
Referee 3 (Dr T Littlewood)

General

An interesting report on the use of CERA in anemic patients with non-small cell lung cancer. The study was well-designed and written.

The results are disappointing with a Hb response (the main criteria used in most previous studies of erythropoietic agents in patients with cancer) of only around 50% of what might normally be expected, even at the highest dose schedule used in this study. It would seem that the CERA dose will need to be reassessed, at least for similar patients in future studies.

The authors do comment on some reasons for the poor response. Could they also comment on the frequency of iron supplementation and whether oral or intra-venous iron was used.

*It was recommended that patients with a TSAT of <20% and ferritin <100 ng/mL during the study received iron supplementation. The preferred method of administration was intravenously, however oral supplementation was permitted.*

*Overall 97 patients received iron therapy and of these most (87 patients [90%]) received oral iron supplementation. The proportion of patients receiving intravenous iron supplementation was similar across all six C.E.R.A. groups. Overall, the percentage of patients receiving concomitant oral iron supplements was higher among patients who received C.E.R.A. Q3W (46% to 53%) than among patients treated QW (26% to 36%). This information has been added to the end of page 15 of the manuscript.*

This is an important early study with this new compound. I think there will be interest in the data and disappointment with the response achieved. Well worthy of publication.
Referee 4 (Dr A Donner)

General

This is well-written methodically strong paper which will serve as a useful addition to the literature provided the points raised below are addressed.

**Major compulsory revisions** (that the author must respond to before a decision on publication can be reached)

1. For the sample size provided on page 11, more detail as to its derivation, or at least an appropriate reference, should be provided.

   The sample size was calculated based on the assumption of an effect size (ie, mean difference divided by its standard deviation) of 1 (a one standard deviation difference) between the lowest and the highest dose groups and an effect size of 0.5 (half of a standard deviation) between the lowest and the medium or medium and highest dose groups. A sample size of 31 patients in each dose group was considered to be sufficient to reject the overall F-test of no difference between the time adjusted Hb AUC of all three dose groups with a power of at least 90% at the significance level of 2.5% (two-sided). A power of 90% and an $\alpha$-level of 2.5% were chosen to address the multiplicity caused by the independent application of the closed test procedure in the once weekly and once every three weeks dose schedules. Thirty five patients were planned to be enrolled, assuming that up to 10% of the patients would not be evaluable for the primary efficacy analysis due to early withdrawal.

   The manuscript gives the following information about the sample size calculation:

   “A sample size of 210 patients (35 per treatment group) was calculated to have 90% power in rejecting the overall F-test of no difference among the three treatment groups in each dose schedule group in the primary efficacy variable at the alpha level of 0.025 (2-sided). The 90% power and 0.025 significance level were chosen to address the multiple testing of the two-dosing schedule. This sample size included an anticipated dropout rate of 10%.”
2. Some discussion as to why the summary measure AUC was chosen as the primary measure of efficacy in this study, rather than other possible choices, such as the final value, average of the last two visits, final value-initial value, etc., would be valuable.

The summary measure of AUC was chosen to assess average Hb response during the initial treatment period. Considering commonly observed large variability of Hb measurement, we considered the Hb value at one or two selected time points would not adequately reflect treatment effect. Instead, an approach measuring the cumulative effects would enable robust evaluation of biological activity of the treatment based on the benefits over the entire course of therapy. The manuscript has been modified to include this information on page 12, last paragraph.

3. In the section on Statistical Analyses, it is stated that ANOCOVA will be used to analyze the primary efficacy variable, while in the results provided on page 14 the analyses are presented instead in terms of mean change from baseline. This should be clarified.

The results are presented in 95% confidence intervals, which were derived from the ANCOVA described in the statistical analysis.

4. The authors present separate analyses for the different dose groups. Given the doses are ordered, would it not be more powerful to perform a trend test across these groups? This would also have the advantage of reducing the multiplicity problems caused by the construction of separate confidence intervals.

The primary focus of the presentation in this manuscript was estimation of treatment effect of each dose to evaluate their clinical relevance. An attempt was made to assess dose-response trends by comparing the estimates among the doses. Assessment of clinical relevance of the dose-response
trend is the main focus of the manuscript, in contrast to its statistical significance from hypothesis testing of the trend test.