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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Point by point response to reviewer comments

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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 reviewer for the useful and interesting comments. Please find below our point by point response to each of these comments. We have also amended the manuscript accordingly, with all new changes highlighted in blue so that they can be seen easily.

1. Overall, the results are not controlled with placebo, appropriate statistical analysis is missing and it sounds to me that drug dosages are not well calibrated.

This study was a dose-finding, phase II study. The doses chosen were based on a previous phase I/II trial that showed efficacy of C.E.R.A. over the dose range 2.0-8.0 µg/kg Q3W in patients with multiple myeloma who were selected to be responsive to ESAs based on their baseline endogenous erythropoietin levels. As patients in the current study were anemic at baseline and this was a dose-finding study, it seemed unnecessary to include a placebo group, as a response to C.E.R.A. was anticipated during the study at least at the higher doses. Indeed, dose-dependent increases in Hb were observed (based on the change from baseline during week 5 to week 13) with the C.E.R.A. doses used (maximum 2.1 µg/kg QW and 6.3 µg/kg Q3W). In retrospect, it would appear that additional higher doses of C.E.R.A. should have been tested in this study. Further controlled trials that evaluate higher doses of C.E.R.A. are currently underway in patients with cancer.
To address the comment regarding statistical analysis, some additional details have been included on pages 12 and 13 of the manuscript. Some details are also included in the description of the efficacy endpoints on page 10. We believe that a comprehensive description of the statistical analysis performed during the study has now been included in the manuscript over some 1.5 pages of text. This section had already been updated based on the comments of reviewer 4 at the time of the first revision of the manuscript and to include any additional information would make the manuscript unnecessarily long without providing benefit to the reader. In addition, based on comments from Dr Mancuso at the time of the first revision, the abstract was modified to include additional statistical analysis information.

2. Moreover, the number of protocol violations is very high and reason of some patient withdrawal is not explained.

We thank the reviewer for this point about the protocol violations in this study and, to avoid any misunderstanding or confusion, we have added a new table 1, which includes the reasons for exclusion from the per-protocol population:
### Table 1. Analysis populations and reasons for exclusion from the per-protocol population

<table>
<thead>
<tr>
<th></th>
<th>C.E.R.A. dose group (µg/kg QW)</th>
<th>C.E.R.A. dose group (µg/kg Q3W)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Number of patients randomized</td>
<td>36</td>
<td>37</td>
</tr>
<tr>
<td>Number of patients in ITT/safety population*</td>
<td>36</td>
<td>37</td>
</tr>
<tr>
<td>Number of patients in PP population</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>Number of randomized patients excluded from PP population **</td>
<td>14</td>
<td>14</td>
</tr>
</tbody>
</table>

**Reasons for exclusion from PP population**

<table>
<thead>
<tr>
<th>Reason</th>
<th>0.7</th>
<th>1.4</th>
<th>2.1</th>
<th>2.1</th>
<th>4.2</th>
<th>6.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood transfusion during study period</td>
<td>13</td>
<td>12</td>
<td>14</td>
<td>16</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Acute infection/inflammatory disease (CRP &gt;50 mg/L)</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Received no study medication</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Blood transfusion during 4-week period before study entry</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Inclusion criteria not met</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

**C.E.R.A.**: Continuous Erythropoietin Receptor Activator.
CRP: C-reactive protein.
ITT: intent to treat.
PP: per-protocol.
QW: once weekly.
Q3W: Once every 3 weeks.

*One patient in the C.E.R.A 2.1 µg/kg QW group, three patients in the 2.1 µg/kg Q3W group and one patient in the 6.3 µg/kg Q3W group were excluded from the ITT and safety analyses because they did not receive any study drug.

**Patients may have had more than one reason for being excluded from the PP population.

*However, we disagree that the number of protocol violations was high in this study. Most patients were excluded from the per-protocol population because they had received blood transfusions. Blood transfusions were permitted according to the protocol in the event of medical need such as marked anemia symptoms or impending septic shock. Rather than being a protocol violation, patients receiving blood transfusions during this study were excluded from the per-protocol population so that the “real” effect of C.E.R.A. could be investigated without the compounding effect of blood*
transfusions on hemoglobin levels. This point has been made more apparent in the description of the per-protocol population on page 12 of the manuscript. In the manuscript, we have always given the results for the intention-to-treat population, and used the per-protocol results to support these.

The only real protocol violations were the inclusion of patients who received blood transfusions in the 4 weeks before study entry (3 of the 218 patients); inclusion criteria not being met (1 of the 218 patients) and acute infection/inflammatory disease (14 of the 218 patients). A rate of 6% for acute infection/inflammation is not unexpected in this patient population, all of whom were receiving first- or second-line chemotherapy for lung cancer. Nevertheless, such conditions are known to result in resistance to ESAs (Bokemeyer et al. Eur J Cancer 2007, 43:258-270).

Reasons for patient withdrawal are given in Figure 1 of the manuscript (copied on to page 4 of this point by point response for your information). Since this information may be missed when reading the manuscript, we have directed the reader to look at Figure 1, when providing additional information on withdrawals on page 14, paragraph 2. All reasons for early withdrawal are given and there is no missing information.
Figure 1: Patient flowchart

Assessed for eligibility (n = 414)

Excluded (n = 196):
Inclusion criteria not met (n = 180)
Refused to participate (n = 6)
Other reasons (n = 7)

Randomized (n = 218)

Allocated to C.E.R.A. QW 0.7, 1.4, or 2.1 μg/kg (n = 109)

C.E.R.A. QW 0.7 μg/kg (n = 36)

Included in ITT/safety analysis (n = 36)

Discontinued (n = 8):
3 AEs;
3 deaths;
1 treatment refusal;
1 investigator decision.

Discontinued (n = 5):
2 AEs;
2 deaths;
1 treatment refusal.

Allocated to C.E.R.A. QW 2.1 μg/kg (n = 36)

C.E.R.A. QW 2.1 μg/kg (n = 35)*

Discontinued (n = 8):
3 AEs;
4 deaths;
1 treatment refusal;
1 failure to return.

Discontinued (n = 5):
2 AEs;
4 deaths;
1 treatment refusal;
1 failure to return.

Excluded (n = 196): Inclusion criteria not met (n = 180) Refused to participate (n = 6) Other reasons (n = 7)

Discontinued (n = 5):
3 deaths;
1 treatment refusal;
1 site error.

Allocated to C.E.R.A. QW 2.1, 4.2, or 6.3 μg/kg (n = 109)

C.E.R.A. QW 2.1 μg/kg (n = 37)

Included in ITT/safety analysis (n = 37)

Discontinued (n = 8):
3 AEs;
4 deaths;
1 treatment refusal;
1 failure to return.

Discontinued (n = 5):
3 deaths;
1 treatment refusal;
1 failure to return.

C.E.R.A. QW 4.2 μg/kg (n = 37)

Included in ITT/safety analysis (n = 34)*

Discontinued (n = 8):
3 AEs;
4 deaths;
1 treatment refusal;
1 failure to return.

Discontinued (n = 5):
3 deaths;
1 treatment refusal;
1 site error.

C.E.R.A. QW 6.3 μg/kg (n = 35)

Included in ITT/safety analysis (n = 34)*

Discontinued (n = 8):
3 AEs;
4 deaths;
3 treatment refusal;
1 site error.

AEs: adverse events.
ITT: intent to treat.
QW: once weekly.
Q3W: once every 3 weeks.

*One patient in the C.E.R.A. 2.1 μg/kg QW group, three patients in the 2.1 μg/kg Q3W group and one patient in the 6.3 μg/kg Q3W group were excluded from the ITT and safety analyses because they did not receive any study drug.