Author’s response to reviews

Title: Brain natriuretic peptide precursor (NT-pro-BNP) levels predict for clinical benefit to sunitinib treatment in patients with metastatic renal cell carcinoma

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Author’s response to reviews: see over
Reply to Editor

Ethics: please name the body that provided ethical approval for your study

- Reply: The study was approved by the local ethics review board (Theagenion Cancer Hospital Research and Ethics Committee). This was added to the revised manuscript.

Reply to reviewer 1 (Torgny Rasmuson)

The reference levels of plasma NT-pro-BNP vary with gender and age. The cut-off value in this study is not related to age and there is no reference to gender differences. The interference of gender and age could be discussed.

- We have added in the results: “NT-pro-BNP levels in healthy population are depended on age and gender (ref 12). In our cohort of metastatic RCC patients, NT-pro-BNP levels were not statistically significantly different in men than women and in older (>60 years old) that younger patients. Age and gender had no impact on the differences observed in fold-increase of NT-pro-BNP between PD and CB patients (supplementary table 1”).

<table>
<thead>
<tr>
<th></th>
<th>Baseline levels (pg/ml)</th>
<th>Ratio (day 15/0)</th>
<th>Ratio in CB patients</th>
<th>Ratio in PD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>391.5</td>
<td>1.85</td>
<td>0.94</td>
<td>3.91</td>
</tr>
<tr>
<td>Women</td>
<td>195.1</td>
<td>1.19</td>
<td>1.19</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.40</td>
<td>0.35</td>
<td>0.21</td>
<td>ND</td>
</tr>
<tr>
<td>≤60 years age</td>
<td>150.7</td>
<td>1.70</td>
<td>1.06</td>
<td>3.47</td>
</tr>
<tr>
<td>&gt; 60 years age</td>
<td>504.3</td>
<td>1.67</td>
<td>1.03</td>
<td>4.84</td>
</tr>
<tr>
<td>p</td>
<td>0.10</td>
<td>0.96</td>
<td>0.88</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Supplementary table 1. Baseline plasma NT-pro-BNP levels (pg/ml) and medianfold ratio after 15 days of sunitinib treatment according to age and gender. CB = Clinical benefit, PD = Progressive Disease.

Reply to reviewer 2 (Christopher W Ryan)

My only comment is to rephrase the 3rd to final sentence in the discussion to read “This is the first time that a potential “surrogate marker”..."

- The commend was rephrased.
Reply to reviewer 3 (Alistair W Stewart)

Comment 1

In the results you show an analysis that includes baseline levels and the change to 15 days. These two measures will be highly negatively correlated even if the baseline and the 15 day measures are independent. This is known as regression to the mean. Using variables of this type as explanatory variables in a regression model needs very careful interpretation. The sentence "Baseline NT-pro-BNP levels were not statistically significant when compared to change at 15 days (p-value=0.2912 and 0.0274 respectively)." does not make sense and does not convey the necessary care. My interpretation based of the information presented is that both the baseline measure and the change are associated with status but, by use of the logistic regression, it appears that the measure, change in the first 15 days, has most of the information in separating the two groups.

- We thank the reviewer for this excellent comment, the interpretation is correct since both the baseline and the 15 days change are associated with status with change at 15 days probably taking the lead in separation ability.

Thus we have replaced the sentences: “Baseline NT-pro-BNP levels were not statistically significant when compared to change at 15 days (p-value=0.2912 and 0.0274 respectively). Furthermore, the area under the ROC curve for the change at 15 days was 94.9%, while the high correlation between change at 15 days and disease progression is also depicted in figure 2 through the sharp increase in predicted probability of disease progression when there is an increase in plasma NT-pro-BNP levels”

With the following leveraging on the reviewer’s suggestion:

“Since in the logistic regression model baseline NT-pro-BNP levels were not statistically significant while change at 15 days was (p-value=0.2912 and 0.0274 respectively) it appears that the latter has most of the information in separating the two groups. Regression to the mean might have influenced this result. Furthermore, the area under the ROC curve for the change at 15 days was 94.9%, while the high correlation between change at 15 days and disease progression is also depicted in figure 2 through the sharp increase in predicted probability of disease progression when there is an increase in plasma NT-pro-BNP levels”
Comment 2

In the abstract please remove the redundancy from the sentence “Median progression-free survival was 12.0 months in patients with less than 1.5 fold increases or lower or equal to baseline NT-pro-BNP levels (n=22) and 3.9 months ...”. The words “or lower or equal to baseline NT-pro-BNP levels” can be removed.

• This was indeed redundant and was removed

Comment 3

In table 2 please clarify whether "Mean fold change" at each time point is in relation to baseline

• We have clarified it