Author’s response to reviews

Title: Predictive value of C-reactive protein in patients treated with sunitinib for metastatic Clear Cell Renal Cell Carcinoma

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Author’s response to reviews:

Dear Editor,

Thank you very much for your e-mail dated June 7, 2017, with constructive comments from the editor and reviewers. We hereby enclose a revised version of the manuscript entitled "Predictive value of C-reactive protein in patients treated with sunitinib for metastatic Clear Cell Renal Cell Carcinoma" for your consideration to be published in BMC Urology.

We kindly refer to the enclosed description of our response and revisions, which are in line with the suggestions from the reviewers. A detailed point-to-point response is given to all requests.

Page numbers and lines written in the replies refer to the revised manuscript.
Editor Comments:

As you will see from the statistical advisers' comments below, the response has been split regarding whether the study is sufficiently powered. We have come to the decision that we would still like to consider this manuscript for publication, but will require you to address the minor comments listed below, and ensure that the limitations are thoroughly acknowledged throughout the manuscript - including the Abstract Conclusions, the Discussion section and main Conclusions section.

Reply: We thank you for this opportunity. In accordance with the comments below, we have now acknowledged the study limitations in the Abstract, Discussion and Conclusion sections.

Pg 2, line 1: I have entered author no. 7’s email address.

Pg 3, line 22-23

Pg 15, line 2-3

Pg 17, line 9-10

Statistical Referee 1:

I would agree that the study is slightly underpowered to conduct specific subset analyses. That being said, I think this is a meaningful paper and would favor its acceptance pending revisions (mostly minor be completed). I would similarly agree with the Author and Editor's comments that the reviewer’s point that the present noted observations could be explained by luck is inaccurate and as you have stated is a P value of less than 0.01 is essentially that there is a 1% chance these observations could be made “by luck” and not due to the fact the null hypothesis is supported. I would in this regard completely dismiss this reviewer’s comment.

Reply: We agree with referee 1.

Statistical Referee 2:

I agree with the reviewer that the sample size is too small to draw any significant conclusion.
Reply: We are aware of the limitations associated with statistical power and sample size, and in the present version we have highlighted the limitations in the text.

Statistical Referee 3:

I my opinion, the small sample size can lead to chance findings in "both" directions, i.e. for showing a association and not showing an association.

So that alone may not be the reason to reject it.

The enthusiasm for the study may be dampened by the fact that it identifies a single variable as a predictor of response. Single, isolated predictors may or may not very useful in the clinical setting.

Reply: We agree that the usefulness of CRP as a single predictive marker of response needs to be confirmed in other studies. This limitation has been discussed in the manuscript, see a listing of changes under “Editor’s comment”.

Statistical Referee 4:

I reviewed the attached manuscript. The sample size is small. They did not do any multivariate analysis as far as I could tell.

Reply: We are aware of the limitations associated with statistical power and sample size, and in the present version we have highlighted the limitations in the text.

Statistical Referee 5:

I think authors should underline the low statistical power and the risk of false negative results. However the small sample size was sufficient to detect differences with a suitable p-value.

In this case sample size is a limit, but not insurmountable.
Reply: We are aware of the limitations associated with statistical power and sample size, and in the present version we have highlighted the limitations in the text. In addition to the corrections listed under “editor’s comments”, please also see page 16 line 23-25 in the manuscript.

Reviewer reports:

(Reviewer 1): This updated manuscript only sporadically addressed my previous comments. Basically, the study is too small for proper conclusions, e.g., several of the subgroups include 2, 3, 3, and 5 patients, rendering proper statistical analysis impossible. The authors finding of CRP as a predictive and prognostic factor might be caused by pure chance, as more established and stronger features in their analyses (e.g. IMDC and NLR) were not significant.

Reply: See also my previous email replies to this specific comment. We do not completely agree with the reviewer, that we only sporadically address his/her previous comments. The manuscript was substantially modified to meet all previous comments, and I refer to the previous cover letter. His/her major issue is the sample size, and we have discussed the limitations caused by small sample size in the revised manuscript. Nevertheless, the small sample size gives the study relative low statistical power to detect small differences in response rates in groups defined by the variables under investigation. Thus, there is a possibility that trials with a larger study cohort would find that variables such as NLR and IMDC are significantly associated with response to sunitinib, which have been shown in other studies. Still, the sample size was sufficient to detect major differences in response rates, like the one we report for CRP at baseline. In contrast to the comment from reviewer 1, this finding is not by pure chance. With a p-value of 0.01, there is only a 1% chance for this being a false positive finding.

Sincerely,

Oddbjørn Straume, MD, PhD (sign.)

Corresponding author