Author's response to reviews

Title: Organ-specific and tumor size-dependent response to sunitinib in clear cell renal cell carcinoma

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Version: 2 Date: 10 December 2013

Author's response to reviews: see over
Replay to Professor Thomas Schwaab

The background is too short and does not accurately reflect the development in TKIs and predictors for response over the past 2 years.

RE: Thank you for your comment regarding the background. As stated in the background, this study was conducted to confirm the association between the pretreatment lesion size and the reduction rate by eliminating the biases of the TKI type, pathological type, and involved organs. This study was not an exploratory study for predictors of tumor responses after TKI therapy; therefore, we did not mention the details of those predictors. We felt that in terms of TKI development, this was an unrelated issue to the present study.

The n=38 is a surprisingly low number of patients to be enrolled in such a significant scientific project.

RE: As the reviewer indicated, the number of enrolled patients was small. In particular, the lesion numbers, excepting those in the lung, were too small to determine statistical significance. Therefore, we added the following sentences in the discussion. “However, as the number of assessed extra-pulmonary tumors was too small to determine statistical significance, further studies with large numbers of tumors will be needed to obtain conclusive results.” (page 9, line 12)

The method of describing treatment response under "statistical analysis" on page 5 is not well established as a response assessment.

RE: This study aimed to investigate 1) whether there was an association between the pretreatment tumor size and the reduction rate and 2) whether there was an organ-specific difference in the response to sunitinib. We used the Pearson correlation analysis to answer the former question. As the distributions of the tumor size and size reduction rate represented departures from normal distribution, the Kruskal-Wallis test was used as a non-parametric ANOVA to compare the values between 4 organs for the latter question, and the Mann-Whitney U test was adopted as a non-parametric test to compare the differences between the 2 groups.
On page 5, it appears that the primary kidney tumor was included in the statistical analysis. It is by now well-established that the primary tumor will show the least tumor response.

8 patients did NOT have a cytoreductive nephrectomy. This appears to be comparing apples to oranges.

On page 5, it is mentioned that there were 19 (!) indicator kidney lesions; yet only 8 patients did NOT have a nephrectomy. So, are these kidney lesions truly "metastatic" RCC or simple cysts?

RE: We thank the reviewer for their helpful comment. We included all the renal tumors, regardless of the primary or metastatic kidney tumor status. However, whether primary and metastatic tumors show similar responses to TKIs is a topic of interest. We wish to address this issue in a future study.

In this study, 8 patients who did not undergo nephrectomy were treated with sunitinib for various reasons. We have added a description regarding the renal tumor status of each patient to the text as follows: “Of the 15 patients with kidney tumors, 7 who underwent nephrectomy had target lesions in the contralateral kidney, including 2 patients with multiple lesions. The remaining 8 patients had primary kidney tumors that were diagnosed by percutaneous needle biopsy.”

Page 7 does not make any sense whatsoever: the authors go to great length to define predictors for 30 and 50% size reduction, but why does this matter clinically. There is no correlation with survival.

RE: The reviewer indicated that a discussion about the predictors of the size reduction rate was clinically meaningless. We assure the reviewer that survival prolongation is of principle importance in cancer treatment, and we are aware that the tumor reduction rate is not directly associated with patient survival. Given that this study aimed to assess the association between the responses to sunitinib as measured by the tumor diameter and pretreatment tumor size, an evaluation of the effect of the tumor size reduction rate on the survival is beyond the scope of this study. Although the results were not clinically insignificant, we believe that the results were of interest with regard to the mechanism of action of TKIs and the appropriateness of the RECIST criteria. We agree with the reviewer with regard to the overestimation of our results and have replaced “better outcome” with
“better tumor size reduction”. However, at ESMO 2013, Grunbald et al. presented excellent data in which the magnitude of tumor shrinkage after TKIs or mTOR inhibitors was significantly associated with the overall survival of 2749 patients with metastatic RCC who were enrolled in phase III and phase II studies (Abs# 2702). Therefore, it might not necessarily be true that the tumor reduction rate is not associated with survival.

Similarly, in the next paragraph there is a correlation between lung lesions and CRP, but there is no scientific explanation for this.

**RE:** We assumed that the tumor reduction rates would be influenced by the host factors listed in risk criteria such as the MSKCC and the Heng criteria. However, to date, there is no universally applicable biomarker in patients receiving any lines of therapy. In our series, more than one-fourth of the patients were treated with sunitinib as a second or further-line therapy; therefore, CRP was used as a biomarker that could possibly reflect the host response. Although CRP has not yet been widely recognized as a distinct prognostic marker, recent studies have demonstrated that CRP is a candidate serum marker for predicting the outcome of TKI-treated patients. We have cited references regarding the use of CRP as a biomarker and have addressed mechanism of influence of CRP regarding the response to sunitinib.
Reply to Professor Mayer Fishman

Major compulsory revisions:

6a. The term “better outcomes” as used in the conclusions (in abstract and also in the text) is overstated, since Quality of Life and Overall Survival were not addressed. Instead of this:
Patients with CCRCC who have smaller lung metastatic lesions and lower CRP levels may achieve better treatment outcomes with sunitinib therapy than those with extrapulmonary lesions, large lung lesions, and/or higher CRP levels.
Change to something such as this:
Patients with CCRCC who have smaller lung metastatic lesions and lower CRP levels may achieve better tumor size reductions with sunitinib therapy than those with extrapulmonary lesions, large lung lesions, and/or higher CRP levels.

6b. And similarly for this:
Patients with CCRCC who have lung metastatic lesions < 20 mm in diameter and lower CRP levels may achieve better treatment outcomes with sunitinib therapy than those with extra-pulmonary lesions, lung lesions diameter # 20 mm, and/or higher CRP levels

RE: We thank the reviewer for this comment. As the reviewer mentioned, “better outcome” could be an overstatement in this context. Therefore, we have corrected these expressions.

6c. Page 9: “However, since the present data demonstrate a greater chance of response with a smaller lung lesion, it is of primary importance not to miss the early time points for initiation of TKI treatment, especially sunitinib.” This discussion point is the only substantive change that is definitely required. The authors appear to be making a recommendation for early, pre-cytokine initiation of VEGFR-TKI on the basis of their data set, which included only patients under treatment with VEGFR-TKI, and no instances of treatment with cytokines, even despite their citation of references (1, 2) cited as showing better responses in smaller lesions, in lung lesions, in cytokine-treated patients.

RE: We thank the reviewer for pointing out a highly important issue. In this discussion, we never intended to recommend the early initiation of TKIs rather than cytokines. Our point is that a switch to TKIs should be strongly considered once the lesions grow to a certain size during watchful waiting or cytokine
treatment because of the limited response of larger tumors, even to TKIs. To avoid any misunderstanding, we have corrected the description as follows: “However, as the present data demonstrates a greater chance of a response with a smaller lung lesion, it is of primary importance not to miss the early time points for TKI treatment initiation in patients with progressive disease during watchful waiting periods or cytokine therapy.” (page 10, line 2)

6d. Page 11: An additional cautionary statement that the percent change of tumor size is not, to this point, demonstrated or necessarily directly connected to progression free survival would be appropriate.

RE: Based on the reviewer’s comment, we have added and corrected some sentences as follows: “Moreover, this study did not demonstrate an association between tumor response and patient survival. The percent change in the tumor size might not be directly correlated with the survival. Further analysis is necessary to determine how organ-specific response patterns to TKI treatments influence survival.” (page 11, line 11)

Minor essential revisions
9a. The bibliography needs to be copy-edited. Almost none of the journal titles in the citations are capitalized or abbreviated correctly. Also, full colon instead of period is used after the list of author names. I am sure I would do a hundred times worse in Japanese.

RE: According to the reviewer’s suggestions, we have edited the bibliography.

9b. Spelling of qd is usually qD; however just the word “daily”, instead of the abbreviation would be preferable. Presumably this was on the 28 days on/14 days off schedule.

RE: According to the reviewer’s suggestion, we have replaced “qd” with “daily” and have added the dosage schedule.

9c. Men and women are words to refer to human patients
30 males and 8 females --> #30 men and 8 women
9d. Words should be spelled:
1st line --> #first line
2nd line --> # second line
RE: According to the reviewer’s suggestion, we have corrected these words.

9e. Clinical benefit rate – although this is obvious from the prior mathematical breakdown, usually this is defined explicitly (CR + PR + SD for at least 3 months).

RE: We have added the definition of the clinical benefit rate.

9f. Page 8, “more advanced disease”: the term should be defined more explicitly, as it is the case that each of the patients under consideration had stage IV cancer. The issue, I think, is that those with larger or more rapidly growing tumors would be more often allocated to sunitinib than to sorafenib in clinical practice.

RE: We agree with the reviewer and have changed the sentence as suggested. “Since sunitinib showed a higher response rate than sorafenib, patients with larger or more rapidly growing tumors may be more often allocated to sunitinib than to sorafenib in clinical practice.” (page 9, line 1)