Reviewer's report

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

Version: 1
Date: 21 October 2013

Reviewer: Mayer Fishman

Reviewer's report:

1. Is the question posed by the authors well defined?
   Yes.

   The paper does give the beginning of a quantitative approach to what is (and has been) a logical, intuitive issue: There are biological differences across metastatic disease of stage IV RCC that depend on size and an anatomic location, and these differences also encompass the chance and magnitude of response to VEGFR-TKI. The quantitative deconstruction is key so as to evolve beyond the assumptions intrinsic in most drug pivotal trials, as well as single arm patient response series that blandly apply a single percent-change metric (generally directly dependent on RECIST assessment) and then consider this to be fair average of the impact of the drug on the disease in members of the population.

   While CRP levels could, again, intuitively be expected to be more elevated among those patients with large tumors and large aggregate tumor burdens, this work does address that question directly, and again with relevance to the issue of biological differences of different size tumors. In the smaller tumors, a discernible difference of response rate could be identified with less elevation of the CRP. This is again a concrete step in understanding that even among lung-only, even among small tumors, differences of biology that are directly measureable do have a relationship to response to a VEGFR-TKI, particularly for this data set for sunitinib.

2. Are the methods appropriate and well described?
   Yes

3. Are the data sound?
   Yes

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   Yes

5. Are the discussion and conclusions well balanced and adequately supported by the data?
   Yes, but some items annotated in #6 should be addressed.

6. Are limitations of the work clearly stated?
Major (very easy) 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.

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.

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.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?

Yes

8. Do the title and abstract accurately convey what has been found?

Yes

9. Is the writing acceptable?

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.

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.

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

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).

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.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

Financial interests relating to the last 5 years: I have been paid for work in advisory programs and in marketing programs for drugs related to kidney cancer including by Pfizer (manufacturer of sunitinib), Bayer, Onyx, Novartis, Prometheus, GSK, Genentech and Aveo. Research interests: I have worked with research trials or co-authored research papers about kidney cancer therapy incorporating sponsorship or drug provision from Pfizer, Bayer, GSK, Novartis, Prometheus, Amgen, BMS, Altor and, SWOG. This paper is one in which it is asserted that there are patients for whom sunitinib is a useful medication. This is not a position that is unusual and I feel that these relationships do not form a basis for a bias of the review of this paper.