Reviewer's report

Title: Circulating endothelial cells are an early predictor of tumor response in renal cell carcinoma patients treated with sunitinib

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Reviewer: Glenn Kroog

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Based on their title, the main thrust of the paper is Figure 2 and the associated text on pp. 7-8. My major concern with their data is how strong the conclusions can be when their study set is small and data on some patients are missing. I recommend obtaining statistician review to comment on how reliable conclusions can be in view of the small numbers, missing data and wide interpatient variation in CECs. This would help determine if the study meets the journal criteria for publication.

Major Compulsory Revisions:

1) Study size and design: Their conclusion that CECs are a predictor of sunitinib “response” depends upon 6 patients who rapidly progress on sunitinib (presumably progression by 12 weeks as per the methods on pp. 4-5) compared with 20 patients who had stable disease or better as best response on study (presumably a time to progression of >12 weeks). They do not state why they divided the patients this way, rather than in 3 categories as RECIST PD vs. SD vs. PR (although it is likely related to the small numbers). They should briefly explain their reasoning.

2) Addition of Figure 2C: If there is a true difference between what the authors refer to as “responders” and “non-responders” (and might more accurately be referred to as time to progression < 3 months vs. > 3 months) the question becomes is that because non-responders have: 1) high baseline CEC levels? (similar to monocyte levels in Figure 3B and sVEGFR2 levels in Fig. 4B) 2) low peak CEC levels? or 3) no increase in CEC levels with sunitinib? Option 3 is the conclusion of the authors. Since the key conclusion depends upon the difference in CEC changes between “responders” and “non-responders”, it would be useful to have a Figure 2C in which non-responders data are included to parallel Figure 2B and show the differences graphically. In that way the reader could reach their own conclusions.

3) Clarification of response by histology: since their study includes patients with both clear cell and non-clear cell histologies and the authors do not tell us which patients were in which group (responders or non-responders), it is possible that histology is driving some or all of their results. For example, the response to sunitinib in papillary renal cancer is poor and papillary renal cancer patients may have different baseline CECs than clear cell patients. The authors should state what the breakdown is for response by histology in order to evaluate this concern.
Specific issues regarding figures:

1) Figure 2A: the p value should not be included on the figure without identifying which time point it refers to. All data points after day 28 (or maybe day 84?) should be removed since there is selection bias in that only patients who have not progressed at a time point are still receiving sunitinib. The authors could choose to show how CECs decline in a subset of patients who continue on sunitinib long-term (and for whom they have samples over time).

2) Figure 2B: while there are 20 patients with baseline CEC levels on day 1, there are only 13 patients with data on day 14 and 18 patients with data on day 28. Other than mentioning on page 5 that 1 to 10 samples were taken per patient, the authors don’t explain who is missing or why and how that affected their analysis. It might be better to leave out data from day 14 from the figure since 1/3rd of patients did not have CECs checked on that date. A possibility is for day 14 data to be stated in the text as from a subset of the 20 patients that is consistent with data from day 28 (without giving a specific number of CECs or the p value).

3) Figure 4A: I have the same concern as in figure 2A. All data points after day 28 (or maybe day 84?) should be removed since there is selection bias in that only patients who have not progressed at a time point are still receiving sunitinib. The authors could choose to show how sVEGFR2 declines in a subset of patients who continue on sunitinib long-term (and for whom they have samples over time).

Discretionary Revision: Table 1 is included in the Methods section. Unless a journal policy to have this in Methods, it would seem more appropriate to include Table 1 in the Results section.

**Level of interest:** An article whose findings are important to those with closely related research interests

**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:**

I declare that I have no competing interests