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: Paul de Souza

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The authors describe interesting findings with regards to circulating endothelial cells (CECs), serum VEGF levels (sVEGFR2), and monocyte counts in relation to baseline and subsequent values during treatment of renal cancer patients with sunitinib. The question is important and the methods are sound. However, establishing potential biomarkers is a difficult thing to do, and the study suffers somewhat from over-interpretation in my opinion.

> - Major Compulsory Revisions

There are some missing data that would be useful to incorporate into this manuscript. For instance, it is stated that 6 patients were defined as non-responders and 20 were defined as responders, but this includes 9 patients who had stable disease. There is no mention of when response was assessed, how long stable disease had to be present, and how many biomarkers were evaluated for each patient.

As a result, there is a serious sampling error that can be inferred. For example, non-responders could have had only 1 or 2 timepoints assessed (before clinical disease progression), whereas responders are most likely to have had multiple measurements. This could introduce a statistical bias since the authors cannot exclude the possibility that CECs (or sVEGFR2 or monocytes) could have had the same patterns in non-responders if they had continued to be assessed at the same timepoints as responders.

One strength of the paper is that normal volunteers were also assessed for baseline biomarkers, giving some comfort in the conclusion that baseline values of patients with renal cancer were abnormal. However, the same cannot be said for the follow up samples. It is entirely possible for example, that the fall in monocyte counts with continuing sunitinib treatment simply reflects the ability of sunitinib to cause a generalised myelosuppression (ie. Side effect) rather than a marker for VEGFR1 expression. I think the discussion should at least allow for this possibility.

Given that the study involves only 26 patients, it is premature to conclude that the proposed biomarkers (CECs, sVEGFR2, monocytes) are actually useful. The findings are provocative, but clearly need to be replicated prospectively. I think the conclusions, as written, are too strong and are not supported by the
data.

Some of these limitations on the interpretation of biomarker studies should be discussed in more detail.

> - Minor Essential Revisions

The corresponding author is not listed as an author.

Figures in the text (Fig 2A, 3A) do not correspond with Figures presented

Labels for the x axis are incorrect for Figures 2 and 3 (still labelled as CECs)

30 patients were evaluable for monocytes (Page 10), but everywhere else in the manuscript, only 26 patients were studied. This discrepancy should be explained.