Reviewer's report

Title: Metastatic renal cell cancer treatments: A mixed treatment comparison meta-analysis involving more than 4,800 patients

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Reviewer: Ronald Bukowski

Reviewer's report:

The authors searched a variety of electronic databases up to 4/2008 to identify randomized clinical trials (RCTs) evaluating either bevacizumab, sunitinib, sorafenib, or temsirolimus. Eight studies were ultimately included. A random-effects meta-analysis with mixed treatment comparison was performed. PFS was utilized as the clinical benefit endpoint.

The authors conclude that treatment with sunitinib was superior to either sorafenib, temsirolimus, or bevacizumab. Significant differences between the other 3 agents were not seen.

The authors conclude that new agents are useful in mRCC patients compared to a placebo or IFN.

1) The incidence figures on p3 are from 2003 and should be updated. The authors also suggest all 4 agents are beneficial compared to IFN as first line therapy – this is incorrect, the study comparing IFN to sorafenib in untreated patients was negative, and PFS was not different.

2) Additionally, it is suggested sorafenib has shown a positive survival endpoint (?PFS or survival) compared to IFN in a phase 3 trial – this is incorrect, the TARGETs trial was in cytokine refractory patients and the comparator was a placebo.

3) The authors suggest disease stabilization is the primary effect of sorafenib, however, it is unclear where the figures for SD and response come from – can this be clarified? The response rate (investigator assessed) in the phase 3 study was 10%, & stable disease rate 70%.

4) On page 6, the authors note investigator assessed PFS was utilized, or if unavailable, independently assessed PFS – can this be clarified?

5) Would independently assessed PFS be more robust? Can these two be mixed in assessing efficacy, since they produce different data?

6) The patients treated in the trials analyzed included untreated and refractory individuals (Yang, Escudier) – it is unclear how these groups can be mixed, since PFS in the refractory patient is generally shorter by definition. Can the authors clarify this issue?

7) The authors mention they also assessed response rates and overall survival, are data on these available?
8) On page 9, references 4 & 10 are cited as trials that were altered to allow crossover – these are incorrect, can this be clarified?

9) In the temsirolimus trial, patients with nonclear cell CA (20%) were entered – this is a different entity compared to clear cell CA. How can these be analyzed together? Can the authors clarify this?

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

Yes:
Consulting & honoraria: Pfizer, Bayer, Wyeth, Genentech, Novartis, Onyx
Stock holdings - none
Patents - none
Non-financial competing interests - none