Reviewer’s report

Title: RECORD-4 multicenter phase 2 trial of second-line everolimus in patients with metastatic renal cell carcinoma: Asian versus non-Asian population subanalysis

Version: 0 Date: 12 Sep 2017

Reviewer: Kevin Courtney

Reviewer's report:

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The authors present a well-organized and succinct analysis comparing safety and efficacy of second-line therapy with everolimus in Asian vs non-Asian patients with clear cell metastatic renal cell carcinoma (mRCC) enrolled in the RECORD-4 phase 2 clinical trial. As the authors note, Tan and colleagues have previously reported on potential differences in the Chinese patient population with everolimus treatment of RCC, and given the high percentage of patients from China enrolled in RECORD-4, the current study affords an opportunity to further evaluate response to everolimus in this patient population. The authors' findings that, "second-line everolimus had comparable efficacy and safety in Asian and non-Asian patients with mRCC" reinforces that everolimus is a reasonable second line therapy for the Chinese patient population. This information may have significant clinical relevance in this patient population. A limitation of this study is the small subset population from which these conclusions are drawn as noted by the authors.

There are recommended items for the authors to address that would increase the impact and relevance of the presented work.

1. This work appears to reinforce the findings published by Guo J et al (BMC Cancer 2013, 13:136), who presented results of a phase 1b study of everolimus in Chinese patients with mRCC resistant to VEGFR TKI therapy. That work warrants citation in the current manuscript and brief discussion of how the current analysis of patients enrolled in RECORD-4 augments those findings.

3. A brief review / hypothesis of potential mechanisms that might differentially impact response to treatment with everolimus in Asian vs non-Asian populations, (eg: differences in metabolism that could impact pharmacokinetics, or potential differences in oncogenic
signaling pathways in ccRCC that might be more commonly identified in Asian vs non-Asian patients) would enhance the impact and relevance of this subset analysis. The authors only state that, "There have been some reported differences in responses to certain targeted agents between Chinese and Western patients with RCC" and cite a single reference. However, that reference (Tan X et al) specifically focuses on everolimus, and so a bit more detailed discussion of what might underlie those differences and regarding the impact of the current findings is warranted.

3. In the US, everolimus has been surpassed as second line therapy by the immune checkpoint inhibitor nivolumab and the VEGFR / AXL / MET inhibitor cabozantinib. Further, the combination of lenvatinib plus everolimus has also shown greater efficacy than everolimus monotherapy. To enhance the relevance of the current analysis of everolimus as a viable second line mRCC therapy option for Chinese patients, a discussion of currently approved mRCC therapies in China should be included for context.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
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Yes

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