Author’s response to reviews

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

Authors:
Lin Yang (lyang69@sina.com)
Anna Alyasova (alyasovaav68@mail.ru)
Dingwei Ye (dwyeli@163.com)
Antonia Ridolfi (antonia.ridolfi@novartis.com)
Luca Dezzani (luca.dezzani@novartis.com)
Robert Motzer (Motzer@mskcc.org)

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Editorial board
BMC Cancer
Re: Submission to BMC Cancer - BCAN-D-17-01078

Dear BMC Cancer Editorial Board,

I would like to thank the reviewers of BMC Cancer for their insightful comments and suggestions regarding my recently submitted manuscript “RECORD-4 multicenter phase 2 trial of second-line everolimus in patients with metastatic renal cell carcinoma: Asian versus non-Asian population subanalysis” for publication. The following is a detailed description of the responses and modifications that I made to the manuscript in response to the reviewers’ comments.
COMMENTS FROM REVIEWERS

Reviewer 1 - Ian Davis

Comment 1: I believe that this paper would actually be strengthened by trimming its content substantially, leaving the actual tables intact if possible. The fact that the entire discussion section of this paper amounts to 56 words suggests that the authors might agree. This would allow communication of the results but would avoid potential overemphasis by the authors (as is the case now) or overinterpretation by readers (which the authors clearly recognize as a risk based on their abstract conclusion and paper Discussion section). This would be far more suitable as a short piece of only a few paragraphs, such as a Letter to the Editor, however BMC Cancer does not publish letters. It might be more suitable for a journal that publishes letters to the editor if it is not accepted for publication by BMC Cancer.

Response 1: We thank Ian Davis for his review of the manuscript and comments. Regarding the recommendation to trim the content to only a few paragraphs to avoid overemphasis and thus overinterpretation by the readers, we believe that the data is already presented in such a manner. We’ve attempted to simply state the results in the few paragraphs included in the original submission. As Dr Davis indicated regarding the potential for overinterpretation, we’ve added the number of patients used for each analysis presented in the Efficacy section to ensure that the reader does not lose sight that the number of patients in some of the populations were relatively small.

Reviewer 2 – Kevin Courtney

Comment 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.

Response 1: We have added a section to the discussion to put our results in context with the phase 1b study by Guo et al, and also contextualized to the results from the pivotal RECORD-1 trial (page 6–7, lines 152–166 with track changes on):

“However, our findings support the comparable efficacy of everolimus in Asian and non-Asian patients with RCC. In this RECORD-4 subanalysis of second-line everolimus, median PFS was 7.4 and 7.8 months in Asian and non-Asian patients, respectively, and the clinical benefit rate was 75% in both patient populations. These findings suggest that second-line everolimus has comparable efficacy in Asian and non-Asian patients with RCC. These results are supported by a
phase 1b study of everolimus in 64 Chinese mRCC patients who were intolerant to, or progressed on, prior VEGFR-TKI therapy, in which median PFS was 6.9 months and the clinical benefit rate was 66 %. Median PFS was comparatively shorter (4.9 months) in the pivotal phase 3 RECORD-1 trial of everolimus in VEGFR-TKI pretreated mRCC patients from centers across Australia, Canada, Europe, the USA, and Japan. However, patients in RECORD-1 were more heavily pretreated, having received a median of 2 prior antineoplastic therapies, and had a poorer risk profile per MSKCC criteria, which may negatively affect outcomes in RECORD-1 compared with RECORD-4.3,”

Comment 2: 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.

Response 2: Results from our study support the comparable efficacy of everolimus in Asian and non-Asian patients. Although there have been reported differences in responses to certain targeted agents between Chinese and Western patients as briefly acknowledged in the discussion, the review by Tan et al. concludes that for everolimus: “Asian patients might respond better than or similar to Western patients.” With the additions made to the discussion in response to the above comment from Reviewer 1, we have clarified that our results support the comparable efficacy of everolimus in Asian and non-Asian patients (page 6–7, lines 152–166 with track changes on), and believe that it may therefore be unnecessary to discuss potential reasons for differences in response between Asian and non-Asian patients as this might undermine and weaken our contention of similar efficacy.

Comment 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.

Response 3: In support of the reviewer’s comment, we have added a section (new text underlined) to the discussion to put our results in context with available therapies approved in
China, and those recommended in Chinese and Asian treatment guidelines (page 7, lines 168–174):

“Five targeted drugs (pazopanib, everolimus, axitinib, sorafenib, and sunitinib) are currently approved for the treatment of advanced RCC in China, and everolimus and axitinib carry the highest level of evidence for second-line treatment after failure of first-line TKI in Chinese and Asia consensus treatment guidelines.7-9 Thus, results of our study are important to physicians who treat these populations of patients, and support the use of everolimus following progression on first-line TKI therapy in Asian patients with mRCC.”

Thank you for your time and consideration. I look forward to hearing from you.

Kind regards,

Lin Yang, M.D.
Medical Department of Cancer Hospital
Chinese Academy of Medical Sciences
No. 17, Panjiayuannanli, Chaoyang District
Beijing, China 100021
Phone (mobile): 13681015148
Fax: 86-10-67734107
Email: lyang69@sina.com