Author's response to reviews

Title: Efficacy of Temsirolimus in Metastatic Chromophobe Renal Cell Carcinoma

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Author's response to reviews: see over
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Dear Editor

RE: MS: 8489103977509333/Efficacy of Temsirolimus in Metastatic Chromophobe Renal Cell Carcinoma

On behalf of myself and my co-authors, I am grateful for giving us an opportunity to respond to the comments of the reviewers and editorial board, and for considering our manuscript for publication in BMC Urology.

The manuscript has been amended in accordance with the comments from editorial board and reviewers. The manuscript contains the comments (along with tracked changes) indicating the changes made as indicated by reviewers and editorial board.

Please see below our point-by-point response to each of the reviewer’s comments and the evidence of amendments in our manuscript. To ensure clarity, our responses to the comments have been italicized.
Reviewer 2: Brian Shuch

1. Discretionary Revision
Hale’s colloidal iron is often positive and immunohistochemical markers are usually negative for cytokeratin 20 and vimentin but positive for cytokeratin 7. Should cite this
Authors’ response: This has been cited; document line 88, page 4. Citation reference: [4], [5].

2. Discretionary Revision
Following this, the decision was then taken to proceed to a left cytoreductive nephrectomy. Just for sake of completeness, please state surgical approach. Laparoscopic? radical? Node dissection?
Authors’ response: The patient underwent laparoscopic left cytoreductive nephrectomy; document line 105, page 5.

3. Discretionary Revision
The phase III trial reported by Hudes et al which compared patients with metastatic RCC who received temsirolimus alone or temsirolimus plus interferon or interferon alone included patients with metastatic RCC who had at least three of the six predictors of short survival namely: haemoglobin less than lower limit of normal, serum lactate dehydrogenase (LDH) levels greater than 1.5 times the upper limit of normal, metastases at multiple organs, Karnofsky performance status score of 60 or 70, time from diagnosis to randomization less than a year or corrected serum calcium more than 2.5 millimole per litre.[4]
Do not need to restate the prior trials criteria. Just state that your patient had 3 high-risk features (anemia, poor performance status, and synchronous metastatic disease) as defined in the trial of Hudes et al.
Authors’ response: This section has been revised to address the concerns of the reviewer; document lines 115-120, page 5-6.
4. Discretionary Revision
When was poor performance status defined? Those with debilitating bone metastases that are treated can have improvement in performance status. Should make it clear if the radiation didn't improve her performance status.
Authors’ response: Our patient described in this case report did not derive benefit from radiotherapy with no improvement in her performance status; document lines 103-104, page 5.

5. Discretionary Revision
At this point, the patient required physical aids to mobilise due to painful lytic bony metastases of the femur. Did you prescribe any bone agents such as zolendronic acid or denosumab.
Authors’ response: Bone protecting agent, zolendronic acid was not prescribed at the outset. Patient received zolendronic acid after three months of treatment with temsirolimus, as the patient was being considered for prophylactic orthopaedic intervention; document lines 143-144, page 7.

6. Minor Essential Revisions
The prognosis of RCC varies significantly depending on histological sub-type, with non-clear cell histology portending a favourable prognosis compared with clear cell RCC.[6, 7] Amongst the non-clear cell variety, patients with chRCC demonstrate significantly higher median overall survival compared to both clear cell and papillary RCC.
You have to make it clearer- first off several studies have demonstrated that histology may not be an independent predictor of outcome. The poor outcome is more associated with stage, size, and grade. Is the survival difference you are trying to refer to for metastatic patients? Cite the studies you wish to reference.
You introduce that these series were prior to the introduction of targeted agents, however if you are talking about all patients- I disagree that median survival would be that different as most papillary or chromophobe patients will not develop metastatic disease.
Authors’ response: We agree with the reviewer’s comment and have modified the manuscript which now explains that besides the histology, tumour staging and grade along with patient’s performance status are also features of poor prognosis. This section is supported by reference [5]. There is current data (as referenced in [5],[8] which indicate that the median survival of metastatic non clear cell RCC is generally poor; document lines 166-168, page 8.

7. Discretionary Revision
It is accepted that abrogation tumour suppressor function of the Von Hippel-Lindau (VHL) gene. This sounds awkward. Also I believe VHL should be italicized.
Authors’ response: This line has been modified and we agree with the reviewer’s comment about italicizing Von Hippel-Lindau; document lines 178-179, page 8.

8. Discretionary Revision
In this trial, there was only one patient with chRCC but the outcome of this specific patient is unknown. Is this true? I have never seen this broken down and I believe they didn't have that data. Please check
Authors’ response: Yes. This statement is true. Please refer to table 2 in the report by Dutcher et al. Reference [10]; document lines 185-190, page 8-9.

9. Minor Essential Revisions
Of the 12 patients with metastatic chRCC, only three had a partial response (two patients treated with sorafenib and one treated with sunitinib). This suggests that VEGF targeted tyrosine kinase inhibitors may only have modest activity against chRCC. I don’t agree that the study suggests anything, especially modest activity. The partial response rate of sorafenib in clear cell is nothing special either (10% in NEJM article). Can we definitively say that this is worse? I would tone this down. It perhaps shows that the papillary RCC patients didn't have a dramatic response rate.
Authors’ response: This section has been modified to concur with the views of the reviewer; document lines 201-202, page 9.
10. Minor Essential Revisions

One additional highly relevant report in the literature should be included:

I would incorporate this and also discuss the registry-based findings regarding the extreme rarity of this cancer (accounting for approximately 1% of all RCC deaths). This can be cited again about the difficulties performing a trial for this patient population at the end of the paper.

Authors’ response: This section has been modified to reflect the views of the reviewer; document lines 211-215, page 9-10.

10. Minor Essential Revisions

Tables and Figures

1) I would state it's a hematoxylin and eosin stained slide at “X” magnification
2) I would label a panel “a” and “b” and reference it in the text this way.

Authors’ response: The figures and captions along with relevant sections of the manuscript have been amended as advised by the reviewer; document lines 138-142, page 6 and document lines 303/307, page 13.

Reviewer 3: Jim Barber

Discretionary revision

It would have been nice to know why temsirolimus was used instead of the usual second line option, everolimus.

Authors’ response: This rationale for treatment with temsirolimus is explained in document lines 131-133, page 6.
In addition, the following changes have been made to manuscript taking note of the 6 editorial point.

1. Abstract
   The abstract should be structured into three sections.
   Authors’ response: The abstract has been divided into three sections (background, case presentation and conclusion) along with a statement of relevance to scientific community; document lines 53-62, page 3.

2. Background
   Following our formatting guidelines, the Background section should end with a very brief statement of what is being reported in the article.
   Authors’ response: A new section has been added as per the requirements of the editorial board; document lines 90-92, page 4.

3. Acknowledgments Section
   Authors’ response: The contribution of all persons for the manuscript has been acknowledged as per the requirements of the editorial board; document lines 245, page 11.

4. Figures
   Can you please remove the figure images from the main manuscript document. These should be uploaded separately. However, the Figure Legends should remain in the main manuscript document.
   Authors’ response: The figures have been removed from the manuscript and will be uploaded separately. The figure legends remain in the main manuscript; document lines 303/307, page 13.
5. Copyedit
We highly recommend that you ask a native English speaking colleague to help you copyedit the paper. If this is not possible, you may need to use a professional language editing service.
Authors’ response: The manuscript has been copyedited by the last author (RJJ) who is a native English speaker.

6. General Formatting
You now have an opportunity to ensure that your revised manuscript conforms to the journal style.
Authors’ response: The manuscript has been revised to conform to the journal style.

I hope that the explanations and revisions to the manuscript would meet the highest editorial standards of your journal and would facilitate the acceptance and publication of our manuscript. I am grateful for the opportunity to submit this manuscript to BMC Urology, and look forward to your comments.

Yours sincerely
Dr B.Venugopal MBBS, MRCP (UK)