Author's response to reviews

Title: Feasibly of axitinib as first-line therapy for advanced or metastatic renal cell carcinoma: A single-institution experience

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Version: 3
Date: 9 January 2015

Author's response to reviews: see over
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Version: 1

Author's response to reviewers: see over
Reviewer's report
Title: Both radical prostatectomy with neoadjuvant LHRH agonist and estramustine and radiotherapy with neoadjuvant hormonal therapy achieved favorable oncological outcome in high risk prostate cancer: a propensity-score matching analysis
Version: 1 Date: 12 February 2014
Reviewer number: 1
Reviewer's report:
Title: Feasibly of axitinib as first-line therapy for advanced or metastatic renal cell carcinoma: A single-institution experience
Version: 2 Date: 23 November 2014
Reviewer: Shintaro Narita
Reviewer's report:
The authors conducted the retrospective study to assess the outcome of first-line axitinib in patients with advanced clear cell renal cell carcinoma. The 1-year PFS was 84.4% with tumor shrinkage in 83.3% patients. Furthermore, there were no serious adverse events reported in this study. Based on this study, first-line axitinib may be a feasible option for advanced clear cell RCC, and the results seem to be important for most of urologists and medical oncologists to some extent. I would suggest to the authors to modify some parts for acceptance of this journal.

General
-The definition of “advanced RCC” seems to be unclear. Does this mean “locally advanced”?  
Yes. The authors have changed “advanced RCC” to “locally advanced RCC”.

Abstract
-Pathological information should be included in the Abstract section.

Background
The authors have added the following sentence to page 2, line 12.
All patients had histologically proven clear cell RCC.

-Axitinib, a potent and selective second-generation inhibitor of VEGF receprots-1,2 and 3, has demonstrated clinical efficacy in phase II studies” should be “Axitinib, a potent and selective second-generation inhibitor of VEGF receprots-1,2 and 3, has demonstrated clinical efficacy in patients with mRCC in
phase II studies”.

The authors have made the recommended change to page 5, line 3 as follows: “…has demonstrated clinical efficacy in patients with mRCC in phase II studies.”

Results

-Page 9, line 11. Does tumor shrinkage mean the shrinkage of primary renal tumor? Please specify the sites measured to assess the tumor shrinkage.
  
  The authors have revised the following sentence to clarify this point on page 9, line 17.
  
  Tumor shrinkage was observed in 15 patients (primary renal tumor in 10 patients and metastatic site in 5 patients).

-Please add the results of the 1-year PFS and mean PFS in patients with locally advanced RCC and metastatic RCC separately.
  
  The authors have added the following sentence on page 10, line 12.
  
  The 1-year PFS rate was 55.6% in the patients with locally advanced RCC (locally advanced group) and 100% in the patients with metastasis (metastasis group) ($P = 0.373$). The median PFS was not reached in the locally advanced group, and it was 20.4 months in the metastasis group.

-The term “axitinib-related adverse event” is inappropriate. Generally, adverse event includes unexpected symptoms and abnormal lab findings during the study and should not divide into related or unrelated events to axitinib.

  The authors have made the recommended change on page 11, line 7 as follows: The axitinib-related adverse events are shown in Table 2.

Discussion

-Page 12, line 11. “respectively” is not necessary.

  The authors have deleted “respectively” on page 13, line 14.

Table 1

- The number of nephrectomy after administration of axitinib does not match with the number in the results section. The number of the patients who underwent nephrectomy should be checked.

  In Table 1, the number of the patients who underwent nephrectomy indicates those who underwent the procedure before the administration of axitinib.
**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interests' below.
Reviewer's report
Title: Feasibly of axitinib as first-line therapy for advanced or metastatic renal cell carcinoma: A single-institution experience
Version: 2 Date: 2 December 2014
Reviewer: Mayer Fishman
Reviewer's report:
1. Is the question posed by the authors well defined?
The question of axitinib tolerability is presented well, with reference to up front use and to Asian populations.
2. Are the methods appropriate and well described?
The retrospective tabulation is appropriate and well described. However the process of determining the number of patients needed to be conclusive was not presented.
3. Are the data sound?
The descriptive data appears sound. There are some corrections and expansions:

Major: (abstract) There's a statement about "tumor shrinkage" but the usual format for this would be to describe frequency of stable disease and partial response and of complete response using a reference standard such as RECIST. Then shrinkage could be described in addition.
The authors have revised the following section starting on page 2, line 13.
According to the response evaluation criteria for solid tumors, five patients (27.8%) achieved a partial response and nine (50%) had stable disease. Tumor shrinkage was observed in fifteen patients (83.3%), with a median decrease of 20% in tumor size.

The authors have revised the following section starting on page 9, line 13.
According to the response evaluation criteria in solid tumors (RECIST) criteria, five patients achieved a partial response, nine had stable disease, and four had PD. The median duration of response was 10.8 months (IQR, 5.6-18.3). Tumor shrinkage was observed in 15 patients (primary renal tumor in 10 patients and metastatic site in 5 patients), with a median decrease of 20% in tumor size (interquartile range [IQR], 4.7–33.5; Fig. 1).

Major: (abstract) Progression free survival should have confidence intervals listed, as also should be in the "Clinical response and PFS" section
The authors have added the recommended revision on page 2, line 18.
The 1-year PFS rate was 84.4%, and the median PFS was 20.4 months (95% confidence interval, 17.5–21.7).

Discretionary: For sample size of 18 only 2 significant digits, not 3 significant digits would be used for the percentages.
The authors deleted all parts of percentage.

In the "Clinical response and PFS" section:
Minor: Results. A dose listed as 6 mg/d, should be listed as 3 mg BID, I assume.
The authors have made the following revision on page 9, line 6.
Five patients received a continuous reduced dose of 3.6 mg twice daily/day:

Discretionary: Results. The dose of 2 mg/day: This is an off-label dose, so there should be some comment about it. Please confirm if it was 2 mg BID or daily.
The authors have revised the following sentence on page 9, line 9.
Two patients received a continuous reduced dose of 1.2 mg twice daily/day for general malaise.

Major: Line 143: Wrong number used in confidence interval. This should be a percent.
The authors have revised the following sentence on page 10, line 11.
The 1-year PFS rate was 84.4% (95% confidence interval, 15.8–21.5; Figure 2). The median PFS was 20.4 months (95% confidence interval, 15.8–21.5 95% CI, 17.5–21.7).

Minor: The confidence intervals on these adverse event frequencies should be given, as later there is allusion to comparison.
As the sample sizes in this study were very small, the authors could not obtain the confidence intervals for the frequency of adverse events.

4. Do the figures appear to be genuine, i.e. without evidence of manipulation?
The figures appeared genuine and accurate.

5. Does the manuscript adhere to the relevant standards for reporting and data deposition?
These appear accurate, but not central to this particular type of presentation.

6. Are the discussion and conclusions well balanced and adequately supported by the data?
The discussion makes conclusive statements about comparisons and that is not supported adequately by the data the way it is described.

7. Are limitations of the work clearly stated?
While acknowledged to be a small series, the comparison of the confidence intervals of the progression free survival and overall survival are not computed using risk stratification.
The authors have added the following sentence on page 10, line 17.
According to the MSKCC risk stratification, the PFS did not differ significantly among all risk groups (P = 0.985).

8. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
Major (discussion) They do appropriately cite (references #13 & #27) prior series describing treatment of Asian patients with axitinib.
Major: Line 190: The issue of comparing to other clinical trials does require that risk stratification of these patients be used so that the appropriate comparative
The authors have added the following sentence on page 14, line 8.
In this study, the differences in PFS were not significant between all risk groups, according to the MSKCC risk stratification.

Major: (discussion) The Rini et al study [27] did include Asian patients. There were 45 listed as Asian (Table 1 in that paper). The Hutson paper [13] has 48 listed as Asian. Those studies had a mixture of risk strata. This study did not have risk strata described and is significantly smaller. That makes this additional data of less impact. The authors should give a quantitative comparison to the overall patients and to the Asian patients in those series and then present specific rationale about how the present study adds to those experiences. This does get to the main weakness of the study, which is that it is small, and thus intrinsically limited in the extent to which conclusions can be drawn. However, the particular difference of their series versus those is not detailed as I would like to see it. For example, the age is older in this series.

The authors have added the following sentences on page 14, line 15.
In this study, the number of enrolled patients was relatively high age compared with other randomized trials [13, 27]. AEs were also effectively managed with medication or axitinib dose reduction in this study. Although a large proportion of patients in other randomized control studies were recruited from North America and Western Europe, few patients were recruited from Asia. Therefore, axitinib as first-line therapy may provide a treatment option for Japanese patients with locally advanced or mRCC.

9. Do the title and abstract accurately convey what has been found?
The title is accurate. The abstract, like the paper, is been on quantitative comparative statistics. Holy comparison is given without quantitation.

10. Is the writing acceptable?
A few minor points can be identified, but generally the writing is excellent.
Discretionary: Page 5: The phrase "a potent and selective second-generation inhibitor" uses the adjective "potent" which sounds more like an advertisement phrase.
The authors have revised the following sentence on page 5, line 2.
Axitinib, an effective potent and selective second-generation inhibitor…

Minor: Line 75 TKI --> VEGFR-TKI
The authors have revised the following sentence on page 6, line 5.
VEGFR-TKIs or mTORs between…

Minor: Line 103 "truly" word not needed.
The authors have revised the following sentence on page 7, line 16.
Bone lesions were considered truly non-measurable.

Minor: Line 139: (minor point) cRCC is not a standard abbreviation. I recommend to just to spell it out.
The authors have deleted cRCC.

Discretionary: It would be of interest to describe the duration and quality of the sunitinib and pazopanib responses.

The authors have added the following sentences on page 11, line 2.

The duration of effectiveness in the patients who were administered sunitinib or pazopanib as second-line treatment were 3 and 6 months, respectively.

Minor: 190. misspelled Rini (not Lini)

The authors have revised the following sentence on page 13, line 18.

RLini et al reported that in…

Discretionary: Line 156: The phrase "more recently" is used in relation to medicines that have been used for over a decade.

The authors have made the following revision on page 12, line 4.

More recently, a A better understanding…

Minor: Line 175: The term Caucasian should be used consistently and not "white

The authors have made the following revision on page 13, line 4.

…relative to Caucasian patients.
Reviewer's report  
Title: Feasibly of axitinib as first-line therapy for advanced or metastatic renal cell carcinoma: A single-institution experience  
Version: 2 Date: 7 December 2014  
Reviewer: Tomoyuki Kato  

Reviewer's report:  
It is a small, retrospective study about feasibility of axitinib as first-line therapy for advanced RCC patients. Throughout the paper, the accuracy of description is lacking.  

Major Compulsory Revisions  
1. Axitinib is a molecular target agent commonly used as a second-line therapy for advanced renal cell cancer patients. The authors should discuss the validity of the use of axitinib as first line therapy.  
The authors have added the following sentence on page 5, line 12.  
In the National Comprehensive Cancer Network guideline 2015, axitinib is recommended as a treatment option for first-line therapy in patients with locally advanced or metastatic RCC.  

Minor Essential Revisions  
2. It is not clear whether the patients were treated with axitinib dose titration or not. The dose of axitinib should be described in more details in the TREATMENT section.  
The authors have addressed this point on page 7, line 4.  
In this study, none of the patients received axitinib dose titration.  

3. Abbreviations should be described in the proper position.  
The authors have checked all abbreviations carefully.  

4. In the description of line 121-123, it is unclear how many patients received 6 mg/day axitinib.  
The authors have addressed this point on page 9, line 5.  
Seven patients received reduced axitinib dosing. Five patients received a continuous reduced dose of 3 mg twice daily; of these patients, four had exhibited systolic blood pressure of 150 mmHg or higher, one had suffered general malaise, and one had developed grade 3 proteinuria. Two patients received a continuous reduced dose of 1 mg twice daily due to general malaise.  

5. Please specify the duration for which the patients underwent the therapies as well the duration for which they were under observation.  
The authors have added the following change on page 9, line 4.  
The median duration of the administration of axitinib was 10.8 months.  

6. It contains multiple mistakes and misprints including misspelling of medical terms (e.g. page 14, 190th line, “Lini” should be changed to “Rini”). Thus, the text should be proofread carefully.  
The authors have made this revision to page 13, line 18 as follows:  
“RLini et al reported that in....”
In addition, the text has undergone additional proofreading.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
'I declare that I have no competing interests