Author's response to reviews

**Title:** Efficacy of Sorafenib on Metastatic Renal Cell Carcinoma in Asian Patients: Results from a Multicenter Study

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**Version:** 2  **Date:** 30 March 2009

**Author's response to reviews:** see over
March 25, 2009

Dear Editors and Reviewers,

Thank you for reconsidering our manuscript “Efficacy of Sorafenib on Metastatic Renal Cell Carcinoma in Asian Patients: Results from a Multicenter Study” for publication in BMC Cancer. Enclosed please find a copy of our detailed reply to the few comments from the reviewers.

We would like to thank both reviewers for their constructive suggestions and comments. Their questions and suggestions were not only important but also provided a useful guideline for our revision. We are in agreement with all suggestions, and have made revisions according to all major, discretionary and minor revision requirements. All changes are marked in red color. We have attached our reply to the comments below for your verification.

If you have any questions regarding our revision, please do not hesitate to contact us at your convenience. We are looking forward to hearing from you about your decision.

Sincerely,

Drs. Dingwei Ye and Yiran Huang
Reply to Comments from Reviewer #1

1. Per the eligibility criteria, all subjects were AJCC stage IV. However, table 1 indicates that only 36.7% of patients were Robson stage IV. Please clarify this discrepancy – perhaps this represents the stage at diagnosis, rather than the stage at study entry?

Reply: Thanks a lot for point this out. The 36.7% of patients presented with stage IV diseases were indeed the stage at diagnosis. Some patients originally presented with more limited diseases but developed disease progression and metastasis. We have clarified this discrepancy in the revised manuscript. We have also changed the Robson stage to AJCC stage at the suggestion of the reviewers (question 4).

2. The response rate (24.5%) and PFS (>12 months) are significantly greater than previous reports with sorafenib (2% and 5.5 months, respectively). The long PFS is commented on in the discussion, but no comment is given by the authors as to why the response rate was so much higher than in previous studies. Some comment should be made as to why this might be. The high response rate may cause some readers to question the methods used in determining radiographic response. Were the responses investigator-assessed, or was there a central review of the scans?

Reply: Thanks for this important question. Both reviewers had suggested further discussion on the improved outcome in our paper. The outcome of our study was better that the results from TARGET. Although we do not know the exact cause, but some inherent difference may be part of the underlying cause. As the second reviewer pointed out, the HFSR is more prevalent in our study and in the Bayer sponsored Asian liver cancer study. It was reported that the response and TTP is proportional to the HFSR according to a recently reported article (discussed and included in the references of our revised paper), thus we postulate that our difference is secondary to ethnic background. Interestingly, the Japanese phase II study showed that their response and disease control was 86.8%, almost identical to ours. But their median PFS was 8 months (32 weeks), which lies in between our results (15 months) and the TARGET results (5.5 months). We have added a section to discuss the longer PFS rate in the discussion section.

The radiological responses reported in the study were evaluated by both diagnostic radiologist (independent) and verified by investigators. We have added clarification in the methods section for this issue.

3. It is understood that this does not represent a phase II study. However, please provide a definition of what is meant by an “Institution treatment protocol?” Was there a primary objective of this protocol?

Reply: A phase II study in a SFDA (the FDA equivalent in China) proven medication is not feasible (also see reply to questions 7). Thus we can only initiate a study that aims to clarify whether the efficacy reported in the phase III study (TARGET) could be repeated in Chinese populations. The institution treatment protocol was designed aimed to study the efficacy and side-effect profile of sorafenib in patients with advanced RCC. Patients’
characteristics for inclusion and the treatment regimen including pre-treatment evaluation, dose and schedule of medication, as well as follow-up tests and frequency were determined prior to the initiation of this protocol. Although all efforts were made to ensure this protocol assimilates a prospective phase II trial except for sample size calculation, we could not claim such study as a phase II trial.

4. Consider using the AJCC stage in Table 1 rather than Robson stage.

Reply: Thanks for point this out. We have changed to the AJCC stage in Table 1.

5. Provide 95% confidence intervals for PFS and OS.

Reply: Thanks and we have added the 95% CI for PFS and OS according to this suggestion. At the request of the second reviewer, we have updated our data and the median PFS is reached at 60 weeks with 95% CI of 41-79 weeks. He median OS is not reached, however.

6. Page 11: "No significant difference was found in patients received sorafenib plus interferon treatment as compare to those received sorafenib alone..." No data is presented to this end. Also, consider referencing the published literature regarding the sorafenib + interferon combination, as there has been several prospective trials that have studied this combination.

Reply: Thanks a lot for this suggestion. We have referred to a phase I trial and 2 phase II studies regarding the combined use of Interferon and sorafenib, and indicated that such combination may produce substantial activity and was well tolerated. We also indicated that due to the small number of our series, particularly only 16 patients received sorafenib+IFN, meaningful comparison was not feasible. And the combined use in such as small group of patients was a pitfall of our report.

7. Page 11: It is unclear why “further investigation for a proven medication in the form of a prospective phase II clinical trial would not be easily acceptable by patients with a terminal disease.” Perhaps the authors are referring to a randomized trial, rather than a phase II study--?

Reply: Since the aim for a phase II trial is to study the efficacy of the medication, patients will have difficulty to understand why a medication with proven efficacy (although data was from USA) need to be studied again for its efficacy, or why a randomized trial need to be done after the TARGET study. In addition, sorafenib was the only available active treatment for RCC at the time we started the project. Therefore, we started this protocol rather than a phase II trial with an aim to study if the efficacy of sorafenib exists in Chinese patients with advanced RCC. We have changed “phase II” to “phase II or randomized trials.” In the discussion we have changed our wordings to “prospective phase II or randomized clinical trials” since both were not feasible, as correctly pointed out by the reviewer.
8. There are grammatical errors throughout document that will need to be corrected. Table 1: Correct spelling of “Robsen”.

Reply: Thanks a lot for point out the grammatical errors. We have proof read the paper and the spelling was also corrected. We have changed to AJCC staging in Table 1 according to the suggestion in question 4.
Reply to Comments from Reviewer #2

Reviewer #2: This study aimed to confirm the efficacy and explore the toxicity or sorafenib treatment for metastatic RCC in an ethnic Chinese patient population. The 98 patients followed prospectively on this study do provide valuable information about this drug therapy that is not available from the western-based TARGET phase III trial or other data. It is of value to practitioners treating Asian populations and contributes to the overall data set for this drug in this disease.

The authors do not over-state their conclusions. This data-set does suggest, but does not prove that sorafenib is well tolerated and at least as efficacious in this population as shown in the TARGET trial.

1. Stable disease is defined as > 4 wks in the abstract and > 4 months in discussion. Please use 1 definition and one really should choose > 4 months as 4 wks is not a clinically meaningful period of stable disease. Use this > 4 months in the disease control rate estimations.

Reply: Thanks a lot for point out this discrepancy. We have corrected the units in the abstract and in the text, and agree that 4 months is a more meaningful period to be used.

2. Table 1: Patient characteristics contains some data relevant to early RCC. Add in recognized prognostic features of metastatic RCC. This will allow this population to be more easily compared to other publications. Please include...
   - MSKCC risk (poor, intermed or high) or a similar prognostication criteria
   - base-line sites of metastatic disease....suggest lung, liver, bone, lymph node
   - number of sites of mets..1,2,3 or more or unknown
   - histology...predom clear cell, non-clear cell, unknown

Reply: We also consider these characteristics important for effective comparison, and have added all above-mentioned prognostic factors in the table except for the MSKCC risk, since not all patients were tested for their LDH and calcium.

3. PFS is very close to median at time of this analysis. Can this not be updated now (Feb 2009)to give a more meaningful estimate than 'not yet reached'?

Reply: We totally agree that a more recent follow up will add more weight to our results. And we have performed another round of follow-up according to the suggestion of the reviewer. The results are updated (with 95% CI as suggested by the first reviewer). The median PFS is 60 weeks, and the changes were indicated in red color in the results section.

4. The PFS and OS estimates appear better than TARGET outcomes (PFS >1 year vs 5.5 months on TARGET). Is this explained by patient selection as per baseline prognostic features (see # 2) or is this perhaps inherent to this ethnic Chinese patient population. Is it influenced by weekly follow-up which likely
exceeds western standards. Please comment.

Reply: Thanks for this important question. The outcome was better than the TARGET study. Although we do not know the exact reason, we speculate that underlying molecular mechanism exists for the difference. However, the HFSR is more prevalent in the current study. As a recent reported on relationship between toxicity and efficacy revealed that “time to disease progression was significantly longer for patients receiving sorafenib at/or close to 400mg bid who experienced grade 2/3 HFSR/rash or diarrhea”, we tent to contribute the difference between our data from the TARGET study to inherent difference in ethnic Chinese. The outcome reported by the Japanese researches (phase II study) showed that their PFS was 32 weeks. This may due to common inherent characteristics in Asian people.

This is a very important point to discuss, so we have revised our discussion and the changes are indicated in red wordings.

5. Hand-foot syndrome appears more prevalent on your study then reported on TARGET. This was also seen on the hepatoma Asian-Pacific sorafenib trial compared with European SHARP trial. Please comment. Is there PK data or preliminary SNP data. Or is this perhaps a 'real world' estimate of true rates of hand-foot syndrome. Worthy of a comment in the discussion.

Reply: We totally agree on this intriguing point, and have expanded our discussion on this issue. The HF syndrome is more prevalent in Chinese patients in both liver cancer and renal cell cancer reports, and there is a recent report on treatment response to the severity of the syndrome. We have discussed about this point. Please also see reply to Question 4.

6. Please comment if, in the authors opinion this data set should influence practice patterns in treating Metastatic RCC in China.

Reply: This is a great suggestion and we consider a change of practice can be suggested, as our data confirmed the efficacy of sorafenib in Chinese patients with advanced RCC. We have added some comments in the discussion and stated that our favorable results supported practice change, as it confirmed the results of the TARGET study. (“As treatment options for metastatic RCC is relatively limited, and response of RCC to chemotherapy or immunotherapy is suboptimal, our favorable results which confirmed the efficacy of sorafenib in Asian particular Chinese patients supported practice change in the treatment of metastatic RCC.”)