Author’s response to reviews

Title: A remarkable response to pazopanib, despite recurrent liver toxicity, in a patient with a high grade endometrial stromal sarcoma, a case report

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Author’s response to reviews:

Leiden, June 17th, 2017

Dear Editor,

Thank you for considering our manuscript: “A remarkable response to pazopanib, despite recurrent liver toxicity, in a patient with a high grade endometrial stromal sarcoma, a case report” by Verschoor, et al. for publication in BMC Cancer.

We thank the editor and reviewers for their comments and have improved the manuscript accordingly, as detailed below. As we did not receive comments from the editor and reviewer 1, we can only address the comments from reviewer 2:

1. Line 18 in background should be changed to temporarily

The requested change was made. (Background, line 18, page 4)
2. Remove "in" from line 4 of the case

The requested change was made. (Case, line 4, page 6)

3. What happened to the liver enzymes after challenged again at 400mg PO Daily pazopanib (line 7, page 9)? This should be clarified, and also why this dose (400mg PO Daily) was chosen after prior LFT increase on 200mg PO Daily and pneumothorax on 200mg PO every other day. The thought process here would be helpful for the reader to understand, and this certainly deviates from the guidance on the approved label.

Because the patient had progressive disease with complaints of shortness of breath due to a pleural effusion a rapid response was thought essential. Therefore, we chose to reinitiate pazopanib on a standard dose of 400mg to be sure to be in a therapeutic range. She was closely monitored and in case of liver function elevations, we would have rapidly decreased the dose of pazopanib. (Case, line 13-15, page 7)

During the second episode of pazopanib no liver enzyme abnormalities were found. (Case, line 19-20, page 7)

4. Was biopsy considered at the time of progression after ifosfamide? Some mention or understands of whether the high grade component is what progressed would be informative in putting this case in the context of the management of ESS.

Although this would indeed be of interest, it was unfortunately not done. It would indeed be informative to know whether the progression was due to the high grade part of the tumour.

5. Lines 4-7 on page 11 (discussion) are somewhat misleading. In reading it seems as though the authors are suggesting their case overexpressed KIT as has been seen in other YWHAE-FAM22 fusion+ ESS, however, the authors do not present KIT IHC data nor note in the case presentation. This should be clarified and is perhaps a grammatical error.

Our case indeed overexpressed KIT. A note of this was added to the case description (Case, line 17,18, page 6)
6. The authors should be more clear that their dosing strategy significantly differs from the guidance, and perhaps suggest a monitoring strategy if clinicians plan to deviate from the label. Would the authors advise weekly, 2x week LFTs in this situation? I believe the conclusion could be tempered with a cautious statement noting the above.

Indeed, the dosing strategy differs significantly from the current guidance and this should be stressed in the discussion. We added the following sentence in the discussion: In case of further dose reductions after reduction to once daily 400mg, we suggest that patients should be monitored closely with once weekly liver function testing. (Discussion, line 31-33 page 8) To the conclusion we added the following sentence: This low dose personalized rechallenge is in conflict with the current SmPC of pazopanib and patients should be closely monitored for liver function abnormalities with for example weekly testing of the liver functions. (Discussion, line 20-22, page 9)

7. The resolution in figure 3 is poor in the provided pdf

A version of figure 3 with an increased resolution is provided with the revision.

8. The authors should note in the case if the patient had any LFT changes on chemo, known baseline liver disease, or hepatic mets. It appears from figure 3 that baseline LFTs were normal though this should be overtly stated in the case.

Before the start of pazopanib, no liver function abnormalities were present. Patient had no history of liver disease and imaging did not show liver metastases. During doxorubicin treatment, patient developed an elevated y-glutamyl transferase up to 20x upper limit of normal and an elevated alanine aminotransferase < 6x upper limit of normal. During ifosfamide treatment only an elevated y-glutamyl transferase up to 2x upper limit of normal was found. This was added to the case report. (Case, line 22-25 page 6, case, line 9-11 page 7)

With these changes we hope that we revised the manuscript adequately for publication.
Yours sincerely,

On behalf of all authors,

Arjan Verschoor and Hans Gelderblom

The authors' letter has also been included as a supplementary file.