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REPLY TO REVIEWERS COMMENTS

REVIEWER 1.

This is a good review article. There is no parts to be revised in the text, but Second table has a misspelling, Table 2 is correct.

Sir, I thank you for your constructive criticism of our article. Table 2 has been corrected.

REVIEWER 2

The manuscript gives an overview of the use of tyrosine kinase inhibitors for the treatment of gastrointestinal stromal tumors. The manuscript is interesting for those who quickly want to learn how GIST is treated nowadays. However, some comments should be addressed before this manuscript can be considered for publication.

Sir, I thank you for your constructive criticism of our article.

Major comments

1. In the abstract the authors mention small GIST lesions with a benign behavior. However, these so called micro-GISTS are not mentioned in the main text. Please include a paragraph on these lesions.

Sir, your point is well taken; however, this was not discussed in the main text as this was outside the purview of the article.

2. Page 4, line 15 - "...induced partial response in 53.7% and led to stable disease in 27.9% of patients." Please correct text.

Sir, I regret for the error; it has been corrected in revised manuscript.

3. Page 9, line 22 - 24 - Can a dose increase from 400 mg to 800 mg /day really overcome resistance if a patient developed "secondary" mutations?

A number of mechanism have been put forward for secondary (acquired) resistance in GIST: occurrence of second mutation in KIT receptor, other gene mutations, KIT genomic amplification and activation of an alternative receptor tyrosine kinase protein in the absence of KIT expression, increased serum acid glycoprotein levels and increased multidrug resistance gene expression, lower bioavailability of Imatinib during chronic therapy possibly due to up-regulation of hepatic enzymes responsible for drug clearance, impaired drug delivery due to formation of fibrous stroma. High dose Imatinib seems one of the approaches to tackle this menace of secondary resistance. It is definitely a

complex issue, and we felt it was outside the purview of the present review.

4. Page 10 – When discussing the potential use of ponatinib also refer to Garner AP et al (2014) Clin. Cancer Res. 20: 5745-5. Please note that multiple references are in fact duplicated in the reference list e.g. Refs 3 and 4 are the same; Refs 5 and 9 are the same; Refs 8 and 10 are the same; Refs 19 and 23 are the same; Refs 20 and 22 are the same; Refs 30 and 47 are the same; Refs 34 and 48 are the same. Furthermore referring to Clinical Cancer Research as “Clin Cancer Res Off J Am Assoc Cancer Res” is extremely confusing. Similar the reference to Journal of Clinical Oncology. Please carefully check references and correct.

Sir, I regret for the error; the whole reference list has been revised thoroughly.

Minor comments

1. Please number the pages.

Sir, the pages have been numbered in the revised manuscript.

2. Carefully proofread the manuscript paying special attention to the english grammar and wording.

Sir, the manuscript has been thoroughly revised.

3. Page 3, final line – “...which have mutations acting on downstream of receptor kinases....” Please rephrase this sentence as it is unclear and give examples which genes are mutated in wild-type GIST.

Sir, I regret for the error; it has been corrected in revised manuscript.

4. Page 4, line 8 – This is the first use of RCT, please explain this abbreviation here.

Sir, I regret for the error; it has been corrected in revised manuscript.

5. Page 4, line 22 – What is meant with: “Grade 3 or 4 toxicities were approximately 21% patients”. Words have been omitted, please correct.

Sir, I regret for the error; it has been corrected in revised manuscript.

6. Page 5, line 19, 20 - What is meant by “wild-type mutation”? Please explain.

Sir, I regret for the error; it has been corrected in revised manuscript.

7. Page 6, line 9 -10 – “...similarly PFS was significantly better PFS” Unclear what the authors try to convey. Please rephrase.

Sir, I regret for the error; it has been corrected in revised manuscript.

8. Page 8. Line 30 – NCCN, please explain abbreviation.

Sir, I regret for the error; it has been corrected in revised manuscript.

9. Table 2 is mistakenly labelled Table 1.

Sir, I regret for the error; it has been corrected in revised manuscript.