

Peer Review File

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Reviewer A

Comment 1: I would suggest that author should summarize different strategies approaches related to different molecular subtypes of GIST as NF1-related, pediatric wild-type, SDH aberrated, exon 9 KIT-mutated, PDGFRA D842V mutated etc as probably they need some different approaches to look at Achilles heel...

Reply: All KIT mutated and PDGFRA GISTs are already addressed in the text. Moreover, we have expanded a section in “Other research approaches” with a recently published article to discuss additional and up-to-date approaches to target *KIT/PDGFR*A mutated GISTs. Also, we have now stated in the text treatments that may be used in GISTs with different drivers.

Changes in the text: Page 12, line 264; page 13, line 296-297; page 13, line 307-309; page 20, lines 552-556; page 21, lines 562-563.

Nonetheless, most of these strategies apply to KIT/PDGFR-A mutant GIST, as it can be seen in each section. Therefore, we have stated it more clearly in the “Concluding remarks” section.

Comment 2: Gene names should be written in Italics.

Reply: Thanks so much. Gene names have all been changed to italics now.

Reviewer B

Comment 1: First, I suggest the authors not to use abbreviations in the title such as GIST. Further, the authors may consider to indicate the article type in the title.

Reply 1: Agree! We changed it.

Comment 2 Second, in the abstract, the authors need to explain the clinical significance of this review topic. They may consider to make the conclusion more specific, i.e., specific approaches and how to develop.

Reply: Clinical significance as well as approaches mentioned in abstract already. Anyway, we have reformatted the abstract so it will be clearer the scope of this review. Moreover,

Changes in the text: Page 3.

Comment 3: Third, the introduction part is a little long. The authors may consider to clearly indicate why there is a need for this review topic and the clinical significance of this review.

Reply: We partially agree with reviewer’s #2 comment in that the introduction can be a bit long. However, we felt it was necessary given the wide range of biological aspects that we are covering in this review (ie: from protein degradation to tumor microenvironment).

Comment 4: Fourth, please briefly indicate how the related studies reviewed were identified, which would make the readers to assess the comprehensiveness and the up-to-date status of this review.

Reply: Added sentence stating how we identified the research selected.

Changes in the text: Page 7, lines 159-160,

Comment 5: Finally, in the conclusion part, please have more specific comments on how to develop novel approaches and suggest possible research topics.

Reply: We have changed slightly the conclusion to be somewhat more specific. However, we feel that we can not enumerate every single topic brought up across the manuscript given the wide scope of this review. Thus, we have maintained a broader perspective.

Changes in the text: Page 22, lines 518-521.
