Reviewer 1: Major revision

Overall the manuscript is well written review of the current understanding of GIST and its management. Furthermore it is without significant bias.

The following suggestions for consideration of revisions include:

1. Page 5 paragraph 2. In addition to the commonly and described mutations to KIT, more recently an additional mutation in exon 8 has been described which has been reported in extra-gastric sites and inclusion should be considered.

2. Page 6 at the conclusion of the paragraph discussing wild type tumors, a description should be considered of the newer definition of quadruple wild type GIST (KIT/PDGFR/SDH/RAS-P WT). Please see Cancer Med 2014 Aug 28 for further information.

3. Page 7 final sentence "median overall survival was 63 patients...." is missing words and requires correction. I suspect it is supposed to say median overall survival is 63 months in patients...".

4. Page 11. In discussion of neoadjuvant imatinib, consideration should be given to discussing the possible increased risk of bleeding which has been describe in duodenal tumors (World J Surg Oncol 2010, 8:47.)

5. Page 12-13. Further discussion is required regarding the differences in patient population of the adjuvant trial for imatinib. The ACOSOG Z9001 trial including essentially any patient who had a tumor > 3 cm in size without taking into account currently accepted risk factors such as mitotic rate, tumor location and therefore included some very low and low risk patients. This is a very different patient population as compared with the SSG trial with the high risk GIST population based on their criteria (which should be defined) as these two trials are therefore not comparable. Furthermore, it needs to be stated that the EORTC 62024 trial again looks at a different subgroups (intermediate and high risk) of patients based on risk criteria as does PERSIST5. It may be summarize these differences in a table.

6. As the main goal of this paper is to discuss targeted therapy, that should also be included in the adjuvant section. There is available publications discussing outcomes based on mutational status of both the ACOSOG and SSG trials.

7. Page 15. It is unclear why the author had suggested that regorafenib is the process of being evaluated. The phase III study is completed and the drug is approved for use in patients who have failed imatinib and sunitinib. Furthermore, the benefit appears to independent of the mutational status. Further information should be provided regarding this accepted standard of care TKI.

8. Page 16. Mention should be made of alternative local therapies for oligometastatic in addition to or alternative to surgical resection such as radiofrequency ablation.
Reviewer 2: Declination

The manuscript summarizes the history of GISTs without any interesting comment. Moreover, the molecular analysis of these tumors is completely absent thus making the manuscript totally missing of the molecular profile of GISTs, in particular in case of acquired resistance to TKIs. This topic, just mentioned, is fundamental for the treatment of these tumors types and for targeted therapy in general.

Reviewer 3: Minor revision

Very interesting review focus On GIST. Clear and well written

1. In the discussion : some mistakes for the references: the authors propose ref 58 as a study comparing Sunitinib and Masatinib with imatinib resistant GIST patient :BUT it was a phase II with patients imatinib naïve patients without comparison with sunitinib! (Eur J Cancer. 2010 May;46(8):1344-51. Phase II study of oral masitinib mesilate in imatinib-naïve patients with locally advanced or metastatic gastro-intestinal stromal tumour (GIST). Le Cesne A1, Blay JY, Bui BN, Bouché O, Adenis A, Domont J, Cioffi A, Ray-Coquard I, Lassau N, Bonvalot S, Moussy A, Kinet JP, Hermine O. )

2. A few tables summarizing some of the very lengthy explanations could be useful, in order to facilitate the reading of the whole paper

(end)