Peer Review File

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Reviewer Comments

Comment 1: Line 37: I believe that "may exhibit little sensitivity" is more appropriate than "do not respond" to sunitinib and regorafenib as D842V patients may respond II and III line therapy as the result of the heterogeneity of tumor cell population.
Reply 1: It was suggested that I replace "do not respond" in relation to the PDGFRA D842V mutation, with "exhibit little sensitivity" – this change is to be found in line 32.

Comment 2: Line 57: "and" instead of "&"

Reply 2: The line in which the request was that & be replaced by "and" has been rewritten

Comment 3: Line 66 and 68: "wild type" and "quadruple wild type GIST". The most appropriate way of defining these entities is "KIT wt and PDGFRA wt" as well as "BRAF wt and NF1 wt" GIST since we cannot exclude additional unrecognized mutations.

Reply 3: The description of "wild-type" GIST has been amplified as requested – it was lines 66 and 68, but this setion is now in lines 57 – 59.

Comment 4: Line 73: "mutational analysis may help confirming the diagnosis". This could be misleading since some GIST are KIT wt and PDGFRA wt.

Reply 4. Line 63 (previously line 73) – the suggestion that the presence of activating mutations may be diagnostic has been changed to "informative"

Comment 5: In the paragraphs on the metastatic disease, I think It would useful to add the expected benefit of imatinib, sunitinib and regorafenib in terms of mPFS.

Reply 5: Expected benefits of treatment in terms of PFS:

i. Imatinib – I have inserted the following paragraph, including a new reference, lines 212 - 219 "A meta-analysis of both the European-Australasian and North American phase III trials, each of which compared 400 mg and 800 mg doses, was published in 2010 (23). Across both studies the median progression-free survival was 1.58 years for 400 mg, and 1.95 years for 800 mg. However, the only significant predictive factor for the benefit of the higher dose was the presence of a *KIT* exon 9 mutation, which clearly requires more intensive treatment. Overall survival was unaffected by dose with a median of just over 4 years"
ii. Sunitinib – I have inserted the following paragraph, lines 241-247

"In the randomised trial median time to progression on sunitinib was 27.3 weekFs, compared with only 6.4 weeks on placebo. Survival was also improved, using a Kaplan-Meier analysis, with a hazard ratio of 0,49, p=0.007. However, median survival had not been reached at the time of reporting and because of cross-over to active treatment at the time the trial was unblinded, once median survival according to initial treatment allocation had been reached the difference was no longer statistically significant"

iii. Regorafenib – I have inserted the following paragraph – lines 261-265: "Median PFS on regorafenib was 4.8 months compared with only 0.9 months on placebo. Cross-over was mandated early in patients profressing on placebo and they were permitted to do so even if their performance status had deteriorated. There was no statistically significant difference in survival between the two groups."

Comment 6: Dose increase from 400 to 800 mg daily is not listed as an option in patients progressing on low dose imatinib.

Reply 6: I have included a statement to the effect that this is an option included in certain treatment guidelines – this is in line 224 page 9 – to 226, page 10.

Comment 7: There is a long paragraph on imatinib plasma level. However, dose modification according to plasma level is still investigational and this should be clearly stated. Moreover, many controversies exist on the technical aspects of imatinib measurements.

Reply 7: It was pointed out that the use of pharmacokinetics to guide imatinib dosing was experimental – I have acknowledged this in line 230.

Comment 8: I think that the only limitation of the paper is the lack of a short paragraph on tumor response evaluation. In fact, the Authors discuss many radiological issues in their paper i.e.

- Line 112, when discussing neoadjuvant therapy with imatinib
- line 120, when discussing the evaluation of response - the Authors did not mention the possibility of PET-FDG negative GIST
- line 310, when discussing nodule within a mass

without describing the peculiarities of tumor assessment on TKI.

Reply 8: A paragraph on tumour response evaluation was requested. I have included this in the section on pre-operative therapy and added two references, one on Choi criteria, one on the usefulness of ^{18}F-PET-CT. This is to be found in lines 114-121.