Author's response to reviews

Title: Survival of Gastrointestinal Stromal Tumor Patients in the Imatinib era: Life Raft Group Observational Registry

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Author's response to reviews:

Sirs:

Please find below our formal response in which we address your comments and those of your esteemed colleagues, Drs Cassier, Rutkowski and Shoffski.

The very purpose of the founding of the Life Raft Group was to provide support to patients and families with GIST in whatever form was required. Part of that foundation has evolved from our registry of periodically-updated member-supplied information into a methodical retrospective analysis to see if the benefits reported from the clinics could be observed in the wider world. Some of our statistically significant observations have indeed been reported in trials, however some also have not, and it is our belief that the one can not only benefit the other, but the reporting of both is indeed in the best interests of patients, as well as their care-givers.

The Life Raft Group has, and shall always hold itself to the highest of ethical standards. After consultation with our clinical, scientific and regulatory advisers, the LRG did not pursue an external IRB approval on the grounds that it constituted an exempted class given its zero-risk, observational and patient-reported nature. Each data point has been provided by members over a long term, and on a voluntary and recurring basis. All records are provided by the member with the exception being death records, that are publicly available e.g., Social Security Death Index. Additionally, the LRG has always abided by the spirit of the Helsinki Declaration, and has also been in full compliance of all relevant HIPPA regulations concerning patient privacy and data security, including a standing policy of not sharing any identifying patient information, despite not being an HHS-defined covered entity.

In turning to address the comments forwarded by your colleagues:

Dr. Rutkowski:

1. It is accurate that this report may not contain unique finds; however we submit
that it does add a unique perspective. For the first time we are starting to get some sense of how many patients might be diagnosed in the critical 18-35 age category and we begin to gain a sense that many presenting within this age-group might have pediatric-type GIST. We also begin to get a better sense of the effect of disease stage on survival, especially of those that present with a primary tumor only, but later develop metastatic disease. While survival data on metastatic trials, adjuvant trials, and case series have been reported individually, there are few reports that look at survival on a more global scale, at a real-world level.

2. Are any data about adjuvant therapy after primary treatment available?
   a. Yes, but this data is still being checked and cleaned. It is not yet ready for analysis.

3. Non metastatic disease means locally advanced cases treated with imatinib and primarily operable cases – these two groups have different prognosis.
   a. It was beyond the scope of this manuscript to segregate patients at this level.

4. Mutational status was known in only one fourth of cases in a random way, what may impact on final results.
   a. The discussion about mutational testing was expanded. In contrast to a research setting, this database is a reflection of real-world data and indicates that, even in very proactive patients, mutational testing remains low (especially in the United States).

5. Lack of age or date of diagnosis in some cases
   a. Acknowledged; in a small percentage of cases data was missing (table 1) and these subjects could not be included in subsequent analyses.

6. Furthermore to other concerns from PR:

   There were a number of discussions between the authors about how to best present the data with respect to the confidence of the report of metastatic disease. Reporting from a patient registry is somewhat different than that from a trial. On the one hand, a registry has the capability to gather survival data that may be lost to traditional RCT studies, which may lose contact with patients as they move, often at new institutions, and onto new trials. Thus in some cases, registries may be given data, such as a report of death, but in some cases without a record of a progression/recurrence event. While we did not separately report the survival of those rated as “intermediate-” or “low-confidence”, we did analyze these data. It was reassuring to observe that the survival times correlated nicely with our rating system, despite its somewhat subjective and arbitrary nature. That is, OS for reports of “no mets-high confidence” was the longest, followed closely by “no mets-intermediate confidence”, and then reports of metastatic GIST. The small group (n=15) that we categorized as no report of metastatic disease (“no mets”), but “low confidence”, had the shortest OS, with 6 of the 15 patients having died; data available upon request.

In addition, in addressing Dr Schoffski’s comments:
1. Abbreviations were removed from the abstract.
2. See comments about ethics committee approval.
3. The introduction was shortened.
4. “How can two out of three diagnoses be a ‘triad’”?

Carney’s triad is the term used to describe the condition, which is capable of producing all three tumor types, GIST, paraganglioma and chondroma. In reality, patients can develop any combination of these 3 tumors. Triad as a description reflects the potential for all three, rather than actually developing all three.
5. We added two sentences to methods stating how date of death was retrieved.
6. We significantly expanded on the discussion of mutational testing, including frequency in the discussion section.
7. We added another sentence in the discussion section explaining that many of these patients participated in clinical trials. This is also noted in the limitations section of the discussion.
8. We made it more clear that the outcome of Carney’s patients is related to the indolent nature of the disease and not to imatinib treatment (discussion section).
9. The abbreviations section was expanded.
10. The Joenssu ASCO 2011 presentation citation was updated.

With respect to Dr. Cassier’s comments:

1. We significantly expanded the discussion about mutational testing, including the limitations we have in identifying this.
2. The references to “wild-type mutations” were corrected.
3. Median follow-up times were added.
4. We removed the multivariate analysis. Our statistician (JE) however, notes that the multivariate analysis has some merit in this setting, i.e., this is a very heterogeneous patient population and the multivariate analysis is one way to account for this heterogeneity.
5. We added additional comments addressing the increased overall survival in the discussion section. The SEER data mentioned is the shortest OS that we have seen for metastatic disease and we don’t have a lot of confidence in that data.
6. The comparison of metastatic disease (Panel A of figure 4) to those that later developed metastatic disease is included as part of a more global look at how stage affects survival. As such, we believe the comparison adds value and respectfully request that it remain.
7. Retroperitoneal spelling was corrected.
8. The introduction was abridged.

During the composition of this response, we identified, and corrected, one error
in our original dataset: a patient identified as having a BRAF mutation. Upon further review, it was found that this patient had wild-type GIST. Relevant text, tables and figures have been updated (table 4, figures 3 & 5).

In closing, we are grateful for your continued consideration and apologize for the delay in our formal response, and please do not hesitate to get in contact should you have any further questions or comments.

Yours respectfully,

NS

JC, CW & JE