Online supplementary information for the article ‘Masitinib in advanced gastrointestinal stromal tumor after failure of imatinib: a randomized controlled open-label trial’

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A. Summary of sensitivity analyses for the primary analysis statistical test and median PFS data (secondary analysis)

The primary efficacy analysis met its stated statistical objective: the lower bound of the 90% unilateral confidence interval for median PFS (central RECIST) was 3.7 months and therefore greater than the threshold of 3 months. This successful result was repeated for sensitivity analyses, including local RECIST PFS, investigator-based PFS, time-to-treatment failure, time-to-treatment switch, and different censoring methods.

Table S1: Summary of sensitivity analyses for the primary analysis statistical test (90% one-sided CI) according to the ITT population - cutoff date: 31 January 2012

| Masitinib arm (n=23) | Median PFS in months [90% one-sided CI] | Patients censored n (%) | Lower bound for primary analysis [90% one-sided CI] | Test conclusive (Yes/No) if CI lower bound > 3 months |
|----------------------|----------------------------------------|-------------------------|----------------------------------------------------|-----------------------------------------------------|
| **PFS (central RECIST)** | | | | |
| Censoring method – PP | 3.71 [3.65] | 5 (22%) | 3.65 | Yes |
| Analysis #1† | 3.71 [3.65] | 2 (9%) | 3.65 | Yes |
| Analysis #2† | 3.71 [3.65] | 5 (22%) | 3.65 | Yes |
| **PFS (local RECIST)** | | | | |
| PP | 3.7 [3.5] | 6 (26%) | 3.5 | Yes |
| Analysis #1 | 3.7 [3.5] | 5 (22%) | 3.5 | Yes |
| Analysis #2 | 3.7 [3.5] | 6 (26%) | 3.5 | Yes |
| **PFS (investigator)** | | | | |
| PP | 3.7 [3.5] | 5 (22%) | 3.5 | Yes |
| Analysis #1 | 3.7 [3.5] | 4 (17%) | 3.5 | Yes |
| Analysis #2 | 3.7 [3.5] | 5 (22%) | 3.5 | Yes |
| **TTS** | | | | |
| PP | 6.2 [4.3] | 3 (13%) | 4.3 | Yes |
| **TTF** | | | | |
| PP | 6.2 [3.7] | 3 (13%) | 3.7 | Yes |

Primary endpoint for primary analysis. CI = confidence interval. PFS = progression-free survival. TTS = time to treatment switch. TTF = time to treatment failure. PP = per protocol. † PFS data of patients considered as censored in the PP analysis were considered for censoring methods #1 and #2. Analysis #1: progression event also registered at the date of switch to any post study treatment or death (whichever came first), otherwise censored at the last date known to be alive. Analysis #2: progression event also registered at the date of death, otherwise censored at the last date known to be alive.

Definition of time-to-event endpoints for evaluating disease progression:
- PFS was defined as the time from the date of randomization to the date of progression according to investigator, or any cause of death during the study.
- PFS (central RECIST): defined as the time from the date of randomization to the date of documented progression, calculated with RECIST from central blind reading, or any cause of death during the study.
- PFS (local RECIST): defined as the time from the date of randomization to the date of documented progression, calculated with RECIST from investigator reading, or any cause of death during the study.
- PFS (investigator-based): in this analysis of PFS, progression was assessed by the investigator on CT scan and/or other clinical assessments by the investigator (e.g. CHOI criteria).
- Time to switch (TTS): defined as the time from the date of randomization to the date of start of next treatment for GIST or death.
- Time to treatment failure (TTF): defined as the time from the date of randomization to the discontinuation of treatment for any reason.
B. Detailed evaluation of possible bias that may influence efficacy analysis

At the cutoff date of 31 January 2012, corresponding to a median follow-up duration of 14 months, results from study AB07001 (the currently reported study) suggested that imatinib-resistant GIST patients from the masitinib treatment arm experienced lower toxicity and longer overall survival (OS) than patients from the sunitinib arm. The 26-month follow-up data for OS indicated that this treatment effect represented a sustainable trend. However, due to the limited number of patients in this study, relatively short follow-up duration, and proportion of censored patients, a detailed analysis of possible confounding sources is critical for meaningful data interpretation. In addition to the standard patient baseline demographics (i.e. tumor localization and classification, prior lines of treatment, ECOG status) parameters warranting particular attention included: possible bias between treatment arms or dissimilarity to the general GIST population relating to *KIT* mutational status; heterogeneity in duration of prior imatinib exposure or maximal dose of imatinib administered; and differences in post study treatments received. The absence of such biases would serve as an endorsement of the data’s credibility, while identification of bias may partially or completely account for the observed treatment response.

No bias exists due to treatment arm demographics

It has already been shown in Table 1 of the main article that patient demographic characteristics were homogenous between treatment arms with no statistically significant difference observed. Therefore, no bias was introduced in terms of patient demographics.

No bias exists due to *KIT* mutational status

Table S2 describes the *KIT* mutational analysis in tumors of patients according to treatment arm. Tumor biopsies were taken from patients at the time of diagnosis and kept at -80°C to be analyzed for *KIT* and *PDGFR* sequences. All patients had *KIT* expressing tumors with a total of 36/44 (82%) patients having mutational data available. Considering the principal GIST mutations affecting exon 11 and 9, it is seen that the overall study population had a *KIT* exon 11:9 ratio of 6:1, with distributions of 5:1 and 7:1 in the masitinib and sunitinib treatment arms, respectively. The exon mutational status between treatment arms was therefore well balanced and also matched the ratio of 6:1 in the general population.1 Among the patients assigned as having a *KIT* exon 11 mutation, two patients (one from each treatment arm) had mutations in both exon 11 and exon 17 (not shown in Table S2). One patient from the masitinib treatment arm expressed wild type (WT) *KIT*, and one patient from the sunitinib treatment arm displayed a mutation in exon 13. Six patients (14%), three from each treatment arm, had a positive expression of PDGFR, while 8 of 44 patients (18%) did not show any PDGFR expression in tumors. PDGFR expression in tumor remained unknown for 30 of 44 patients (68%).

Table S2: *KIT* and *PDGFR* analysis

| Exon mutation; n (%) | Masitinib (N=23) | Sunitinib (N=21) | P-value |
|----------------------|------------------|------------------|---------|
| Mutational data available | 19 (82.6%) | 17 (81.0%) | 1.000 (F) |
| *KIT* positive expression | 23 (100.0%) | 21 (100.0%) | |
| Exon 11 | 15 (78.9%) | 14 (82.3%) | |
| Exon 9 | 3 (15.8%) | 3 (14.3%) | |
| Exon 13 | 0 (0.0%) | 0 (0.0%) | |
| No mutation (WT) | 1 (5.3%) | 0 (0.0%) | |
| Unknown | 4 (17.4%) | 13 (61.9%) | |
| **PDGFR expression; n (%)** | | | |
| Positive | 3 (13.0%) | 3 (14.3%) | |
| Negative | 3 (13.0%) | 5 (23.8%) | |
| Unknown | 17 (74.0%) | 13 (61.9%) | |

(F) Fisher's exact test. WT = wild type *KIT*.

Treatment arms were well balanced with respect to mutational status with no statistically significant difference observed. Therefore, no bias was introduced between treatment arms in terms of GIST mutational status.
No bias exists due to localization or classification of tumor or presence of metastases
Table S3 summarizes information regarding tumor classification and localization. At the time of initial GIST diagnosis, patients in the masitinib and sunitinib treatment arms had respective mean ages of 57.7 and 62.2 years, with an average of 4.9 years before study entry in both arms. Localization of primary tumors was homogeneously distributed between masitinib and sunitinib treatment arms with a majority found in the small intestine (48% versus 52%, respectively), and gastro-esophageal (35% versus 29%, respectively). Tumor classification was also similar between masitinib and sunitinib treatment arms with the majority of patients having metastatic tumors (83% versus 91%, respectively).

Table S3: Localization of primary tumors and diagnosis

| Time since first diagnosis (years) | Masitinib (N=23) | Sunitinib (N=21) | P-value |
|-----------------------------------|------------------|------------------|---------|
| Mean ± SD                         | 4.9 ± 3.1        | 4.9 ± 4.0        | 0.605 (W) |
| Median                            | 3.8              | 3.1              |         |
| Range                             | 1.2-11.7         | 0.2-12.6         |         |
| Time since first diagnosis >3 years; n (%) | 16 (69.6%) | 12 (57.1%) | 0.533 (F) |
| Age at first diagnosis (years)    | 57.7 ± 15.9      | 62.2 ± 13.9      | 0.398 (W) |
| Mean ± SD                         | 61.2             | 62.6             |         |
| Median                            | 21.7-78.4        | 35.8-84.4        |         |
| Primary tumor localization; n (%) | Intestinal 11 (47.8%) | 11 (52.4%) | 0.582 (F) |
| Gastro-esophageal                 | 8 (34.8%)        | 6 (28.6%)        |         |
| Colorectal                        | 1 (4.3%)         | 3 (14.3%)        |         |
| Other                             | 3 (13.0%)        | 1 (4.8%)         |         |
| Tumor classification at baseline; n (%) | Locally advanced 2 (8.7%) | 3 (14.3%) | 0.658 (F) |
| Presence of metastases at baseline | 21 (91.3%) | 18 (85.7%) |         |
| Liver metastases                  | 19 (82.6%)       | 15 (71.4%)       | 0.481 (F) |

(F) Fisher’s exact test. (W) Wilcoxon test. *Liver metastases at diagnosis or baseline. SD = standard deviation.

No bias exists due to prior surgery or radiotherapy
Table S4 describes the surgeries and radiotherapies previously experienced by patients for GIST before study entry. The majority of patients from each treatment arm had undergone surgical resection, with tumorectomy being the most common procedure. One patient from the masitinib treatment arm had received curative radiotherapy while none from the sunitinib treatment arm had done so.

Table S4: Surgeries and radiotherapies for GIST at baseline

| Prior treatment | Masitinib (N=23) | Sunitinib (N=21) | P-value |
|-----------------|------------------|------------------|---------|
| Surgery/resection | 21 (91.3%) | 18 (85.7%) | 0.658 (F) |
| Tumorectomy     | 12 (52.2%) | 14 (66.7%) |         |
| Other surgery   | 14 (60.9%) | 9 (42.9%) |         |
| Time since first surgery (years) | n 21 | 18 | 0.746 (W) |
| Mean ± SD       | 5.0 ± 3.4 | 7.2 ± 8.6 |         |
| Median          | 3.6      | 4.3     |         |
| Range           | 0.5-11.7 | 0.4-37.0 |         |
| Radiotherapy    | 1 (4.3%) | NA | 1.000 (F) |

(F) Fisher’s exact test. (W) Wilcoxon test. NA = not applicable. SD = standard deviation.

No statistical differences were observed between treatment arms for surgeries and radiotherapies before inclusion of patients in the study. As a conclusion, surgery and radiotherapy characteristics were homogenous between treatment arms and no bias was attributable due to this factor.

No bias exists due to maximal dose of prior imatinib treatment or prior exposure to imatinib
Table S5 describes the maximal imatinib dose received before study entry and also the total duration of prior imatinib treatment in both treatment arms. Disease progression was observed for all patients receiving imatinib at doses of at least 400 mg/day. The highest dose of imatinib received before study entry was 400 mg/day for 70% versus 81% of patients from the masitinib and sunitinib treatment arms, respectively. Of the remaining patients, a greater proportion from the masitinib treatment arm had previously received a maximal imatinib dose of 800 mg/day although this difference was not statistically significant, i.e. 30% versus 19%, respectively (P=0.5). It has been documented that prior imatinib dosage is a prognostic factor affecting clinical outcome for the treatment of imatinib-resistant GIST patients with subsequent tyrosine kinase inhibitors (TKI). For example, in a large-scale sunitinib ‘treatment-use’ study (n=1117) a difference was observed in median OS for prior imatinib treatment ≤400 mg (20.7 months; n=351) compared with prior imatinib treatment >400 mg (16.1 months; n=368). Data was further broken down into prior imatinib treatment groups of ≤400 mg; >400–600 mg; >600–800 mg; and ≥800 mg, with corresponding median OS of 21.4, 15.6, 16.8, and 7.8 months, respectively. This indicates that patients previously treated with a maximal imatinib dose of 800 mg/day appear to be more refractory to second-line treatment. Although the discrepancy in prior imatinib dose between the masitinib and sunitinib treatment arms was not statistically significant it is worth noting that if any minor bias was introduced to survival data, it would be in favor of the sunitinib treatment arm.

Considering the number of patients that experienced relatively rapid disease progression under imatinib treatment before study entry (i.e. within 6 months), there was no significant difference observed between the masitinib and sunitinib treatment arms; specifically, 3 of 23 patients (13.0%) versus 4 of 21 patients (19.0%) (Table S5). Thus, we may conclude that no positive bias was present in the masitinib treatment arm due to aggressive disease progression while under imatinib treatment. Finally, regarding duration of prior imatinib treatment, patients from the masitinib treatment arm received imatinib for a median exposure of 33 months versus 28 months for patients from the sunitinib treatment arm. No statistically significant differences were observed between treatment arms, although there was a trend of longer imatinib treatment duration for the masitinib treatment arm as compared with the sunitinib arm.

Table S5: Previous treatment with imatinib

|                          | Masitinib | Sunitinib | P-value |
|--------------------------|-----------|-----------|---------|
| N                        | 23        | 21        |         |
| Imatinib treatment termination because of lack of efficacy; n (%) | 23 (100.0%) | 21 (100.0%) |         |
| Progression ≤6 months with imatinib; n (%) | 3 (13.0%) | 4 (19.0%) | 0.693 (F) |
| Maximal previous dose of imatinib |         |           |         |
| 400 mg/day               | 16 (69.6%) | 17 (81.0%) |         |
| 800 mg/day (after progression with 400 mg/day) | 7 (30.4%) | 4 (19.0%) | 0.494 (F) |
| Cumulative duration (months) |         |           | 0.707 (W) |
| Mean ± SD               | 41.4 ± 26.8 | 45.9 ± 38.1 |         |
| Median                  | 32.7      | 28.2      |         |
| Min; Max                | 8.8; 103.3 | 5.4; 114.3 |         |
| Cumulative duration; n (%) |       |           |         |
| >6 months               | 23 (100%) | 20 (95.2%) | 0.477 (F) |
| >12 months              | 22 (95.7%) | 19 (90.5%) | 0.599 (F) |
| >24 months              | 17 (73.9%) | 11 (52.4%) | 0.211 (F) |
| >36 months              | 9 (39.1%) | 7 (33.3%) | 0.761 (F) |

(F) Fisher’s exact test. (W) Wilcoxon test. SD = standard deviation.

Prior imatinib treatments were similar between treatment arms, both in the duration and the dose of imatinib treatment received by patients. Thus, no bias was observed for these factors.

No bias exists due to masitinib position in terms of treatment-lines received for GIST

A patient’s first-line treatment was defined as the specific dose of the initial treatment administered. Subsequent lines of treatment were defined as: 1/ an increment in dose of the previous treatment because of disease progression, or 2/ discontinuation of the previous treatment with a switch to an alternative treatment. At the time of study entry masitinib was administered as the patients second-line, third-line, or fourth-line of treatment in respectively, 6 of 23 patients (70%), 4 of 23 patients...
(17%), and 3 of 23 patients (13%). This compared to 12 of 21 patients (57%), 7 of 21 patients (33%), and 2 of 21 patients (10%), respectively, from the sunitinib treatment arm (Table S6). No significant difference was observed between treatment arms. Hence, no bias was introduced between treatment arms in terms of number of treatment-lines received before study entry.

**Table S6: Masitinib position in terms of treatment-line for GIST**

|          | Masitinib     | Sunitinib     | P-value   |
|----------|---------------|---------------|-----------|
| N        | 23            | 21            | 0.673 (MH)|
| First-line; n (%) | NA            | NA            |           |
| Second-line; n (%) | 16 (69.6%)    | 12 (57.2%)    |           |
| Third-line; n (%)  | 4 (17.4%)     | 7 (33.3%)     |           |
| Fourth-line; n (%) | 3 (13.0%)     | 2 (9.5%)      |           |

* A patient’s first-line treatment was defined as the specific dose of the initial treatment administered with subsequent treatment lines defined as: 1/ an increment in dose of the previous treatment because of disease progression, or 2/ discontinuation of the previous treatment with a switch to an alternative treatment. MH = Mantel Haenszel test. NA = not applicable.

No bias exists due to post progression treatment

Upon study termination patients were allowed to switch from masitinib to sunitinib, followed by other therapies (including off-label use of TKIs); conversely, no cross-over from sunitinib to masitinib was permitted. This one-way cross-over complies with the ethical and pragmatic obligations that all patients should receive the standard of care following study withdrawal. Furthermore, it is the recommended trial design for evaluating an experimental treatment in the setting of effective subsequent therapies. Table S7 describes the various post study TKI therapies administered according to treatment arm.

No difference between treatment arms was observed for either the average number of post study treatments received or distribution of other TKIs administered. The vast majority of masitinib-treated patients were administered at least one subsequent treatment-line following study termination, with 85% of patients switching to sunitinib as their initial post study treatment. Thus, when comparing treatment regimens from study entry to death the major difference between treatment arms was that one cohort received masitinib immediately following progression under imatinib. However, this difference should not be considered as a bias as it is consistent with the study’s design of testing the hypothetical scenario of masitinib being administered as the approved second-line treatment compared against it being unobtainable. Hence, post study treatment in terms of number received and distribution of other TKIs administered was homogenous between treatment arms and no bias was attributable due to this factor.
Table S7: Post study treatments

| Initial post study treatment administered | Masitinib (N=23) | Sunitinib (N=21) |
|------------------------------------------|-----------------|-----------------|
| N                                        | 20              | 18              |
| Temporary unknown                        | 0 (0.0%)        | 1 (5.6%)        |
| No declared treatment – patient died     | 1 (5.0%)        | 5 (27.8%)       |
| Sunitinib                                | 17 (85.0%)      | 2 (11.1%)       |
| Imatinib                                 | 2 (10.0%)       | 2 (11.1%)       |
| Pazopanib                                | 0 (0.0%)        | 2 (11.1%)       |
| Nilotinib                                | 0 (0.0%)        | 3 (16.7%)       |
| Sorafenib                                | 0 (0.0%)        | 2 (11.1%)       |
| Regorafenib                              | 0 (0.0%)        | 1 (5.6%)        |

Masitinib treatment arm: post study treatments received after sunitinib

| N                                        | 10              | NA              |
| Unknown treatment                        | 0 (0.0%)        |                 |
| No post study treatment – patient dead   | 2 (20.0%)       |                 |
| No post study treatment – patient alive  | 1 (10.0%)       |                 |
| Imatinib                                 | 0 (0.0%)        |                 |
| Sunitinib                                | 0 (0.0%)        |                 |
| Pazopanib                                | 3 (30.0%)       |                 |
| Nilotinib                                | 1 (10.0%)       |                 |
| Sorafenib                                | 3 (30.0%)       |                 |
| Regorafenib                              | 0 (0.0%)        |                 |

(F) = Fisher’s exact test. (W) = Wilcoxon test. NA = not applicable.

Concluding remarks on quality of data from study AB07001

These data indicate that biases typically associated with limited sized study populations or TKI treatment of imatinib-resistant GIST are not in evidence for this dataset. Taken together with observations that there was no post study treatment bias beyond what was intentionally simulated via the one-way cross-over design, one may conclude that the observed treatment effect on OS was unlikely due to chance finding but rather attributable to a substantive masitinib response.
C. Analysis of post study treatment received

Of those patients terminating study treatment, 19 of 20 (95%) from the masitinib treatment arm received at least one post study treatment as opposed to 13 of 18 (72%) from the sunitinib arm, with death or poor health condition precluding any option for post study treatment in the remaining patients (Table S8).

Analysis of death in patients who did not receive a post study treatment showed that in the sunitinib treatment arm: two patients died while under study treatment, one for unknown reason and one unrelated to treatment; one patient died 10 days after study termination due to disease progression; and two patients died 1.6 months after study termination due to pulmonary embolism for one, and progressive disease for the other. In comparison, one patient died from disease progression 4.7 months after study termination in the masitinib treatment arm.

Table S8: Therapies administered after study discontinuation

| Patients terminating treatment | Masitinib (n=23) | Sunitinib (n=21) |
|-------------------------------|-----------------|-----------------|
| At least one post study treatment received | 19/20 (95%) | 13/18 (72%) |
| Sunitinib as initial post study treatment | 17/20 (85%) | N/A |
| Other TKIs as post study treatment | 9/20 (45%) | 12/18 (67%) |
| No post study treatment received | 1/20 (5%) | 5/18 (28%) |
| Death during the study* | 0 | 3 |
| Death shortly after the end of the study | 1 | 2 |
| Number of post study treatment-lines received | | |
| Mean (SD) | 1.5 (0.9) | 1.4 (1.5) |
| Median | 1.0 | 1.0 |
| Range | 0.0–4.0 | 0.0–6.0 |

*Death under study treatment (plus 28 days post therapy). TKI=tyrosine kinase inhibitor. N/A=not applicable. SD=standard deviation.
D. Comparison of data from the masitinib AB07001 study with historical sunitinib data, including assessment of the impact KIT exon distribution has on PFS and OS

Published data show that KIT mutational status is predictive of clinical response to tyrosine kinase inhibitor (TKI) therapy. Three large randomized studies of imatinib treatment for advanced GIST have shown that KIT exon 11 mutations are associated with higher response rates and longer progression-free survival (PFS) than KIT exon 9 mutations or wild-type GIST.\textsuperscript{3,8} A contrary influence was evident for second-line treatment with sunitinib; response rates in imatinib-resistant GIST being significantly higher for patients with the KIT exon 9 mutation as opposed to the KIT exon 11 mutation.\textsuperscript{9} As a consequence of the observed KIT mutational status influence on TKI treatment of GIST, it is important for any clinical trial to perform subanalyses on these subpopulations, i.e. stratification based on KIT mutational status. It also follows that the distribution of a study population’s KIT mutational status between treatment arms will impact on the results and should be taken into consideration for interpretation and comparison between clinical trials. A meta-analysis based on 772 GIST patients receiving imatinib treatment revealed that the general GIST population has a KIT exon 11 to KIT exon 9 ratio (exon 11:9) of 6:1; these mutations representing the main KIT mutation subpopulations in GIST.\textsuperscript{1}

The efficacy and safety of sunitinib in imatinib-resistant GIST have been evaluated in an open-label phase II study,\textsuperscript{9,10} a placebo-controlled phase III trial,\textsuperscript{11,12} a large scale treatment-use study,\textsuperscript{2,3} and post registration single institution trials.\textsuperscript{13-15} Notably, the sunitinib phase II study population had a KIT exon 11:9 ratio of approximately 2:1.\textsuperscript{1} Comparing this to the ratio reported for the general GIST population indicates an imperfect representation.\textsuperscript{1} KIT mutational status was not reported for the phase III sunitinib trial or the large scale treatment-use trial. However, it is a fair supposition that patient distribution in these study populations was also skewed toward KIT exon 9 patients because earlier studies had established that sunitinib preferentially affected this patient subpopulation and that these patients were at highest risk of imatinib-resistance. Comparable efficacy results across these studies as well as the patient exon 11:9 ratios reported in recent institution trials support this assumption (Table S9).

Table S9: Comparison of data from the masitinib AB07001 study with historical sunitinib data survival data for clinical trials reporting sunitinib treatment of imatinib-resistant GIST, including breakdown of study’s KIT exon 11 to KIT exon 9 patient distribution.

| Study                                      | N   | Median PFS (months)\textsuperscript{†} | Median OS (months) | Exon 11:9 ratio | Ref  |
|--------------------------------------------|-----|----------------------------------------|--------------------|-----------------|------|
| AB07001 (SUN treatment arm)                | 21  | 1.9 [1.8:4.4]                          | 17.4 [9.4:28.6]    | 7:1             | †    |
| SUN Phase II                               | 97  | 7.8                                    | 19.0               | 2:1             |      |
| SUN Phase III Blinded                      | 207 | 6.4 [4.0:7.8]                          | NR                 | NP              | 11   |
| SUN Phase III Extension                    | 243 | 5.3 [2.5:6.4]                          | 16.7 [14.1:19.1]   | NP              | 12   |
| SUN Open label treatment-use               | 1117| 9.4 [8.3:10.8]                         | 17.3 [15.6:19.3]   | NP              | 2    |
| SUN Single-institute (Poland)              | 137 | 9.9                                    | 16.9               | 4:1             | 14   |
| SUN Single-institute (Korea)               | 88  | 7.1 [4.5:9.7]                          | 17.6 [14.1:21.2]   | 4:1             | 15   |

NP = not published. NR = Not reached. SUN = sunitinib. PFS = progression-free survival. OS = overall survival. Median data are expressed as months with their 95% confidence intervals. \textsuperscript{†}A conversion factor of 0.23 has been used to convert data reported in weeks into months for direct comparison between studies. \textsuperscript{1}Study AB07001 is reported in the article associated with this online supplemental information; median follow-up of 14 months for PFS according to central RECIST (univariate model) and median follow-up of 26 months for OS (univariate model). \textsuperscript{1}Time to progression reported instead of PFS.

A logical consequence to sunitinib’s superior response rates in patients with KIT exon 9 mutant imatinib-resistant GIST is that the PFS observations associated with this historical data will have been positively biased when compared with what would have been expected for the general GIST
population. The magnitude of this effect is clearly seen in the divergence of PFS-rate curves according to KIT mutational status for data taken from the sunitinib phase II study (Figure S1).9 Apparent also from this comparison is that the influence of KIT mutational status is more pronounced for PFS. Therefore, a larger deviation from the general GIST population would be expected in terms of PFS, suggesting that median OS is the most appropriate survival data to use in any comparative analysis. In the present study (AB07001) it follows that the observed overall sunitinib efficacy response will have been suppressed in comparison with these historical data merely because of the difference between their population’s KIT exon 11:9 ratios. Considering only the KIT exon 11 cohorts from the sunitinib treatment arm of study AB07001 (n = 14) and the sunitinib phase II study,9 in which this bias should not be present and for which there are adequate population size for a useful comparison, it can be seen that both studies have a similar downward trend in PFS-rate and OS-rate curves for the sunitinib-treated patients (Figure S1). By contrast, the KIT exon 9 cohort from the sunitinib phase II study tended to stabilize for both survival variables.

Figure S1. Survival rates according to KIT exon mutational status comparing data from the historical sunitinib scientific literature with the currently reported AB07001 study sunitinib treatment arm KIT exon 11 cohort. This shows that KIT exon status has an important impact on sunitinib PFS response and that the data for KIT exon 11 patients is well matched between study AB07001 and historical sunitinib data. It is also seen that KIT exon status has far less impact on OS indicating that comparison to historical OS data provides a valid approximation. Historical literature values for PFS-rates and OS-rates were estimated from published Kaplan-Meier curves.9

The dissimilar response for sunitinib-treated KIT exon 9 patients when compared with KIT exon 11 patients serves to illustrate the important influence KIT exon mutational status will have on survival rate data for the overall population (and in particular the KIT exon 11:9 population ratio). Also evident from this historical comparison is that patients with the KIT exon 11 mutation from the sunitinib treatment arm of study AB07001 show a similar PFS trend as the exon-related historical sunitinib
literature. Hence, the sunitinib treatment arm represents a valid active control and its associated data can be considered as reliable for the tested population. This is further corroborated by considering the PFS rates of the sunitinib treatment arm’s overall population \((n = 21)\), i.e. regardless of exon mutational status (Figure S2). As predicted above, for an overall population weighted heavily towards \(KIT\) exon 11 patients, and therefore consistent with the general GIST population, the PFS response will more closely resemble the historical sunitinib \(KIT\) exon 11 cohort than the historical sunitinib \(KIT\) exon 9 cohort. It is highly plausible that reducing the exon 11:9 population ratio will effectively move the overall population rate curves further towards that observed for the historical sunitinib \(KIT\) exon 9 cohort.

**Figure S2.** PFS rates of the sunitinib treatment arm’s overall population from the currently reported AB07001 study compared against the historical sunitinib response according to \(KIT\) exon mutational status. These curves show that PFS data from the overall sunitinib treatment arm of study AB07001 is closely matched to historical sunitinib data for \(KIT\) exon 11, which is to be expected given an exon 11:9 ratio of 7:1. Hence, PFS for the overall population of study AB07001 is expected to be lower than that presented in the sunitinib historical data due to differences in exon distribution of their respective populations. Historical literature values were estimated from published Kaplan-Meier curves.9

These observations support our conclusion that the relatively low PFS value reported in the sunitinib treatment arm of study AB07001 was related to the influence of \(KIT\) mutational effects rather than inadequate treatment outcome of the active control. Survival data from the sunitinib treatment arm of study AB07001 can be considered as representative of the study population tested. Therefore, this treatment arm serves its purpose as an active comparator for the study.
E. The reported survival advantage for the masitinib treatment arm is consistent with results from an independent dataset in a closely matched cohort demonstrating external validity

Masitinib activity in imatinib-resistant GIST has been previously identified in a phase I dose-escalating study (AB03002) carried out in 40 patients with advanced and/or metastatic cancer; including 19 patients with GIST. Among these GIST patients, 12 patients received masitinib doses ranging from 6.8 to 13 mg/kg/day, making this cohort consistent with those from study AB07001 (the currently reported study). Findings from study AB03002 regarding determination of the maximum tolerated dose for orally administered masitinib and its pharmacokinetic profile have been published, although no efficacy data from this matched imatinib-resistant GIST cohort were reported at that time.17

Post-hoc analyses from study AB03002 showed masitinib (6.8 to 13 mg/kg/day) to generate an important effect on overall survival (OS) in imatinib-resistant GIST patients despite having only modest impact on progression-free survival (PFS). Median PFS was 2.5 [1.3; 6.5] months in the matched imatinib-resistant GIST cohort receiving masitinib, which was no better than that reported in the sunitinib literature (e.g. median time-to-progression according to investigator local assessment is 6.4 [4.0; 7.8] months).11 Masitinib did however demonstrate an important OS in the matched imatinib-resistant GIST cohort, with a median OS of 23.4 [12.4; 34.4] months at a time when sunitinib had not been registered. Therefore, the primary objective of study AB07001 was to ensure that masitinib could achieve a minimum threshold of PFS so that further evaluation of masitinib could be warranted. Its secondary objective was to confirm whether masitinib compared favorably to sunitinib in terms of OS. Findings from this phase I study also represent an independent dataset and therefore provide external validation of the OS benefit observed for imatinib-resistant GIST patients in the masitinib treatment arm of the currently reported study (Table S10).17

Table S10: Survival data for masitinib treatment arm from two independent clinical trials treating imatinib-resistant GIST

| Study identifier (N) | AB03002 (12)* | AB07001 (23) |
|----------------------|----------------|----------------|
| Median OS [95% CI] (months) | 23.4 [12.4;34.4] | 29.8 [17.8; NR] |
| OS 6-month (%) | 92 | 96 |
| OS 12-month (%) | 75 | 83 |
| OS 18-month (%) | 58 | 69 |
| OS 24-month (%) | 50 | 64 |
| OS 30-month (%) | 42 | 46 |

NR = Not reached. OS = overall survival. 95% confidence intervals shown as [##;#]. *Cohort of 12 patients with clinically relevant masitinib dose (between 6.8–13 mg/kg/day).

These results compare well with findings from the masitinib treatment arm of the currently reported study (AB07001), i.e. median OS of 29.8 months (95% CI [17.8; NR]). At the time study AB03002 was conducted sunitinib has not been registered in this indication and therefore was not widely used as a post study treatment after termination of masitinib. It is however possible to estimate the effect of sunitinib in third-line by considering historical data from a study comparing sunitinib to placebo after imatinib resistance; with median OS of approximately 16.8 and 15.0 months, respectively.12 In that study, patients from the placebo treatment arm were allowed to switch to the sunitinib treatment arm upon disease progression, thereby simulating sunitinib as a third-line treatment, albeit in a scenario of an inactive second-line therapy. It has been reported that by carrying out a rank preserving structural failure time (RPSFT) analysis on the placebo group who had switched to sunitinib after disease progression, the median OS related to placebo alone was approximately 9.0 months. We may therefore infer that median OS generated by sunitinib in third-line was 6.0 months (i.e. 15.0–9.0 months). Taking together the observed median OS for masitinib treated-patients from study AB03002 and the
inferred median OS generated by sunitinib following a placebo treatment line in imatinib-resistant GIST patients, the estimated median OS generated by administering masitinib as a second-line therapy followed by sunitinib would be 29.4 months (23.4 + 6.0 months).

Thus, within the limitations of historical comparisons, the OS benefit reported in these two independent datasets for imatinib-resistant GIST patients treated with masitinib followed by the standard of care (typically sunitinib) generates remarkably similar median OS results. The implication being that the OS benefit observed for the masitinib treatment arm of the currently reported study is not without precedent.
F. The significant improvement in overall survival reported for masitinib when compared with sunitinib in the absence of any difference in progression-free survival can be explained by masitinib’s secondary mechanisms of action

A 12-month overall survival (OS) advantage was reported in study AB07001 for the masitinib treatment arm relative to the sunitinib arm, despite showing no discernible difference on measures of disease progression such as progression-free survival (PFS). Although the observation of a median OS benefit in the absence of PFS gains is an unusual finding, it is not entirely unexpected that PFS for masitinib and sunitinib were in the same range considering that at therapeutic doses both TKIs inhibit c-Kit and PDGFRA by a similar magnitude.18 Logically therefore, alternative mechanisms of action (MoA) must be implicated. Emergent comprehension about masitinib’s secondary mechanisms of action (MoA) indicates that the observed long-term survival benefit is related to its ability to induce changes in the tumor microenvironment; predominantly via dendritic-cell mediated activation of Natural Killer (NK) cells, and via promotion of a macrophage-mediated anti-tumoral response. Mast cells are also implicated in the tumorigenesis of GIST via their influence on the tumor microenvironment, which is of relevance because these cells are the primary cellular target of masitinib through its inhibition of KIT and Lyn.19 Taken together, these modifications of the tumor microenvironment may prevent dissemination; reducing aggressiveness of the tumor without direct inhibition of tumor growth. This may explain the profound effect of masitinib on long-term but not short-term survival. Herein, a more detailed discussion of masitinib’s secondary MoA via dendritic-cell mediated activation of NK cells is provided.

In general, the Th2-type response is associated with oxidative stresses whereas the Th1-type response is associated with anti-oxidant effects.20-25 Several lines of evidence suggest that the health degradation occurring in GIST could be due to a dominant Th2-type of immune response leading to a polarization of pro-oxidative M2-macrophages. For example, it has been shown that increased levels of M2-polarized macrophages are found in metastatic GIST tumors when compared against primary tumors, suggesting a worsening of the redox state in these GIST patients.26 A similar shift of the immune response towards an immunosuppressive Th2-type of response was shown to occur in several animal models of cancer,27, 28 as well as in humans.29, 30 Additionally, mast cell infiltration and activation in tumors such as GIST will exacerbate inflammation and immunosuppression in the tumor microenvironment, further contributing to the Th2-type response.31 Hence, any therapeutic strategy capable of switching the balance of the immune response towards a Th1-type response and/or inhibits mast cell activity should counteract oxidative stresses generated within the tumor; notably through promoting the intake of iron and by generating antioxidants under the influence of the interferon-gamma.32,33

This rationale of promoting a Th1-type of immune response to improve the survival of GIST patients is supported by in vitro data indicating that impaired dendritic cell-mediated natural killer (NK) cell activation was associated with reduced survival in GIST patients and a concomitant depressed production of Th1 cytokines such as TNF-alpha and interferon-gamma. These harmful effects were countered by blocking IL10, which is a major Th2 cytokine, hence supporting the possibility to produce a clinical benefit in GIST by promoting a Th1-type of immune response.34 Notably, this represents an independent disease mechanism from that of KIT mutations. Further evidence is found in research showing that increased survival in GIST patients correlated with an increased production of interferon-gamma by NK cells when compared against baseline level.35 Additionally, promoting a Th1-type of immune response in GIST patients through the combined treatment of PegIFNa2b and imatinib demonstrated significant induction of innate immunity and Th1-type response, resulting in encouraging clinical outcomes when compared with imatinib monotherapy.36

Experimental data indicate that masitinib is capable of modulating the immune response in such a way as to positively impact on physiological disturbances such as oxidative stress. The effect of masitinib on dendritic cells and subsequent activation of NK cells leading to release of interferon-gamma has been demonstrated in vitro.37 As seen in Figure S3, bone marrow derived dendritic cells produce low amounts of interferon-gamma when compared with NK cells. When masitinib in its free base form
(AB1003) was incubated with dendritic cells, no effects were seen concerning the secretion of interferon-gamma. Similarly, dendritic cells in the presence of NK cells only slightly augmented the NK cell secretion of interferon-gamma. However, when masitinib was added to a mixture of dendritic cells and NK cells, the secretion of interferon-gamma was increased by approximately 50%. Interferon-gamma is a Th1-type cytokine that promotes Th1 differentiation, ultimately leading to cellular immunity and macrophage activity. It is also important for cell self-activation during the onset of the cell-mediated immune response and has anti-tumor properties. Concomitantly, interferon-gamma suppresses Th2 differentiation, which would otherwise cause a pro-tumoral response. This result provides proof that masitinib has the potential to stimulate a NK cell anti-tumoral immune response through a dendritic cell mediated mechanism. In turn this would conceivably promote an M1-polarization of macrophages leading to reduction of oxidative stress.

**Figure S3.** Masitinib induces the secretion of IFN-gamma by NK cells in the presence of dendritic cells. Masitinib (AB1010) is the mono mesylate salt of the free base AB1003. BM-DC = bone marrow derived dendritic cells. IFNγ = interferon-gamma. NK = natural killer cells. GM/IL4 = granulocyte-macrophage colony-stimulating factor / interleukin 4.
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