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KIT and *PDGFRA* Mutations and Survival of Gastrointestinal Stromal Tumor Patients Treated with Adjuvant Imatinib in a Randomized Trial

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ABSTRACT

Purpose: Limited data are available about the influence of *KIT* and *PDGFRA* mutations on overall survival (OS) of patients with gastrointestinal stromal tumor (GIST) treated with adjuvant imatinib.

Patients and Methods: The Scandinavian Sarcoma Group XVIII/AIO multicenter trial accrued 400 patients with a high risk for GIST recurrence after macroscopically complete surgery between February 4, 2004, and September 29, 2008. The patients received adjuvant imatinib 400 mg/day for either 1 year or 3 years based on random allocation. We analyzed using conventional sequencing *KIT* and *PDGFRA* mutations centrally from 341 (85%) patients who had localized, centrally confirmed GIST, and correlated the results with recurrence-free survival (RFS) and OS in exploratory analyses.

Results: During a median follow-up time of 10 years, 164 RFS events and 76 deaths occurred. Most patients were re-treated with imatinib when GIST recurred. Patients with *KIT* exon 11 deletion or indel mutation treated with 3 years of adjuvant imatinib survived longer than patients treated for 1 year [10-year OS 86% versus 64%, respectively; HR, 0.34; 95% confidence interval (CI), 0.15–0.72; $P = 0.007$], and also had longer RFS (10-year RFS 47% versus 29%; HR, 0.48; 95% CI, 0.31–0.74; $P < 0.001$). Patients with *KIT* exon 9 mutation had unfavorable OS regardless of the duration of adjuvant imatinib.

Conclusions: Compared with 1 year of imatinib, 3 years of adjuvant imatinib led to 66% reduction in the estimated risk of death and a high 10-year OS rate in the subset of patients with a *KIT* exon 11 deletion/indel mutation.

Introduction

Gastrointestinal stromal tumor (GIST) is usually localized when first detected and potentially curable with surgery, but some GISTs give rise to metastases that are often found in the liver and at intra-abdominal sites (1). The risk for GIST recurrence despite macroscopically complete surgery can be estimated using prognostication schemes based on the validated prognostic factors, GIST mitotic rate and diameter, tumor site in the gastrointestinal tract, and tumor rupture (1).

Patients with a high estimated risk for GIST recurrence are recommended to be treated with adjuvant imatinib for 3 years according to the European Society for Medical Oncology guidelines (2), and at least for 3 years following the National Comprehensive Cancer Network of the U.S. guidelines (3). This recommendation is based on the randomized adjuvant trials carried out (4–7), and the 3-year duration on the Scandinavian Sarcoma Group (SSG) XVIII/AIO trial, where patients with GIST with a high-risk of recurrence were randomly assigned to receive adjuvant imatinib 400 mg/day orally for either 1 year or 3 years (6, 7). In the SSGXVIII/AIO trial, the patients who received 3 years of adjuvant imatinib had significantly better overall survival (OS) than those allocated to 1 year of imatinib with a HR for death of 0.55 during a median follow-up of 10 years after the date of randomization (7).

Imatinib inhibits a few tyrosine kinases including KIT and the platelet-derived growth factor receptor alpha (PDGFRα; ref. 8). About 75% of GISTs harbor an activating mutation in *KIT*, usually in exon 11 or exon 9, 10% to 15% in *PDGFRA*, and the remaining GISTs (about 10%, formerly known as "wild type" GIST) may have an aberration in one of several genes, such as *SDH* (encodes succinate dehydrogenase), *NF1* (encodes neurofibromatosis-1 protein), or *BRAF* (1). The sensitivity of different *KIT* and *PDGFRA* aberrations to imatinib varies. In general, overtly metastatic GISTs with *KIT* exon 11 mutation are considered most responsive to imatinib (9), whereas at the other end of the spectrum, *PDGFRA* D842V mutation confers insensitivity (but sensitivity to avapritinib; refs. 10, 11). Therefore, carrying out mutational analysis of the key

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Translational Relevance

Adjuvant imatinib administered for 3 years is the standard treatment of patients with gastrointestinal stromal tumor (GIST) who have a high risk for recurrence after surgery, but it is unknown how 3-year adjuvant imatinib influences overall survival (OS) in subsets of patients with various *KIT* and *PDGFRA* mutations. We investigated this within the context of the SSGXVIII/AIO trial patient population who received adjuvant imatinib 400 mg/day for either 1 year or 3 years based on random allocation. The risk of death decreased 66% with 3-year imatinib compared with 1 year of imatinib when GIST harbored a *KIT* exon 11 deletion/indel mutation (the most common type of mutation) even though the patients were usually treated with imatinib after GIST recurrence in both groups. The patients with exon 11 deletion/indel mutation allocated to 3-year imatinib achieved a high (86%) 10-year OS rate. Patients with *KIT* exon 9 mutation did not benefit from the longer duration of imatinib.

target genes is considered standard practice when planning adjuvant therapy for patients with GIST (2, 3).

In an earlier analysis on the SSGXVIII/AIO trial patient population, we found that patients with *KIT* exon 11 deletion mutation or insertion-deletion (indel) mutation had longer recurrence-free survival (RFS) when treated with 3 years of adjuvant imatinib compared with 1 year of treatment, but patients with GIST with other types of mutations did not derive significant RFS benefit from the 3-year treatment (12). In this analysis, the effect on OS could not be addressed due to a small number of OS endpoints in the mutational subgroups. We now report the associations of different mutation types with RFS and OS based on a longer follow-up of the trial patients and a larger number of survival endpoints. The current duration of patient follow-up, a median of 10 years after the date of randomization, is the maximum follow-up time achievable in the trial, because the patients were scheduled for 10 years of follow-up after randomization, and the last patient accrued has now been followed up for 10 years (7). The current results indicate that about two thirds of deaths can be avoided during the first decade of follow-up with 3-year adjuvant imatinib compared with 1-year imatinib in the subset of patients with *KIT* exon 11 deletion or indel mutation despite patients are treated with imatinib when GIST recurs. This observation suggests that imatinib and other tyrosine kinase inhibitors administered for advanced GIST do not compensate for suboptimal duration of adjuvant imatinib treatment. No OS benefit from the longer adjuvant imatinib was found in the subgroup of patients with *KIT* exon 9 mutation. To our knowledge, these observations are novel.

Patients and Methods

Patients and treatment

Adult patients with histologically confirmed KIT-positive GIST were eligible for the randomized, multicenter, open-label, phase III SSGXVIII/AIO trial (www.ClinicalTrials.gov identifier NCT00116935). In this trial, the patients received adjuvant imatinib orally 400 mg per day for either 1 year or 3 years based on random allocation (6). Eligible patients had received no neoadjuvant therapy, their GIST was macroscopically completely excised at open surgery, the Eastern Cooperative Oncology Group performance status was ≤ 2, and they had adequate bone marrow, liver, and kidney function (6). Patients with metastatic or recurrent GIST were not eligible; patients who had all detectable abdominal metastases completely excised were eligible until October 2006 when the study protocol was amended, and such patients were excluded thereafter. Information about the mutational status of *KIT* (HGNC:6342) or *PDGFRA* (HGNC:8803) was not required at the time of study entry.

The risk of GIST recurrence was required to be high. The risk was assessed using the modified NIH Consensus Criteria, where high risk GIST is required to fulfill ≥ 1 of the following factors: diameter > 10 cm, > 10 mitoses per 50 high power fields (HPF) of the microscope, diameter > 5 cm and the mitotic count > 5, or presence of tumor rupture (1). The key prognostic factors in GIST, tumor mitotic count, size, site, and rupture, were balanced between the two groups (6). Tumor rupture occurred in 30 (17%) of the 174 patients in the 1-year group and in 41 (25%) of the 167 patients in the 3-year group. GIST risk stratification was done by local pathologists, who also assessed tumor KIT expression using immunohistochemistry.

The study protocol was approved by the institutional review committees. The patients provided written informed consent before entering the study. The trial was conducted following the Good Clinical Practice and Declaration of Helsinki guidelines.

Assessments

The patients were allocated to the two groups in a 1:1 ratio centrally (6). The median duration of imatinib administration was 12.0 months and 35.9 months in the 12-month group and the 36-month group, respectively. None of the patients received adjuvant imatinib longer than for 37.2 months. Contrast enhanced CT or MRI of the abdomen and the pelvis, and chest CT or X-ray were used as staging examinations. The patients were scheduled for regular follow-up visits for 10 years counting from the date of randomization. The examinations at the follow-up visits consisted of physical examination, blood cell counts and blood biochemistry, and CT or MRI of the abdomen, which were done at 6-month intervals for the first 7 years on study, and annually thereafter.

When GIST histology was reviewed centrally during the study by one of two professional pathologists, 15 tumors turned out not to be GISTs, but usually some other type of sarcoma (6). GIST mitotic counts were reassessed centrally. *KIT* exons 9, 11, 13, and 17, and *PDGFRA* exons 12 and 18 were sequenced centrally using conventional gene sequencing during the study (6).

Statistical analysis

The trial primary endpoint was RFS, defined as the time interval from the date of randomization to the date of GIST recurrence or death, whichever occurred first; patients alive without recurrence were censored on the date of the last follow-up. OS, a secondary endpoint, was defined as the time between the date of randomization and the date of death, censoring patients alive on the date of last follow-up.

We estimated the survival curves for the groups using the Kaplan–Meier method. A univariate Cox model was used to compute the HRs, their confidence intervals (CI), and *P* values. We analyzed the frequency tables with the chi-square test and compared continuous distributions between groups with the Mann–Whitney U-test. The *P* values are two-sided and unadjusted for multiple testing. The statistical analyses were carried out with SAS statistical software for Windows (v. 9.4; SAS Institute Inc., Cary, NC).

Data availability

The study protocol has been available since the time of primary publications and is available in the Supplement. Considering patients'

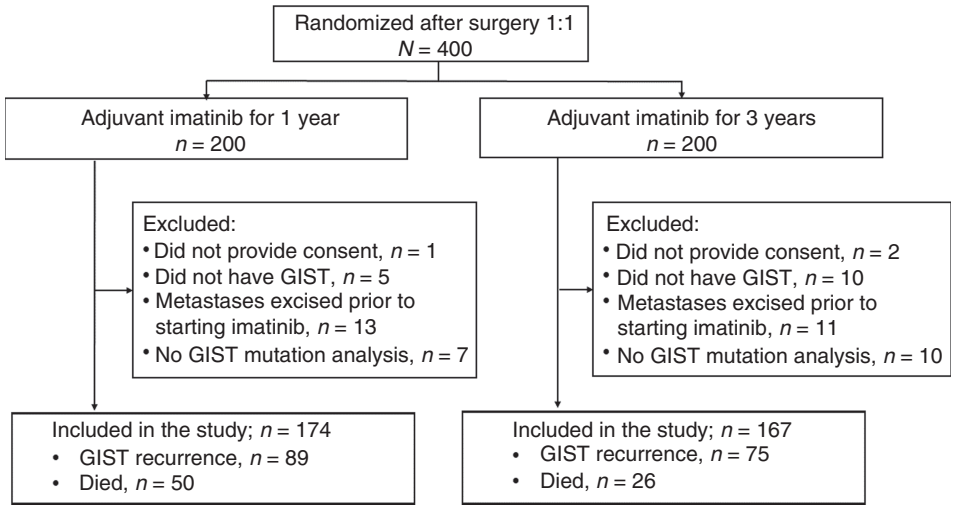

Figure 1.
CONSORT diagram of the study population.

privacy and related regulations in the countries that participated in the SSGXVIII/AIO trial, we chose not to make the database public. Address requests for the dataset to the corresponding author (heikki.joensuu@hus.fi). Reasonable requests will be evaluated and approved by the SSGXVIII/AIO trial Steering Committee.

Results

Patients and GIST mutations

Four hundred patients were accrued to the trial from 24 study sites between February 4, 2004 and September 29, 2008. We excluded from the analysis three patients who were randomized without the patient signing informed consent, 15 patients who did not have GIST at central tumor tissue pathology review carried out during the study, 24 patients who had GIST metastases resected at surgery, and 17 patients who did not have *KIT* and *PDGFRA* mutation analysis performed centrally, leaving 341 (85%) patients for analysis (1-year group, 174; 3-year group, 167; **Fig. 1**).

The characteristics of the 341 patients and GISTs, stratified by the *KIT* or *PDGFRA* mutation subtype, are provided in **Table 1**. A slight majority (175, 51%) were male. The age and gender distribution of the study patients is similar as in population-based GIST patient series (Supplementary Table S1). The patient population was at a high risk for GIST recurrence based on the key prognostic factors; 71 (21%) patients had ruptured GIST, the median GIST diameter was large (10 cm), and 156 (46%) patients had non-gastric GIST.

Survival

During a median follow-up of 120 months 164 RFS events occurred, and 76 patients died. Patients with a *KIT* exon 11 deletion mutation or an insertion/deletion (indel) mutation ($n = 149$, 44% of 341 patients) benefitted from 3-year adjuvant treatment. In this subset, the 10-year RFS rate was 47% in the 3-year group and 29% in the 1-year group (HR, 0.48; 95% CI, 0.31–0.74; $P < 0.001$; **Fig. 2**), and the 10-year OS rate 86% and 64%, respectively (HR, 0.34; 95% CI, 0.15–0.72; $P = 0.007$; **Fig. 3**). Seven (5%) of the 149 patients with *KIT* exon 11 deletion or indel mutation had GIST recurrence while the patient was on adjuvant imatinib.

When patients with a *KIT* exon 11 deletion mutation and those with a *KIT* exon 11 indel mutation were analyzed separately, the

Table 1. Characteristics of the 341 patients and tumors stratified by GIST mutational status.

KIT or *PDGFRA* mutation	*N*	Median age, years (range)	Gender M/F *n/n*	Gastric origin[a] *n* (%)	Median size, cm (range)[a]	Median mitotic count per 50 HPFs (range)[a,b]	Tumor rupture *n* (%)
All patients	341	61 (22–84)	175/166	183 (54)	10 (2–35)	6 (0–135)	71 (21)
KIT, any	274	61 (22–83)	137/137	135 (49)	10 (2–30)	7 (0–135)	59 (22)
Exon 11 deletion	102	59 (22–80)	50/52	52 (51)	10 (3–30)	9 (0–129)	23 (23)
Exon 11 indel	47	61 (36–79)	26/21	20 (43)	9 (2–22)	7 (0–135)	8 (17)
Exon 11 substitution	68	62 (26–83)	35/33	41 (60)	10 (3–26)	6 (0–66)	10 (15)
Exon 11 duplication or insertion	22	61 (32–81)	8/14	14 (64)	9 (2–21)	6 (0–35)	4 (18)
Exon 9	26	55 (36–76)	13/13	1 (4)	10 (2–16)	7 (0–39)	13 (50)
Other[c]	9	64 (47–73)	5/4	7 (78)	11 (3–13)	3 (1–122)	1 (11)
PDGFRA, any	43	61 (44–78)	28/15	39 (91)	13 (5–35)	1 (0–29)	7 (16)
D842V	30	59 (44–78)	18/12	29 (97)	12 (5–35)	1 (0–25)	4 (13)
Neither detected	24	63 (23–84)	10/14	9 (38)	7 (2–26)	8 (1–90)	5 (21)

Abbreviation: *PDGFRA*, platelet-derived growth factor receptor alpha gene.
[a]The tumor site in the gastrointestinal tract was not available for two tumors, size (diameter) for two tumors, and the mitotic count for nine tumors.
[b]Centrally assessed mitotic count by one of two pathologists from 50 HPFs. The total area of the 50 HPFs was either 11.24 mm^2 or 12.50 mm^2.
[c]*KIT* exon 13 mutation, $n = 4$; *KIT* exon 11 duplication or insertion mutation and a substitution mutation, $n = 2$; *KIT* exon 11 deletion mutation and an insertion mutation, $n = 1$; *KIT* exon 11 insertion mutation and an insertion-deletion mutation, $n = 1$; an unspecified *KIT* mutation, $n = 1$.

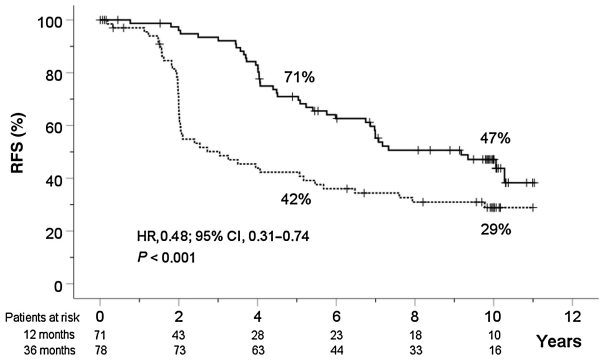

Figure 2.

Kaplan–Meier estimate of RFS of patients with *KIT* exon 11 deletion or indel mutation. Dashed line, 12 months of adjuvant imatinib; solid line, 36 months of imatinib. The 5-year and 10-year survival rates are shown. Censored patients are indicated with a bar.

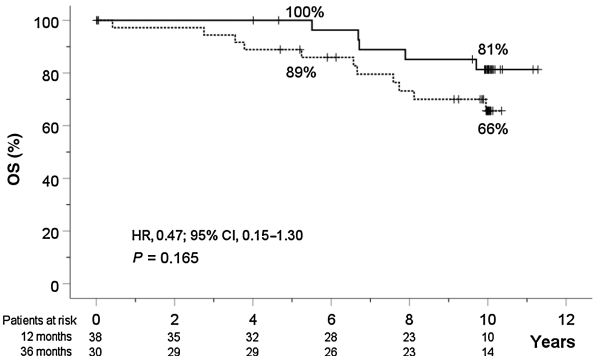

Figure 4.

Kaplan–Meier estimate of OS of patients with *KIT* exon 11 substitution mutation. Dashed line, 12 months of adjuvant imatinib; solid line, 36 months of imatinib. The 5-year and 10-year survival rates are shown. Censored patients are indicated with a bar.

102 patients with a deletion mutation benefitted substantially from 3-year adjuvant treatment (the 10-year RFS rate was 47% and 17% in the 3-year and 1-year groups, respectively, HR, 0.34; 95% CI, 0.20–0.56; $P < 0.001$; and the 10-year OS rate 83% and 59%, respectively, HR, 0.35; 95% CI, 0.14–0.81; $P = 0.017$), whereas in the smaller subset of 47 patients with an indel mutation there was no statistical difference in either RFS or OS between the two treatment groups (Supplementary Fig. S1).

In the subgroup of 68 patients with *KIT* exon 11 substitution mutation, patients treated with 3 years of adjuvant imatinib had numerically higher RFS and OS than patients with 1-year treatment, but neither survival analysis was statistically significant (for RFS, HR was 0.60; 95% CI, 0.26–1.30; $P = 0.204$; Supplementary Fig. S2; for OS, HR was 0.47; 95% CI, 0.15–1.30; $P = 0.165$; **Fig. 4**).

Most patients with *KIT* exon 9 mutation had GIST recurrence during the follow-up, and the 10-year RFS was low both in the 1-year group (17%) and the 3-year group (12%). Six (23%) of the 26 patients with *KIT* exon 9 mutation had GIST recurrence during administration of adjuvant imatinib. There was no significant difference in either RFS (HR, 0.86; 95% CI, 0.36–2.05; $P = 0.729$; Supplementary Fig. S2) or OS (HR, 1.62; 95% CI, 0.54–5.39; $P = 0.401$; **Fig. 5**) between the 3-year and the 1-groups in the subset of patients with *KIT* exon 9 mutation.

Patients with *KIT* exon 11 duplication/insertion mutation and those with *PDGFRA* exon 18 D842V mutation had high 10-year OS regardless of the duration of adjuvant imatinib treatment (Supplementary Fig. S3). Only two (9%) of the 22 patients with *KIT* exon 11 duplication/insertion mutation died during the follow-up; the 10-year OS was 88% in the 3-year group and 92% in the 1-year group. Similarly, only two (7%) of the 30 patients with *PDGFRA* exon 18 D842V mutation died during the follow-up (1-year group, 2 of 16 patients; 3-year group, none of 14 patients).

Treatment after GIST recurrence

Data about GIST treatments after recurrence were captured whenever feasible, since these treatments may influence OS. Of the 164 RFS events, 150 (91%) were GIST recurrences, and in 14 (9%) cases the patient died without a prior recurrence. Most ($n = 115$, 77%) of the 150 patients whose disease recurred received imatinib as the first-line treatment for advanced GIST [1-year group, 63 (80%) of 79; 3-year group, 52 (73%) of 71], and 10 (7%) further patients received nilotinib and 5 (3%) sunitinib as the first-line treatment. Eight (5%) patients did not receive systemic first-line treatment (one of these patients had *PDGFRA* D842V mutation), and no information about the first-line treatment was available from 12 (8%) patients (four of these had

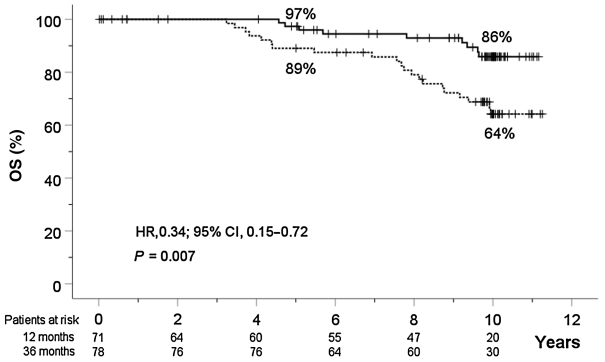

Figure 3.

Kaplan–Meier estimate of OS of patients with *KIT* exon 11 deletion or indel mutation. Dashed line, 12 months of adjuvant imatinib; solid line, 36 months of imatinib. The 5-year and 10-year survival rates are shown. Censored patients are indicated with a bar.

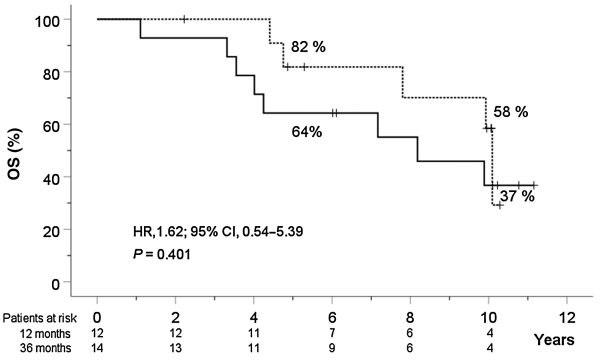

Figure 5.

Kaplan–Meier estimate of OS of patients with *KIT* exon 9 mutation. Dashed line, 12 months of adjuvant imatinib; solid line, 36 months of imatinib. The 5-year and 10-year survival rates are shown. Censored patients are indicated with a bar.

PDGFRA D842V mutation, and three did not have mutation in *KIT* or *PDGFRA*). Therefore, at least 130 (87%) of the 150 patients who had GIST recurrence either during or after adjuvant imatinib received tyrosine kinase inhibitor therapy as their first-line treatment for GIST recurrence. Information about the second-line systemic treatment administered for advanced GIST was available from 54 patients, of whom a majority ($n = 38$, 70%) received sunitinib.

Discussion

We found that patients who have a *KIT* exon 11 deletion or indel mutation (the largest mutational subgroup) survive longer when treated with 3 years of adjuvant imatinib compared with 1 year of imatinib. The survival benefit from the longer adjuvant therapy in this group of patients was substantial, because after a median of 10 years of follow-up, 86% of the patients who were allocated to 3 years of adjuvant imatinib were alive compared with 64% in the 1-year group with a HR of 0.34 for death. The longer adjuvant treatment improved OS despite most patients whose GIST recurred had imatinib restarted in both treatment groups, indicating that administration of imatinib for advanced GIST did not compensate for the efficacy that the longer adjuvant imatinib treatment had on survival.

The 10-year OS rates observed in patients with a *KIT* exon 11 deletion or indel mutation are high considering that these patients had GIST with a high risk for recurrence and 21% had ruptured GIST (13). Besides adjuvant imatinib, several other factors may contribute to the high OS rates observed. These include the trial inclusion and exclusion criteria that lead to patient selection, and the substantial efficacy of imatinib and some other tyrosine kinase inhibitors for advanced GIST (14–18). Hypothetically, imaging of the patients with CT or MRI during the follow-up may also have contributed favorably to OS, since longitudinal imaging allows early detection of GIST recurrence and rapid reinstitution of imatinib when the tumor volume is still small, the small tumor burden possibly favoring late emergence of imatinib resistance in the advanced disease setting.

In the SSGXVIII/AIO trial, the median duration of OS counting from the date of GIST recurrence to death is similar in the 1-year group and the 3-year group and exceeds 6 years in both groups (6.7 years and 6.4 years, respectively) (7). This suggests strongly that the difference in OS in favor of the 3-year group stems from the adjuvant treatment and not from the various treatments administered after GIST recurrence to advanced GIST. These OS durations achieved after GIST recurrence compare favorably to trials where patients with advanced GIST were treated with first-line imatinib and without adjuvant imatinib (19, 20).

We analyzed *KIT* exon 11 deletion mutations and exon 11 indel mutations also separately, although these two groups are often merged in survival analyses (12, 21). There may be little biological difference between *KIT* exon 11 deletion and indel mutations, but in the current analysis the HR point estimate for RFS in the subset of patients with a *KIT* exon 11 indel mutation (0.87) was outside of the HR 95% CI of the patients with a *KIT* exon 11 deletion mutation (0.20–0.56) suggesting difference between the groups. Yet, the number of patients with *KIT* 11 indel mutation was relatively small, and the HR for OS in the *KIT* exon 11 indel group (0.21) was within the 95% CI (0.14–0.81) of the HR in the *KIT* exon 11 deletion group.

The survival benefit associated with the 3-year treatment was less clear in the other mutational subgroups investigated, but the numbers of patients, RFS events, and deaths was limited in these subgroups, which makes drawing firm conclusions challenging. Patients with a *KIT* substitution mutation might benefit from 3-year adjuvant treatment, whereas patients with a *KIT* exon 9 mutation had generally poor outcome regardless of the duration of adjuvant imatinib. In a meta-analysis of two randomized trials that compared the daily imatinib dose of 800 mg to the standard 400-mg dose, patients with *KIT* exon 9 mutation benefitted from the 800-mg dose (15), but it is uncertain whether this exploratory observation made in the advanced setting can be generalized to the adjuvant setting (22). In the current analysis, patients with *KIT* exon 9 mutation did not appear to benefit from 3-year adjuvant imatinib, but there were only 26 patients in this survival analysis.

Patients with a *KIT* exon 11 insertion/duplication mutation and those with a *PDGFRA* D842V mutation had generally favorable RFS and OS regardless of the duration of adjuvant imatinib and despite only patients with a high estimated risk of recurrence were accrued to the trial. The *PDGFRA* exon 18 mutation D842V is considered to confer insensitivity to imatinib (10), but sensitivity to avapritinib (11), and treating patients with GIST with *PDGFRA* D842V mutation with any duration of adjuvant imatinib is not recommended (2).

The study has some limitations. The trial was powered for a RFS difference between the two allocation groups with a sample size of 400 patients. Therefore, subgroup analyses on RFS and OS are likely underpowered. Yet, the survival benefit observed in favor of the longer adjuvant imatinib treatment in the subgroup of patients with a *KIT* exon 11 deletion mutation seems a robust finding, likely due to the high sensitivity of KIT kinases with these mutations to imatinib and the relatively large size of this mutational subgroup. The observations made in the other mutational subgroups need to be interpreted with caution due to the relatively small numbers of patients and events in these subgroups. The data available about the systemic treatments administered for advanced disease after GIST recurrence was not complete, particularly concerning the later lines of therapy. This may not be unexpected, because the primary endpoint in the trial was RFS and many of the patients live several years with advanced disease. The strengths of the study include the setting of a randomized trial where the data captured were monitored, central tumor specimen histological review by experienced pathologists, central mutational testing, and completion of the maximal patient follow-up planned in the study protocol.

We conclude that patients with GIST who have a high risk for GIST recurrence and have *KIT* exon 11 deletion or indel mutation survive longer when treated with 3 years of adjuvant imatinib compared with patients who are treated with 1 year of imatinib despite most of the patients whose GIST recurred received imatinib for advanced GIST. The survival benefit associated with the 3-year treatment was substantial in this mutational subgroup with about two thirds of deaths avoided during the 10 years that followed random allocation. The favorable effect of the 3-year adjuvant treatment on OS could not be convincingly demonstrated in other mutational subgroups, which may be due to a limited statistical power in these subgroups, lack of adjuvant imatinib efficacy, too short adjuvant imatinib treatments, or in case of *KIT* exon 9 mutations, too small imatinib dose. Two randomized trials (NCT02260505 and NCT02413736) are currently comparing longer than 3 years of adjuvant imatinib treatment to 3 years of imatinib.

Authors' Disclosures

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Authors' Contributions

H. Joensuu: Conceptualization, resources, data curation, formal analysis, supervision, funding acquisition, validation, investigation, methodology, writing–original draft, project administration, writing–review and editing. **E. Wardelmann:** Conceptualization, formal analysis, supervision, investigation, methodology, project administration, writing–review and editing. **M. Eriksson:** Conceptualization, resources, supervision, funding acquisition, investigation, project administration, writing–review and editing. **A. Reichardt:** Resources, supervision, funding acquisition, investigation, project administration, writing–review and editing. **K.S. Hall:** Conceptualization, investigation, project administration, writing–review and editing. **J. Schütte:** Investigation, writing–review and editing. **S. Cameron:** Investigation, writing–review and editing. **P. Hohenberger:** Resources, investigation, writing–review and editing. **H. Sihto:** Formal analysis, investigation, methodology, writing–review and editing. **P.J. Jost:** Resources, investigation, writing–review and editing. **L.H. Lindner:** Resources, investigation, writing–review and editing. **S. Bauer:** Resources, investigation, writing–review and editing. **B. Nilsson:** Investigation, writing–review and editing. **R. Kallio:** Resources, investigation, writing–review and editing. **T. Pesonen:** Formal analysis, investigation, writing–review and editing. **P. Reichardt:** Conceptualization, resources, supervision, funding acquisition, investigation, project administration, writing–review and editing.

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Note

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