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Philippe Cassier, Elena Fumagalli, Piotr Rutkowski, Patrick Schöffski, Martine van Glabbeke, et al.. Outcome of Patients with Platelet-Derived Growth Factor Receptor Alpha–Mutated Gastrointestinal Stromal Tumors in the Tyrosine Kinase Inhibitor Era. *Clinical Cancer Research*, 2012, 18 (16), pp.4458-4464. 10.1158/1078-0432.ccr-11-3025 . hal-03623776

HAL Id: hal-03623776

<https://amu.hal.science/hal-03623776>

Submitted on 6 Jun 2023

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Outcome of Patients with Platelet-Derived Growth Factor Receptor Alpha–Mutated Gastrointestinal Stromal Tumors in the Tyrosine Kinase Inhibitor Era

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Abstract

Purpose: Platelet-derived growth factor receptor-alpha (*PDGFRA*) mutations are found in approximately 5% to 7% of advanced gastrointestinal stromal tumors (GIST). We sought to extensively assess the activity of imatinib in this subgroup.

Experimental Design: We conducted an international survey among GIST referral centers to collect clinical data on patients with advanced *PDGFRA*-mutant GISTs treated with imatinib for advanced disease.

Results: Fifty-eight patients were included, 34 were male (59%), and median age at treatment initiation was 61 (range, 19–83) years. The primary tumor was gastric in 40 cases (69%). Thirty-two patients (55%) had *PDGFRA*-D842V substitutions whereas 17 (29%) had mutations affecting other codons of exon 18, and nine patients (16%) had mutation in other exons. Fifty-seven patients were evaluable for response, two (4%) had a complete response, eight (14%) had a partial response, and 23 (40%) had stable disease. None of 31 evaluable patients with D842V substitution had a response, whereas 21 of 31 (68%) had progression as their best response. Median progression-free survival was 2.8 [95% confidence interval (CI), 2.6–3.2] months for patients with D842V substitution and 28.5 months (95% CI, 5.4–51.6) for patients with other *PDGFRA* mutations. With 46 months of follow-up, median overall survival was 14.7 months for patients with D842V substitutions and was not reached for patients with non-D842V mutations.

Conclusions: This study is the largest reported to date on patients with advanced *PDGFRA*-mutant GISTs treated with imatinib. Our data confirm that imatinib has little efficacy in the subgroup of patients with D842V substitution in exon 18, whereas other mutations appear to be sensitive to imatinib. *Clin Cancer Res*; 18(16); 4458–64. ©2012 AACR.

Introduction

Gastrointestinal stromal tumors (GIST) are rare neoplasms of mesenchymal origin, sharing differentiation characteristics with the interstitial cells of Cajal. Although rare, GISTs make-up approximately 20% of all sarcomas (1). These tumors may arise from anywhere along the gastrointestinal tract, but the most common locations of primary

tumors are the stomach and the jejunum. GISTs are characterized by activating *KIT* mutations in 70% to 85% of cases. The remaining 15% to 30% either harbor activating mutations of the gene encoding platelet-derived growth factor receptor-alpha (*PDGFRA*; 5%–15% of cases; ref. 2) or *BRAF* (1%–3%; ref. 3) or are considered "wild-type" when no mutations of *KIT*, *PDGFRA*, and *BRAF* are found

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (<http://clincancerres.aacrjournals.org/>).

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doi: 10.1158/1078-0432.CCR-11-3025

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Translational Relevance

Gastrointestinal stromal tumors are driven by mutually exclusive activating mutations of *KIT* or platelet-derived growth factor receptor- α (*PDGFRA*), which makes them sensitive to inhibition of these tyrosine kinases by small-molecule tyrosine kinase inhibitors such as imatinib and sunitinib. Previous studies have shown that the type of *KIT* mutations may impact patient management. In this study, we confirm that as described in previous studies, when PDGFR α is the mutated kinase in gastrointestinal stromal tumors, the location of the mutation in the *PDGFRA* gene also impacts sensitivity to currently available tyrosine kinase inhibitors, whereas some mutations, such as *PDGFRA*-D842V, seem to be clearly imatinib- and sunitinib-resistant.

(4–6). *KIT*, *PDGFRA*, and *BRAF* mutations have been shown to be mutually exclusive (7).

In patients with advanced disease, *PDGFRA* mutations seem to be less frequent (1%–3%; refs. 8, 9), probably as a result of the better prognosis associated with this mutation in patients with localized disease (10). In the advanced setting, the type of *KIT* mutation (exon 9 vs. exon 11) has been shown to influence the probability of response and the duration of progression-free survival (PFS; refs. 7, 11, 12). Furthermore, evidence suggests that starting with a higher dose of imatinib (800 mg daily) upfront may benefit patients with exon 9-mutant GISTs. Sensitivity of *PDGFRA*-mutant GISTs to the tyrosine kinase inhibitor imatinib has been assessed *in vitro* (5) and *in vivo* in clinical trials (7, 8, 11, 13), but studies have shown conflicting results, and only the D842V mutant has been consistently shown to be imatinib-resistant. Activity of imatinib in patients with *PDGFRA*-mutant GISTs has previously been reported but data are scarce because of the rarity of this subgroup of patients. Our goal in this study was to better assess the *in vivo* activity of tyrosine kinase inhibitors on a larger cohort of patients with *PDGFRA*-mutant GISTs treated with imatinib for advanced disease.

Patients and Methods

We conducted a retrospective survey among referral centers and collaborative groups with experience in conducting clinical studies in sarcoma and/or GISTs in Europe. These institutions/investigators were members of the European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG), the French Sarcoma Group (GSF-GETO), the Italian Sarcoma Group (ISG), or the Spanish Sarcoma Group (GEIS). This study was approved by the ethics committee in Lyon, France (Comité de Protection des Personne Lyon Sud-Est IV). In each institution's database, data were collected for all patients with *PDGFRA*-mutant GISTs treated with imatinib for advanced disease. Patients who had received prior imatinib in the adjuvant setting were excluded because the

primary objective of this study was to assess primary sensitivity of *PDGFRA*-mutant GISTs to imatinib, and it was felt that prior imatinib given in the adjuvant setting may promote secondary resistance. Most of the samples (32 of 58) were analyzed using a similar technique: genomic DNA from the tumor tissues was extracted from paraffin-embedded 10- μ m sections using microdissection technique to reduce contamination with nonneoplastic tissue or from slides showing more than 80% tumor cells. Exons 9, 11, 13, and 17 of *KIT* and exons 12, 14, and 18 of *PDGFRA* were amplified by PCR, and amplicons were analyzed for mutations by a combination of D-HPLC prescreening (Transgenomic WAVE DHPLC system; Transgenomic, Ltd.) and bidirectional sequencing, as previously described (11, 14, 15). In one center, screening was done using capillary electrophoresis followed by sequencing of PCR amplified exons. Data were extracted from individual patients' files and analyzed. Because only expert centers were involved, there was no central review of either radiology or pathology of retrieved cases. All centers conducted routine follow-up imaging studies [computed tomographic (CT) scan or MRI] at 3-month intervals. In EORTC study 62005, CT scan was done after 2, 4, and 6 months of treatment and every 3 months thereafter (16). In EORTC study 62001, imaging studies were done every 8 weeks (17). Patients and tumor characteristics were described using the median and range for continuous variables and percentages with 95% confidence interval (CI) for categorical variables. Response was assessed per-investigator (or trial data) using Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 (18) and described as a response rate (RR) defined as the percentage of patients with partial or complete response (CR). Overall survival (OS) was defined as the time from the date imatinib was started to the date of death. PFS was calculated as the time from the date imatinib was started to the date of disease progression or death whichever occurred first. Survival times were plotted using the Kaplan–Meier method. We compared different groups of *PDGFRA* mutants: *PDGFRA* exon 12 mutants, *PDGFRA* non-D842V-exon 18 mutants, and *PDGFRA*-D842V mutants. RRs between subgroups were compared with the χ^2 and the Fisher exact test where appropriate, and survivals were compared using the log-rank test. All statistical analyses were conducted using the SPSS 12.0 package.

Results

Patients

Institutional databases from 12 institutions and comprising a total of 3,510 patients with genotyped GISTs were searched for patients with *PDGFRA*-mutant GISTs. *PDGFRA* mutations were found in 382 patients (11%), of which 44 (1.2%) had advanced disease. Two patients were excluded from further analysis: one patient because he had received adjuvant imatinib before relapse and one patient because he was never treated due to rapid clinical deterioration. Data of 16 additional patients (28% of the patients in this study) were retrieved from EORTC database (studies EORTC

62001 and 62005) in which genotype information was available for 465 patients with advanced GISTs. Overall, 58 patients from 12 European centers and from 2 EORTC studies were identified for this study. Their main characteristics are described in Table 1. The date of starting imatinib ranged from January 2001 to November 2010 (10 years). The median age at initiation of imatinib for advanced disease was 61 years (range, 19–83). Fifty-six patients (97%) had metastatic disease. Two patients had locally advanced or recurrent disease. Eighteen patients (31%) initially presented with metastatic disease, whereas 40 suffered from metastatic and/or local recurrence at a median of 20.2 months (range, 1.2–111.8) after initial surgery. Most of these patients had high-risk disease at presentation based on the NIH consensus classification and the National Comprehensive Cancer Network-Armed Forces Institute of Pathology risk classification (Table 1). Information on primary tumor size and mitosis count [per 50 high-power field (HPF)] was available for 37 and 50 patients respectively; median tumor size was 145 mm (range, 25–500) and median mitosis count was 10 (range, 0–126). The primary tumor location was unknown for 4 patients, and the stomach was the primary tumor location for the majority of the remaining patients (69%; Table 1). Interestingly, while *PDGFRA* mutations were described more often in patients with KIT-negative GISTs by immunohistochemistry, most of the patients in our series (49 of 58, 85%) were KIT-positive; however, several cases were noted to be "faintly positive" or "positive staining on few cells" ($n = 6$). Median time from diagnosis to initiation of imatinib was 12 months (range, 0–202) for the whole cohort and 23 months (range, 3–202) for patients with initially localized disease who later developed a recurrence ($n = 40$). Forty-four patients (76%) were treated with imatinib 400 mg daily and 14 (24%) with imatinib 800 mg daily. Of the 14 patients treated with 800 mg upfront, 11 were assigned this dose level in a clinical trial (EORTC studies). Fifteen different types of *PDGFRA* mutations were found and grouped into 3 different groups for analysis (1 patient with a GIST harboring a *PDGFRA* exon 4 mutation was described separately; Supplementary Table S1); the most common single type of mutation was the D842V substitution (Table 1).

Efficacy of first-line imatinib in patients with advanced *PDGFRA*-mutant GIST

Fifty-seven patients (98%) were evaluable for response, and 1 patient died of hemorrhage before the first assessment. There were 2 CRs (4%) and 8 partial responses (PR; 14%) for an overall RR of 18% (Table 2). The median PFS in the whole group was 6.4 months (95% CI, 3.1–9.7). There was no significant difference in the distribution of responses (CR + PR) or stable disease (SD) between patients treated with imatinib 400 or 800 mg daily ($P = 1.0$, Fisher exact test, data not shown).

Efficacy of first-line imatinib by mutation group

Patients with D842V substitution ($N = 32$, 55.2%) had the poorest outcome, with a median PFS of 2.8 months

Table 1. Main characteristic of the 58 patients included in this study

| Characteristic | N (%) |
|-----------------------------------|-----------------|
| Total | 58 (100) |
| Gender | |
| Male | 34 (59) |
| Female | 24 (41) |
| Primary tumor location | |
| Stomach | 40 (69) |
| Small bowel | 7 (12) |
| Peritoneum/mesentery | 3 (5) |
| Rectum/anus | 1 (2) |
| Other ^a | 3 (6) |
| Unknown | 4 (7) |
| NIH risk group ^b | |
| NA | 17 (—) |
| Very low | 0 (0) |
| Low | 2 (5) |
| Intermediate | 2 (5) |
| High | 37 (90) |
| Miettinen risk group ^b | |
| NA | 24 (—) |
| Very low | 1 (3) |
| Low | 1 (3) |
| Intermediate | 11 (32) |
| High | 21 (62) |
| KIT/CD117 expression | |
| Positive | 49 (84) |
| Negative | 9 (16) |
| Type of mutation | |
| Exon 18 D842V substitution | 32 (55) |
| Other exon 18 mutation | 17 (29) |
| Exon 12 mutation | 8 (14) |
| Exon 4 mutation | 1 (2) |
| Metastatic sites | |
| Liver | 36 (62) |
| Peritoneum | 33 (57) |
| Liver and peritoneum | 15 (26) |
| Other | 15 (26) |
| WHO performance status | |
| 0 | 28 (48) |
| 1 | 19 (33) |
| 2 | 2 (3) |
| Unknown | 9 (16) |

^aOther primary tumor locations included scrotum ($n = 1$), retroperitoneal ($n = 1$), and extragastrointestinal not otherwise specified ($n = 1$).

^bRisk classification was not assessable (NA) for 17 and 24 cases for the NIH consensus and Miettinen classification, respectively, most of these cases were patients that presented with metastatic disease at the time of diagnosis.

(95% CI, 2.4–3.2). The RR in this group was 0%, and the majority of patients (21 of 31, 68%) had progressive disease (PD) as their best response (Table 2). Dose was not

Table 2. RR to imatinib per group of PDGFRA mutation and overall

| Response | D842V ^a N (%) | Non-D842V exon 18 N (%) | Exon 12 N (%) | Exon 4 N (%) | Overall ^a N (%) |
|----------|-----------------------------|----------------------------|------------------|-----------------|-------------------------------|
| CR | 0 (0) | 1 (6) | 1 (13) | 0 (—) | 2 (4) |
| PR | 0 (0) | 4 (24) | 3 (38) | 1 (—) | 8 (14) |
| SD | 10 (32) | 10 (59) | 3 (38) | 0 (—) | 23 (40) |
| PD | 21 (68) | 2 (12) | 1 (13) | 0 (—) | 24 (42) |

^aOne patient with a D842V-mutant GIST died of gastrointestinal hemorrhage before his first assessment and was therefore not evaluable for response.

statistically correlated with response in patients with *PDGFRA*-D842V-mutant GISTs (Supplementary Table S2). Eight patients with D842V mutations had PFS longer than 6 months (range, 6.4–50.8). Four of these 8 patients had metastatic disease at time of diagnosis, whereas 4 relapsed 15, 19, 27, and 31 months after surgery. Most of these patients had mitosis counts lower than the median for the entire group of patients with D842V mutation, although this was not significant (Mann-Whitney *U* test, $P = 0.110$).

Patients with non-D842V-exon 18 mutation ($N = 17$, 29.3%) and patients with exon 12 mutation ($N = 8$, 13.8%) had similar outcome in terms of RRs (ORR for both groups combined was 36%), and despite a difference in the median PFS (28.5 months for exon 18 vs. 12.6 months for exon 12), the curves were overlapping (log-rank test, $P = 0.5571$; Supplementary Fig. S1). The median PFS of all patients with non-*PDGFRA*-D842V-mutant GISTs was 28.5 months (95% CI, 5.4–51.6) and was significantly different from that of patients with D842V-mutant GIST ($P = 0.0001$; Fig. 1). The response distribution (CR, PR, SD, and PD) between patients in the exon 18 non-D842V-mutant group and the exon 12-mutant group were not statistically different ($P = 0.426$), whereas they differed significantly from that of the D842V group ($P < 0.0001$; Table 2). The

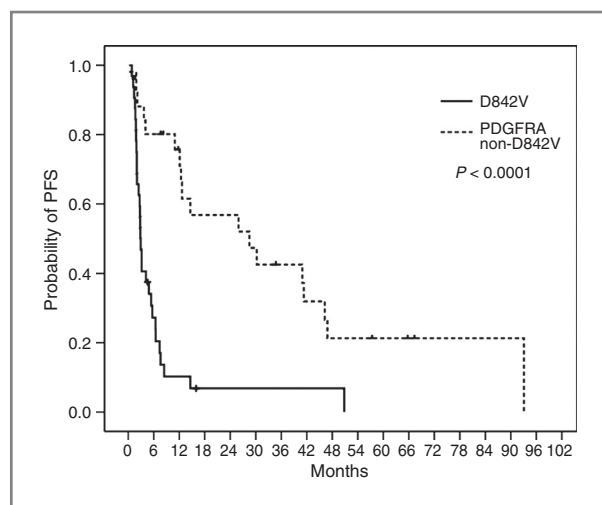


Figure 1. PFS of patients with advanced *PDGFRA*-mutant GISTs on first-line imatinib according to the type of *PDGFRA* mutations.

only patient with an exon 4 mutation had a PR lasting 57+ months.

Overall, the PFS of patients with *PDGFRA* mutations other than D842V treated with first-line imatinib appeared comparable with those previously published for patients with *KIT* exon 11 mutations, although RRs in the former seemed lower.

Efficacy of subsequent lines of treatment after failure of first-line imatinib

Forty-eight patients (81%) have progressed on first-line therapy. Of those, 32 (67%) received second-line therapy. For 14 of them, second line consisted of a dose increase of imatinib from 400 to 600 ($n = 2$) or 800 mg ($n = 12$) daily. Eleven patients received sunitinib and 7 received other treatments: PEGylated liposomal doxorubicin ($n = 1$), doxorubicin ($n = 1$), imatinib + sunitinib ($n = 1$), PTK787 ($n = 1$), motesanib ($n = 1$), and PKC412 (phase I trial, $n = 2$). Median PFS with second-line treatment was short (2.1 months) and was not significantly different between imatinib, sunitinib, and other treatments (2.4, 2.0, and 1.8 months, respectively, $P = 0.4811$; Fig. 2A). However, 5 of 32 patients (16%; imatinib, $n = 3$; sunitinib, $n = 1$, imatinib + sunitinib, $n = 1$) had disease stabilization for more than 6 months (range, 7.8–37.8 months). Likewise, no difference in outcome could be shown between the different *PDGFRA* mutation groups (2.1 months for D842V mutant and 7.8 months for other mutations, $P = 0.2489$; Fig. 2B). In both cases, the lack of statistical difference may reflect the limited number patients in each group and therefore a lack of power rather than a lack of effect.

Only 16 patients received third-line treatment. One patient received imatinib after failure of sunitinib, another 7 patients received sunitinib after failure of imatinib (400 mg followed by 800 mg, in 5 cases) and 8 received other treatments: nilotinib ($n = 2$), sorafenib ($n = 3$), imatinib + sirolimus ($n = 1$) and etoposide ($n = 1$), PKC412 + sirolimus (phase I trial, $n = 1$).

OS of patients with *PDGFRA*-mutant GIST

The median follow-up for surviving patients was 45.3 months. Median OS for the whole cohort was 23.7 months. Here again, patients with D842V substitutions had poorer outcome than other molecular groups (median 14.7

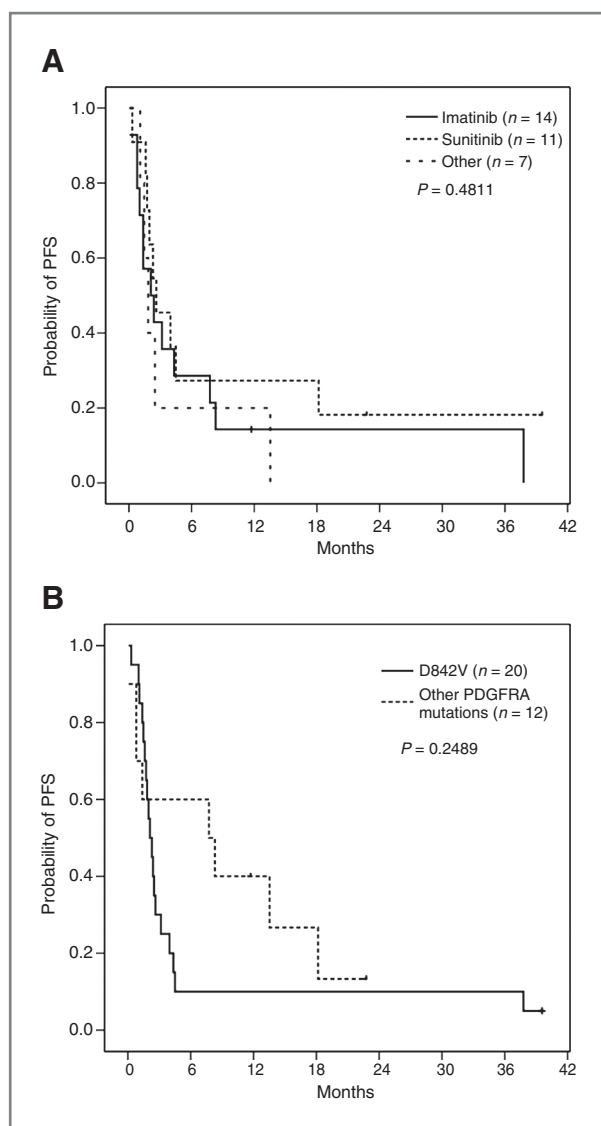


Figure 2. PFS with second-line treatment ($n = 32$) according to the type of treatment (A) and according to the type of *PDGFRA* mutation (B).

months vs. not reached for D842V mutation and non-D842V mutations, respectively; Fig. 3).

Discussion

This study is the largest to report specifically on the outcome of patients with advanced *PDGFRA*-mutant GISTs treated with imatinib. Most previously reported trials investigating the activity of tyrosine kinase inhibitors enrolled patients with *PDGFRA*-mutant GISTs, these studies provided evidence that D842V substitution of exon 18 of *PDGFRA* is resistant to imatinib (7–9, 11), but we sought to provide a more comprehensive analysis of imatinib sensitivity in *PDGFRA*-mutated GISTs. Our study therefore provides additional information, albeit biased by the retrospective nature of our study. Our data confirm that although *PDGFRA*-mutant GISTs are probably more frequent than

initially reported (~11% of GIST patients with genotyping information had *PDGFRA* mutation), metastasis in this subgroup is rare: only 60 patients identified over a 10-year period across 12 European referral centers, and only 11% (44 of 389) of patients with *PDGFRA*-mutant GISTs had metastasis in our study. This was already observed in clinical trials of imatinib in patients with advanced GISTs, where *PDGFRA*-mutant GISTs usually represented only 2% to 5% of the whole study population (7–9, 11). Most of the patients in our study had CD117/KIT-positive GISTs. However, we and others (2, 15) have shown that *PDGFRA* mutations can be found in up to 15% of patients with GIST whereas only 4% to 5% are CD117/KIT negative by immunohistochemistry. Likewise, in a gene expression study by Subramanian and colleagues, although KIT was significantly less expressed in *PDGFRA*-mutant GISTs than in KIT-mutant GISTs, only one *PDGFRA*-mutant GIST sample was negative for KIT using immunohistochemistry (19). These data suggest that in fact only a minority of *PDGFRA*-mutant GISTs are CD117/KIT negative by immunohistochemistry.

As expected from *in vitro* data (5, 20, 21), patients with D842V mutation failed to respond to first-line imatinib: most of them progressed at their first assessment (2–3 months of treatment, depending on individual institutions' standards). Some patients in this group had long lasting SD on first-line imatinib, which was already observed by others (13). In our series patients with D842V and PFS longer than 6 months tended to have lower mitotic count suggesting that this may be related to more indolent disease. Median OS in this group was close to the historical controls for patients with GISTs treated with chemotherapy (ref. 16; which is considered ineffective in this disease). Taken together, these data suggest that imatinib is ineffective in this subgroup of patients and that alternative therapies should be evaluated for D842V-mutant GISTs. This finding

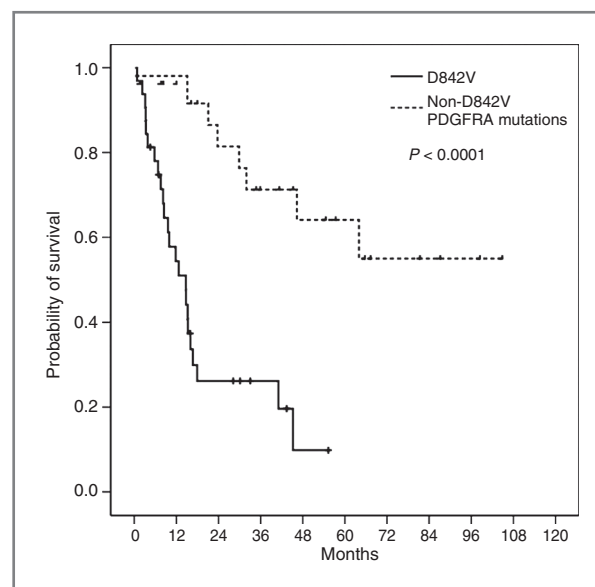


Figure 3. OS of patients according to the type of *PDGFRA* mutations.

also has implications in the adjuvant setting as *PDGFRA*-D842V-mutant GISTs made up approximately 10% of patients in the SSGXVIII/AIO randomized phase III study comparing 12 with 36 months for high-risk GISTs (22).

Imatinib was active in patients with GISTs harboring a non-D842V *PDGFRA* exon 18 mutation or a *PDGFRA* exon 12 mutation, and median PFS in this group was close to that reported for patients with GISTs with *KIT* exon 11 mutations with a median PFS over 2 years (23). These patient subgroups also had longer OS (median not reached) than in patients with *PDGFRA*-D842V mutations. Of note, response and PFS appeared comparable in patients with non-D842V *PDGFRA* exon 18 mutations or an exon 12 mutation. These findings had already been suggested by subgroup analyses done on clinical trial data (7, 8, 13, 24) as well as *in vitro* work (5). Interestingly, of 2 patients with D842del, one had very long PR whereas the other had PD as best response. These discrepancies suggest that both the location and the nature of the mutation are important for imatinib sensitivity (D842V vs. D842del) but is not the sole factor affecting response. Dewaele and colleagues previously reported the activity of tyrosine kinase inhibitor against DIM842-844 del of exon 18 *PDGFRA* and the resistance of D842V substitution, as previously observed (5, 7, 20). In a recently published article, Dileo and colleagues, using *in silico* modeling, show that the DIMH842-845del of *PDGFRA* exon 18 (3 patients in our study) and the V561D substitution in *PDGFRA* exon 12 (7 patients in our study) do not negatively affect the affinity or binding of imatinib to the kinase, unlike the D842V substitution (24).

We also report here a new mutation in *PDGFRA* exon 4. The tumor sample from this patient was analyzed twice in 2 different laboratories, which confirmed the presence of a L221F substitution. Exon 4 mutations have previously been reported in lung carcinomas (Catalogue of Somatic Mutations in Cancer) but never in GISTs. Although no protein modeling was done to investigate the conformational changes associated with this mutation, our clinical data (long lasting PR) indicate that this mutation is imatinib-sensitive *in vivo*.

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Overall our study provides evidence that imatinib has activity in patients with advanced non-D842V *PDGFRA*-mutant GISTs and suggests that other approaches should be explored for patients with advanced GISTs harboring a *PDGFRA*-D842V substitution. Heinrich and colleagues recently showed that crenolanib, a new tyrosine kinase inhibitor targeting PDGFR α , had *in vitro* activity against D842V mutants (25). A phase II trial is currently open to recruitment for patients harboring such *PDGFRA* mutations (trial NCT01243346 www.clinicaltrials.gov).

Disclosure of Potential Conflicts of Interest

P. Rutkowski is on the advisory board and speakers bureau of Novartis and has honoraria and travel grants from Novartis and Pfizer. J.-F. Emile received honoraria from Novartis and Pfizer. O. Bouché, I. Judson, J. Verweij, and P. Casali are consultant/advisory board members for Novartis. I. Judson, J. Verweij, and P. Casali have honoraria from speakers bureau of Novartis and Pfizer. P. Casali is a consultant/advisory board member for Novartis. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

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Received November 28, 2011; revised April 23, 2012; accepted April 29, 2012; published OnlineFirst June 20, 2012.

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