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

Philippe A. Cassier\textsuperscript{1}, Elena Furmagalli\textsuperscript{10}, Piotr Rutkowski\textsuperscript{11}, Patrick Schöffski\textsuperscript{12}, Martine Van Glabbeke\textsuperscript{14}, Maria Debie
ccycl-Rychter\textsuperscript{13}, Jean-François Emile\textsuperscript{2}, Florence Duffaud\textsuperscript{3}, Javier Martin-Broto\textsuperscript{15}, Bruno Landi\textsuperscript{5}, Antoine Adenis\textsuperscript{6}, Françoise Bertucci\textsuperscript{4}, Emmanuelle Bompas\textsuperscript{7}, Olivier Bouche\textsuperscript{8}, Serge Leyvraz\textsuperscript{16}, Ian Judson\textsuperscript{17}, Jaap Verweij\textsuperscript{18}, Paolo Casali\textsuperscript{10}, Jean-Yves Blay\textsuperscript{1,9}, and Peter Hohenberger\textsuperscript{19} for the European Organisation for Research and Treatment of Cancer

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* 1–7. ©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.

Authors’ Affiliations: \textsuperscript{1}Department of Medicine, Centre Léon Bédar, Lyon, France; \textsuperscript{2}EA4340, Versailles University, Versailles; \textsuperscript{3}Medical Oncology, Hôpital de la Timone; \textsuperscript{4}Medical Oncology, Institut Paoli-Calmettes, Marseille; \textsuperscript{5}Gastroenterology, Hôpital Européen Georges Pompidou, Paris; \textsuperscript{6}Medical Oncology, Centre Oscar Lambret, Lille; \textsuperscript{7}Medical Oncology, Centre René Gauducheau, Nantes; \textsuperscript{8}Gastroenterology, University Hospital, Reims; \textsuperscript{9}University of Lyon, Villeurbanne, France; \textsuperscript{10}Sarcoma Unit, Department of Cancer Medicine, Istituto Nazionale Tumori, Milan, Italy; \textsuperscript{11}The Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Department of Soft Tissue/Bone Sarcoma and Melanoma, Warsaw, Poland; \textsuperscript{12}Department of General Medicine Oncology, Leuven Cancer Institute; \textsuperscript{13}Department of Human Genetics, University Hospitals and Catholic University Leuven, Leuven; \textsuperscript{14}EORTC Data Management Center, Brussels, Belgium; \textsuperscript{15}Sarcoma and Melanoma Units, San Espases Hospital, Palma de Mallorca, Spain; \textsuperscript{16}Medical Oncology, University Hospital, Lausanne, Switzerland; \textsuperscript{17}Sarcoma Unit, Royal Marsden Hospital, London, United Kingdom; \textsuperscript{18}Erasmus University Medical Center, Daniel den Hoed Cancer Center, Rotterdam, Netherlands; \textsuperscript{19}Mannheim University Medical Center, Mannheim, Germany

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

Corresponding Author: Philippe A. Cassier, Centre Léon Bérard, 28 rue Laennec, Lyon 69008, France. Phone: 334-78792908; Fax: 334-78752716; E-mail: cassierp@hotmail.com
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Translational Relevance

Gastrointestinal stromal tumors are driven by mutually exclusive activating mutations of KIT or platelet-derived growth factor receptor-alpha (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 PDGFRAs is the mutated kinase in gastrointestinal stromal tumors, the location of the mutation in the PDGFR gene also impacts sensitivity to currently available tyrosine kinase inhibitors, whereas some mutations, such as PDGFRAD842V, 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 (GES). 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 paraaffin-embedded 10-µm 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; Transgenic, 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 χ² 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 (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>
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<th>Characteristic</th>
<th>N (%)</th>
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<tr>
<td>Gender</td>
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<tr>
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<td>34 (59)</td>
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<tr>
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<td>21 (62)</td>
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<tr>
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<td>Exon 12 mutation</td>
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<td>Exon 4 mutation</td>
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</tr>
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<td>2</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (16)</td>
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</table>

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.
different (group and the exon 12–mutant group were not statistically PD) between patients in the exon 18 non-D842V–mutant 0.0001; Fig. 1). The response distribution (CR, PR, SD, and from that of the D842V group (P non- Supplementary Fig. S1). The median PFS of all patients with that of patients with D842V-mutant GIST (95% CI, 5.4–51.6) and was significantly different from (PFS (28.5 months for exon 18 vs. 12.6 months for exon 12), had similar outcome in terms of RRs (ORR for both groups D842V–mutant GISTs was 28.5 months statistically correlated with response in patients with PDGFRA-D842V–mutant GISTs (Supplementary Table 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 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 = 1). 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

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

<table>
<thead>
<tr>
<th>Response</th>
<th>D842V&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Non-D842V exon 18</th>
<th>Exon 12</th>
<th>Exon 4</th>
<th>Overall&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>CR</td>
<td>0 (0)</td>
<td>1 (6)</td>
<td>1 (13)</td>
<td>0 (–)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>PR</td>
<td>0 (0)</td>
<td>4 (24)</td>
<td>3 (38)</td>
<td>1 (–)</td>
<td>8 (14)</td>
</tr>
<tr>
<td>SD</td>
<td>10 (32)</td>
<td>10 (59)</td>
<td>3 (38)</td>
<td>0 (–)</td>
<td>23 (40)</td>
</tr>
<tr>
<td>PD</td>
<td>21 (68)</td>
<td>2 (12)</td>
<td>1 (13)</td>
<td>0 (–)</td>
<td>24 (42)</td>
</tr>
</tbody>
</table>

<sup>a</sup>One 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).

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Figure 1. PFS of patients with advanced PDGFRA-mutant GISTs on first-line imatinib according to the type of PDGFRA mutations.
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 2. PFS with second-line treatment (n = 32) according to the type of treatment (A) and according to the type of PDGFRA mutation (B).](image)

![Figure 3. OS of patients according to the type of PDGFRA mutations.](image)
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 D842–844 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.

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 PDGFRα, 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

F. Rutkowski is on the advisory board and speaks for Novartis and has honoraria and travel grants from Novartis and Pfizer. J.-F. Emile received honoraria from Novartis and Pfizer. O. Bouché, J. Judson, J. Verweij, and P. Casali are consultant/advisory board members for Novartis. J. Judson, J. Verweij, and P. Casali have honoraria from speakers bureaus 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

Conception and design: P.A. Cassier, P. Rutkowski, J. Verweij, P. Hohenberger, P. Casali, J.-Y. Blay.
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): P.A. Cassier, P. Hohenberger, J.-Y. Blay.
Study supervision: P.A. Cassier, J.-Y. Blay.
Mutational analysis of tumor genotype: M. Debieb-Rychter.

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References


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Philippe A. Cassier, Elena Fumagalli, Piotr Rutkowski, et al.

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