TITLE

Clinical characteristics and treatment outcome in a large multicenter observational cohort of *PDGFRA* exon 18 mutated gastrointestinal stromal tumor (GIST) patients

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ABSTRACT *(233 words)*

Purpose: *PDGFRA* D842V mutated GISTs are known for their insensitivity to imatinib. However, in clinical practice responses have been observed in some patients. We describe the natural history and treatment outcomes in a cohort of *PDGFRA exon 18* mutated GIST patients.

Patients and methods: A retrospective cohort study was conducted in *PDGFRA exon 18* mutation GIST patients treated in 6 expert centers in the Netherlands and the United States. Two independent radiologists assessed radiological response to imatinib according to Choi's criteria in all patients with measurable disease treated with imatinib in neo-adjuvant or palliative intent.

Results: Seventy-one patients with *PDGFRA exon 18* mutation were identified of whom 48 patients (69%) had a D842V mutation. Twenty-two (45.8%) D842V-mutated GIST patients received imatinib treatment, 16 had measurable disease. Fourteen out of the 23(60.9%) patients with non-D842V mutations received imatinib treatment, 8 had measurable disease. Two out of 16 (12.5%) D842V-mutated GIST patients had partial response, 3 patients (18.8%) had stable disease and 9 patients (56.3%) had progressive disease as best response. Two patients did not have follow-up CT scans to assess response. Six out of 8 (75%) patients with non-D842V exon 18 mutations had partial response and 2 (25%) had stable disease as best response.

Conclusion: Patients with D842V-mutated GISTs can occasionally respond to imatinib. In the absence of better therapeutic options, imatinib should therefore not be universally withheld in patients with this mutation.

Keywords: Gastrointestinal stromal tumor; GIST; PDGFRA exon 18; D842V; Imatinib

INTRODUCTION

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract. Important to their tumorogenesis is an activating mutation involving a gene, which encodes for a tyrosine kinase receptor (TKR). Most commonly, this TKR is *KIT* (~75%) and in 10% of patients, platelet-derived growth factor receptor alpha (*PDGFRA*). Approximately 15% of all GISTs are wild type for *PDGFRA* and *KIT*.[1]

Systemic treatment with imatinib, an oral tyrosine kinase inhibitor (TKI), has been proven effective for a majority of patients with advanced GIST, showing response in up to 85% of advanced GIST patients.[2] In addition, patients with an operable GIST with a high risk of recurrence can improve their progression free survival (PFS) with adjuvant imatinib. For these patients, adjuvant treatment with imatinib for 36 months increased PFS from 36% to 65.6%.[3], [4] However, the affinity of TKIs depends on the type of mutation. The most common *PDGFRA* mutation, a D842V substitution in exon 18, shows primary resistance to imatinib in *in vitro* and *in vivo* studies.[5]–[7] Although D842V-mutated GISTs comprise a large majority of *PDGFRA* exon 18 GISTs, other mutations in exon 18 differ in their sensitivity to imatinib. It is therefore important to distinguish between resistant and sensitive mutations. However, few non-D842V GISTs have been described. [5], [6], [8]

According to the international guidelines, adjuvant treatment is not recommended for patients with D842V-mutated GIST.[9] However, there are no specific recommendations on treatment of these GIST patients with advanced disease.[9], [10] Despite expected resistance to imatinib, some advanced D842V-mutated GIST patients end up receiving imatinib either because of an unknown mutation status at the time of treatment or due to the absence of better therapeutic options. In our daily practice we noted some D842V-mutated GIST patients who appeared to respond to imatinib treatment. Based on these anecdotal findings we conducted an observational study including data from six expert centers in the Netherlands and the United

States. We describe treatment and responses in all GISTs harboring a mutation in *PDGFRA* exon 18.

METHODS

Patient population

Three cohorts of patients were defined: 1) patients included in the Dutch GIST Registry (DGR); 2) patients with a *PDGFRA* exon 18 mutation identified from the pathology database of the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital (NKI-AvL) in Amsterdam, Netherlands; and 3) patients with a *PDGFRA* exon 18 mutation identified from the pathology database of the MD Anderson Cancer Center (MDACC), Houston, USA.

The DGR includes all GIST patients diagnosed with GIST between January 2009 and March 2015 in the 5 GIST centers in the Netherlands: the NKI-AvL, Leiden University Medical Centre, Erasmus University Medical Centre, Radboud University Nijmegen Medical Centre and the University Medical Center Groningen.

Within the pathology database of the NKI-AvL all GIST patients diagnosed before January 2009 with *PDGFRA* exon 18 mutations were identified. Patients identified from the pathology databases were included in the analyses when a medical record was available. Data acquisition was approved by the local independent ethics committees, and the study was conducted in accordance with the Declaration of Helsinki.

Clinical data selection

The DGR contains demographic and clinical variables, including age, gender, relevant family history, and primary tumor location, size, and stage. Furthermore, pathology reports describing histology, immunohistochemistry, and mutational status are entered in the database. Local and systemic therapies and all hospital visits were registered, including

computed tomography (CT) scans and magnetic resonance imaging (MRI). For patients who were not entered in the DGR, clinical data points were collected using medical records.

Molecular diagnosis

For MDACC patients, PCR based DNA sequencing for *KIT* and *PDGFRA* was performed at the Molecular Diagnostics Laboratory at the University of Texas MDACC. Formalin fixed paraffin embedded blocks with tumor were selected and 4 um-thick sections prepared. Genomic DNA samples were isolated from micro-dissected paraffin-embedded slides using a QIAamp DNA minikit (Qiagen, Germantown, MD, USA). For PCR, primer sets for exons 9. 11, 13, and 17 of the *KIT* gene and for exon 18 of the *PDGFR* gene were used. PCR was carried out in a total volume of 25 μl containing 50–100 ng of genomic DNA and 0.25 uL of DNA polymerase (Bioline, London, UK). Mutations were identified by sequencing the PCR products on a 3730×1 DNA analyzer (Applied Biosystems, Carlsbad, CA, USA).

For most Dutch sites, routine mutation analysis included analysis of *KIT* (exons 9, 11, 13 and 17) and *PDGFRA* (exons 12, 14 and 18) by Sanger Sequencing. 5-10um FFPE sections of tumor material were used for DNA isolation using standard procedures (KAPA Express Extract Kit, Kapa Biosystems, Massachusetts, USA). An area for micro-dissection of tumor cells was indicated by a pathologist. Sequencing was performed on a capillary sequencer (ABI 3730 DNA Analyzer, Life Technologies, USA), mutation analysis was performed using specific software (MutationSurveyer, Softgenetics, USA).

For validation purposes, repeated molecular analyses were performed in samples from multiple sites of the resected tumors for all patients with a D842V-mutated GIST with partial response (PR).

Radiological response evaluation

In all patients with measurable disease treated in neo-adjuvant or palliative setting radiological tumor measurements were re-evaluated by two independent radiologists using Choi's criteria: partial response (PR) was defined as at least 10% decrease in maximal diameter as measured according to Response Evaluation Criteria in Solid Tumors (RECIST) or 15% decrease or more in hounsfield units (HU); progressive disease (PD) was determined in case of an increase in tumor diameter of 10% and if the tumor does not meet the PR criteria by tumor attenuation on CT; if the tumor did not meet either of the criteria for PR or PD, response was defined as stable disease (SD).[11] If the outcomes of both radiologists did not correspond, an outcome was determined based on consensus.

Pathological response evaluation

Histologic response evaluation was conducted in patients who received imatinib prior to surgery. Response was graded based on the microscopic amount of necrosis and fibrosis according to the following scheme, that is based on consensus between pathologists in the MD Anderson and the NKI-AvL: 1) minimal (<10%); 2) moderate (10-50%); and 3) good (>50%). Grading was done at the MDACC and in the AvL-NKI population separately.

Statistical analysis

Median time to progression (TTP) was calculated for all patients with measurable disease treated with neo-adjuvant or palliative intent. It was calculated from the date of initiation of imatinib treatment to the date of radiological or clinical progression prompting the physician to change treatment strategy. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 22.0.

RESULTS

Patient numbers

In the DGR, 678 GIST patients were identified of whom 42 patients with GIST harboring a mutation in *PDGFRA* exon 18. The pathology databases of the NKI-AvL and the MDACC revealed 29 additional *PDGFRA* exon 18 mutated GIST patients; 10 at the NKI-AvL and 19 at the MDACC. In total 71 non-overlapping GIST patients were identified with a *PDGFRA* exon 18 mutation of whom 48 (69%) patients with a D842V-mutated GIST. (Figure 1)

D842V-mutated GISTs

Over 90% of patients had local or locally advanced disease at registry entry. Twenty-two patients received systemic treatment with imatinib out of which 17 patients were treated with neo-adjuvant or palliative intent. All but one had measurable disease at the start of therapy, since this lesion was below the detection criteria for CT evaluation. (Table 1) Two patients had PR. (Figure 2) Three patients had SD, and 9 patients had PD as best response. For 2 patients no follow-up CT scans were available; one patient underwent resection shortly after the start of therapy and one patient had started therapy recently and was therefore not evaluable yet. Pathological response was evaluated in 7 out of 12 neo-adjuvant treated patients. None of these cases showed a good pathologic response. (Table 2). Repeated molecular analyses in different parts of the tumor from the two patients showing PR confirmed a D842V mutation in all tumor regions.

Median follow-up time for all patients receiving imatinib with neo-adjuvant and palliative intent was 11 months (range 0-131). Out of 17 patients treated with neo-adjuvant and palliative intent, 10 patients showed PD. Median TTP was 8 months (range 0-42). Patients who progressed on imatinib showed a median TTP of 2.5 months (range 0-8). Five patients had died during follow-up, 3 due to disease progression.

Three out of 11 patients in the high-risk category received adjuvant treatment, and no patients showed recurrence in this group during median follow-up period of 23 months (range 1-84). Out of 8 high-risk patients who did not receive adjuvant treatment two had recurrence during the follow-up period.

Non-D842V mutated GISTs

Seventeen patients with a non-D842V mutated GIST had local or locally advanced disease at registry entry. Three patients received imatinib with neo-adjuvant intent and 5 with palliative intent, resulting in 8 non-D842V mutated GIST patients with measurable disease. Six patients had PR and two patients had SD as best response. Good pathologic response was seen in one patient harboring a I843_D846del mutation out of two patient who had pathologic evaluation. Table 2 describes all specific mutations in *PDGFRA* exon 18 in patients with measurable disease and their responses. (Table 2)

Median follow-up time for patients receiving imatinib with neo-adjuvant or palliative intent was 24.5 months (range 3-132). Two patients had progression; one patient progressed within 7 months and the other patient progressed within 27 months.

Three out of the four high-risk patients received adjuvant treatment. One had recurrence after one year of adjuvant imatinib therapy. Two patients, who did not receive adjuvant treatment, also had recurrence. One of them had high-risk disease, the other had an unknown risk category.

DISCUSSION

We assessed responses to imatinib in GIST patients harboring a *PDGFRA* exon 18 mutation in a large observational cohort treated in routine clinical care. Interestingly, we showed that a small fraction of D842V-mutated GISTs respond to treatment with imatinib. One remains

recurrence free after neo-adjuvant treatment for almost 3 years and the other is progression free during the 10 years of follow-up.

The response to imatinib in D842V-mutated GIST in our study contrasts the responses described in prior *in vivo* and *in vitro* studies. In these studies, D842V mutation has consistently shown to be imatinib-resistant.[5], [6] In one study by Cassier et al (2012), *in vivo* response was described in 32 D842V-mutated GIST's, showing no PR, 21 patients with PD and the rest with SD as best response.[6] These findings are similar to those found in the study conducted by Corless et al in 2005.[5] They found 35 patients in their study and 181 unique patients in total described in literature with a D842V mutation in exon 18. None of these patients showed response to imatinib. In these studies response evaluations were conducted by RECIST. It is well known that response by Choi's criteria is correlated with TTP and that size-based response criteria may lead to an underestimation of the imatinib response in GIST.[12], [13] However, the responses in the two D842V-mutated GIST patients in our study would have been classified as PR even by RECIST guidelines. Though no additional mutations were detected in our patient samples and repeated molecular analyses confirmed D842V mutation, one could speculate that heterogeneity within the tumor might have resulted in the responses noted in our patients. [14]

Similar to the earlier studies a large proportion of the D842V-mutated patients had PD as best response with a short TTP. This resistance to imatinib is thought to be the result of D842V mutation affecting the tyrosine kinase receptor activation loop. A D842V mutation in *PDGFRA* leads to reduced accessibility of the ATP pocket and thereby to relative resistance to imatinib.[1] Corless et al have found that other substitutions in codon 842, except for D842Y, also show resistance to imatinib.[5]

In line with prior studies we found that patients with a non-D842V mutated GIST respond well to imatinib. Despite the fact that the imatinib resistant D842V mutation comprises a large majority of mutations in *PDGFRA* exon 18, approximately 30% have other mutations involving exon 18 of *PDGFRA* and all have shown favorable responses to imatinib.[5], [15], [16] Also, median TTP in our non-D842V mutated GIST patients with advanced disease was similar to other imatinib sensitive GIST patients.

International guidelines regarding adjuvant and neo-adjuvant treatment do not recommend imatinib for GIST patients harboring a D842V mutation.[9] It is therefore important to perform mutation analysis to determine the driver mutation and its sensitivity to imatinib. Interestingly, imatinib with neo-adjuvant and adjuvant intent was still frequently given in our cohort of D842-mutated GIST. It is possible that the mutation results were not available at the time of initiation of therapy. Nine D842V-mutated GIST patients in our cohort were given adjuvant or neo-adjuvant treatment. Patients with *PDGFRA* exon 18 mutated GIST often have low mitotic activity and are considered to be low risk. Joensuu et al. showed that a mitotic count of over 5 per 50 high power field (hpf) predicts for high risk for recurrence.[15] It is unknown whether with D842V-mutated GIST might benefit from adjuvant treatment. Although in our cohort slightly more recurrences occurred in non-treated patients with a high risk tumor, no conclusions can be drawn considering the low patient numbers and heterogeneous follow-up time.

In case of a locally advanced tumor, the ESMO guideline recommends resection without prior imatinib therapy in less sensitive tumors like D842V-mutated GISTs. Twelve of our patients with locally advanced GIST received imatinib and a quarter did not undergo surgery

eventually. Again, it is unclear if the treating physician had the mutation data available at the time of treatment initiation.

For GIST patients harboring a D842V mutation with advanced disease no specific recommendations on treatment are described in international guidelines.[9], [10] Given the known resistance to imatinib in D842V-mutated GIST, therapeutic alternatives are being investigated but proven therapies are still lacking.[17]–[20] Therefore, it was not a surprise to us that imatinib is still given in routine clinical care and this helped us evaluate the utility of imatinib in this population.

Patients in our study were treated in 6 different expert centers, resulting in a representative sample of patients. Evaluation of best response was confirmed by two independent radiologists according to Choi's criteria. No prior study has described *in vivo* pathologic response in *PDGFRA* exon 18 patients. Agaram et al show little to no correlation between radiological and pathological response in GIST patients.[21] There is however evidence that patients with good pathological response show better PFS and overall survival (OS).[22] In our cohort only one patient with good radiological response to imatinib had good pathologic response. Further interpretation is limited due to small numbers.

Even though our sample size is small, considering the rarity of *PDGFRA* exon 18 mutated GISTs, this is the first and largest cohort to date of patients treated in routine clinical care described in the literature. Unlike what has previously been described we have found clinical and radiological responses in few patients with D842V-mutated GIST. Considering that GIST might be a multiclonal disease, one might argue that these patients could have had different clones within their tumours. Therefore, in our view imatinib treatment should not be

universally denied in D842V-mutated GISTs who are not surgically resectable. Given the lack of alternative treatments in advanced disease, it may be worthwhile to start imatinib treatment in D842V-mutated GISTs with frequent response evaluations.

Conflict of interest statement

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A research grant for the Dutch GIST Registry was received from Novartis, Bayer and Pfizer.

Disclosures:

- Dr. Neeltje Steeghs received a research grant from Novartis, Bayer and Pfizer for the Dutch GIST Registry
- Prof. Winette van der Graaf received a preclinical research grant from Novartis

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TABLES AND FIGURES

Fig.1. Flowchart describing inclusion of GIST patients with PDGFRA exon 18 mutations.

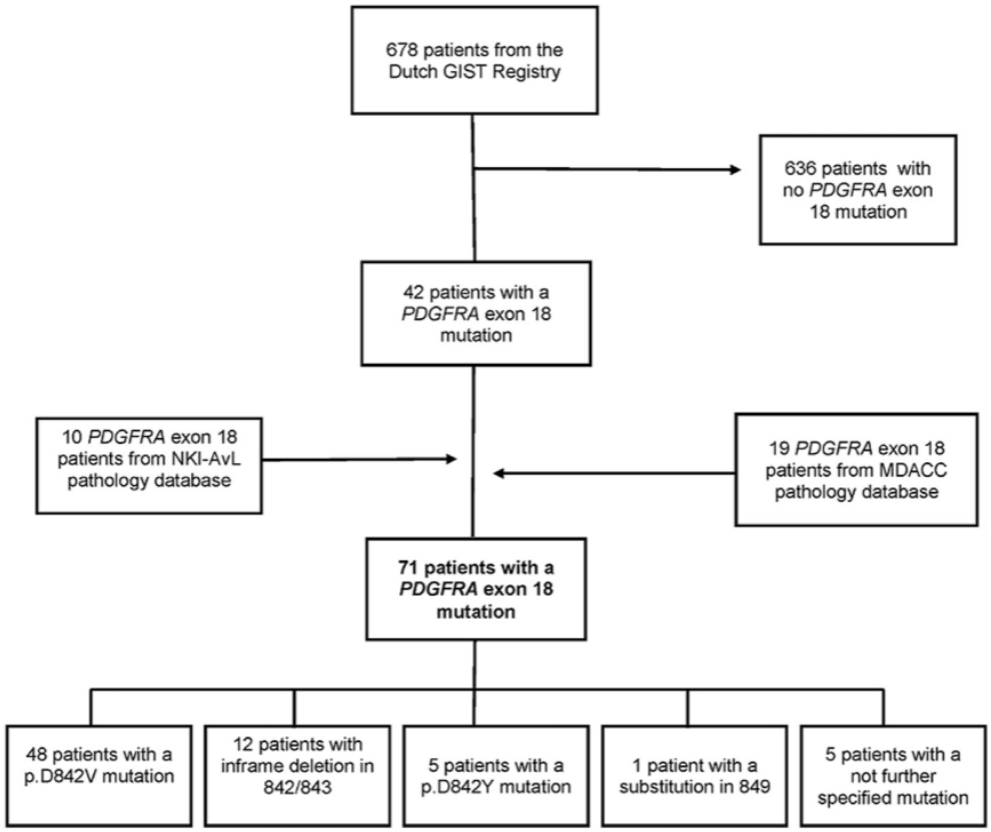

Fig 2. Radiological response in a neo-adjuvant treated D842V-mutated GIST patient (A). Radiological response in a D842V-mutated GIST patient treated with palliative intent (B).

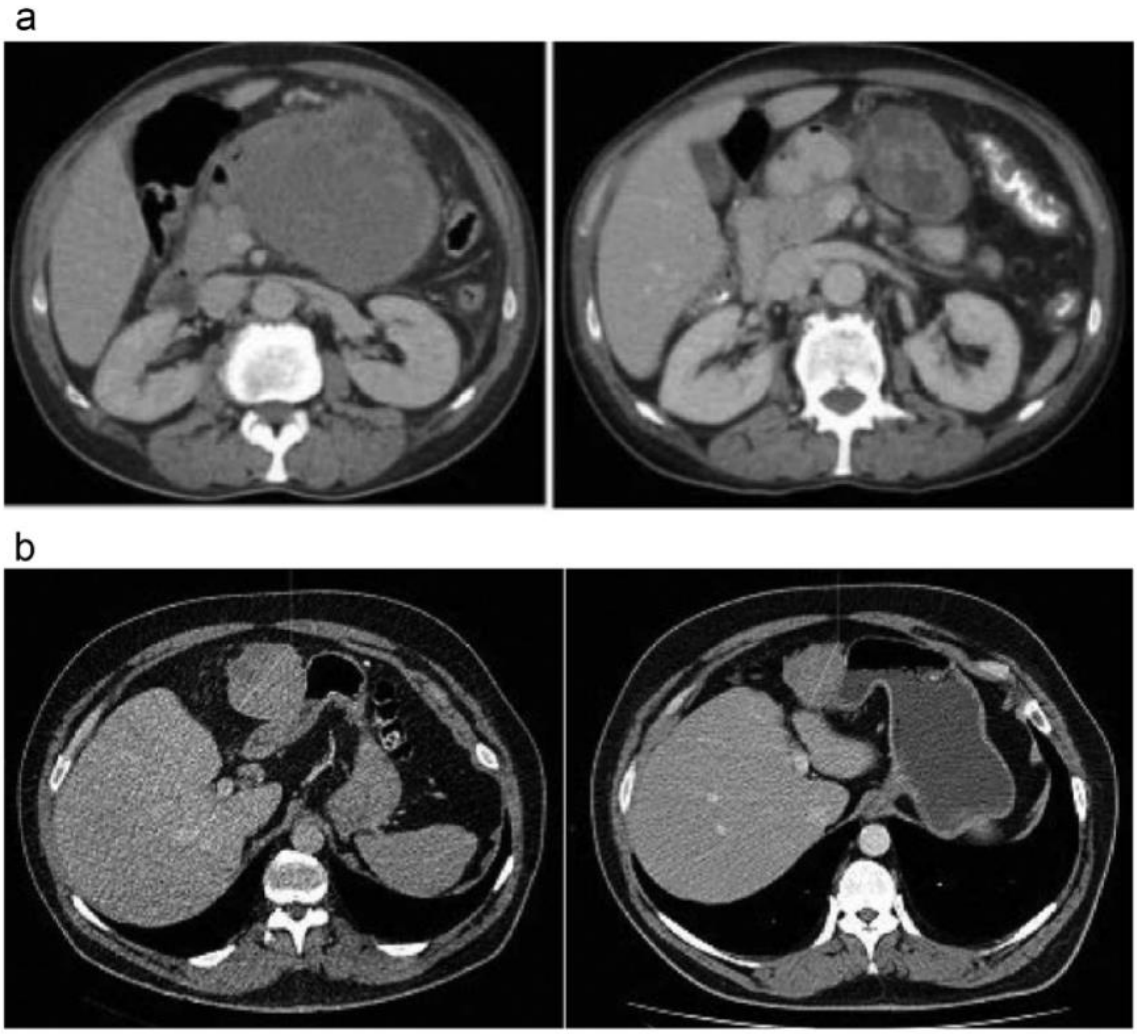

Table 1. Patient characteristics

Characteristics	Total (71)	D842V-mutated GISTs (48)	Non-D842V–mutated GISTs (23)
Gender (male)	43 (60.6%)	28 (58.3%)	15 (65.2%)
Age in years (median; range)	58 (23–87)	56 (23–80)	62 (46–87)
Tumour status at registry			
Localised disease	48 (67.6%)	33 (68.8%)	15 (65.2%)
Locally advanced	13 (18.3%)	11 (22.9%)	2 (8.7%)
Metastasised	10 (14.1%)	4 (8.3%)	6 (26.1%)
Primary tumour location			
Gastric	65 (91.5%)	44 (91.7%)	21 (91.3%)
Oesophagus	1 (1.4%)	–	1 (4.3%)
Unknown/miscellaneous	5 (7.1%)	4 (8.3%)	1 (4.3%)
Primary tumour size in mm (median; range)	85 (7–310)	90 (12–310)	62 (7–260)
Histology			
Spindle cell	32 (45.1%)	26 (54.2%)	6 (26.1%)
Epitheloid	24 (33.8%)	12 (25.0%)	12 (52.2%)
Mixed	11 (15.5%)	7 (14.6%)	4 (17.4%)
Not reported	4 (5.6%)	3 (6.3%)	1 (4.3%)
Mitotic index (per 50 hpf)			
≤5	41 (57.7%)	31 (64.6%)	10 (43.5%)
>5	16 (22.5%)	10 (20.8%)	6 (26.1%)
Unknown	14 (19.7%)	7 (14.6%)	7 (30.4%)
Risk category[a]			
Low risk	35 (53.5%)	26 (60.4%)	9 (39.1%)
High risk	15 (14.1%)	11 (12.5%)	4 (17.4%)
Insufficient information	11 (18.3%)	7 (18.8%)	4 (17.4%)
NA[b]	10 (14.1%)	4 (8.3%)	6 (26.1%)
Surgery			
Yes	64 (90.1%)	43 (89.6%)	21 (91.3%)
No	7 (9.9%)	5 (10.4%)	2 (8.7%)
Imatinib treatment			
Yes	36 (47.9%)	22 (45.8%)	14 (60.9%)
No	35 (52.1%)	26 (54.2%)	9 (39.1%)
Treatment objective			
Neo-adjuvant	15 (18.3%)	12 (20.8%)	3 (13.0%)
Palliative	10 (14.1%)	5 (12.5%)	5 (17.4%)
Adjuvant	11 (18.3%)	5 (12.5%)	6 (30.4%)
No treatment	35 (49.3%)	25 (54.2%)	9 (39.1%)

GISTs, gastrointestinal stromal tumours; hpf, high power field.

[a] Risk category according to Miettinen's criteria.

[b] Patients presented with metastatic disease, therefore no risk category is applicable.

Table 2. Radiological Choi responses and pathological responses in patients with measurable disease treated with palliative or neo-adjuvant intent.

PDGFRA exon 18 mutation type	Radiological responses				Pathological responses				Total*
	Partial response	Stable disease	Progressive disease	No data	Good response	Intermediate response	Little to no response	No data	
D842V	**2 (12.5%)**	**3 (18.8%)**	**9 (56.3%)**	**2 (12.5%)**	**0 (0.0)**	**1 (6.3%)**	**6 (37.5%)**	**9 (56.3%)**	**16**
Other exon 18 mutations	**6 (75.0%)**	**2 (25.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (12.5%)**	**0 (0.0%)**	**1 (12.5%)**	**6 (75.0%)**	**8**
p.D842_D846delinsG	0	1	0		0	0	0	1	
p.D842_H845del	1	0	0		0	0	0	1	
p.D842_N848del	1	0	0		0	0	1	0	
p.D842Y	1	0	0		0	0	0	1	
p.I843_D846del	1	0	0		1	0	0	0	
p.I843_S847delinsT	0	1	0		0	0	0	1	
p.Y849H	1	0	0		0	0	0	1	
Other mutations in exon 18 not further specified	1	0	0		0	0	0	1	

* Could only be assessed in patients treated with imatinib prior to surgery.