

# Adjuvant Imatinib Therapy of 208 Gastrointestinal Stromal Tumor (GIST) Patients: Dose, Duration, and Risk Assessment

J. C. Trent, M. von Mehren, P. W. T. Pisters, E. Stealey, L. A. Sirulnik, C. D. Blanke

University of Texas MD Anderson Cancer Center, Houston, TX, USA; Fox Chase Cancer Center, Philadelphia, PA, USA; University of Texas MD Anderson Cancer Center, Houston, TX, USA; Novartis Pharmaceuticals, East Hanover, NJ, USA; Novartis Pharma, East Hanover, NJ, USA; University of British Columbia/British Columbia Cancer Agency, Vancouver, BC

## UPDATED ABSTRACT

**Background:** In December 2008, imatinib was approved for adjuvant treatment of adult patients following complete, gross resection of gastrointestinal stromal tumor (GIST). In the imatinib registrational study, imatinib 400 mg was administered for one year.<sup>1</sup> However, patient characteristics, tumor characteristics, dose, and duration of therapy are not known outside the context of a clinical trial.

**Methods:** Data (e.g. demographics, clinical characteristics, therapy, and outcomes) from consented patients have been entered into a secure, Internet-based portal. Analyses of the database are performed every 6 months, with data from unique sites being compared to the aggregate. There are no reGISTry required interventions or procedures. This abstract represents the first presentation on the use of adjuvant imatinib therapy in GIST.

**Results:** Since November 2004, 1,053 patients have entered the reGISTry. This analysis reflects data reported as of September 17, 2009. Most patients (56%) received adjuvant imatinib therapy for over one year. Patients treated in the community setting seemed to receive a longer duration of adjuvant therapy than those at academic centers (424 days [2-1970] vs 348 days [16-1762], but this finding was not statistically significant ( $P=0.21$ ). Patients with small intestine and stomach primary tumors appeared to have a similar median duration of adjuvant therapy (366 days, each), and there was no correlation of treatment duration with tumor size or mitotic count. Most patients (87%, 181/208) received imatinib 400 mg daily as the initial dose; 17.3% of adjuvant imatinib dose changes were due to disease recurrence. Baseline mitotic count was only reported in 33.6% of pts receiving adjuvant therapy.

**Conclusions:** In reGISTry, pts remain on adjuvant therapy for approximately a year, which is consistent with the clinical trial experience. Additional effort is needed to ensure clinicians are obtaining necessary information to assess risk of recurrence which can drive treatment decisions. Duration of therapy didn't appear to closely correlate with known prognostic factors preferentially (e.g., tumor size, site or mitotic rate). Adjuvant imatinib in the treatment of most patients with GIST does not appear to be based on standard, published, recurrence risk factors. Iterative data analyses over the next 2 years will allow for comparison of management patterns as advances in the understanding of GIST evolve.

The data presented in this poster reflects information in the reGISTry database as of September 17, 2009.

## INTRODUCTION

- Gastrointestinal stromal tumors (GIST) are the most common type of gastrointestinal mesenchymal tumors.
  - Annual incidence of GIST in United States is about 4,500-6,000 patients.
- Most GIST arise from the stomach and small intestine.
- Tumor size, mitotic index, complete resection without rupture, and location of primary tumor have been demonstrated in clinical trials to be prognostic factors for recurrence.
- Treatment results of surgery alone have historically been inadequate, with up to 50% of patients developing tumor recurrence within 5 years and eventually dying from the disease.<sup>1</sup>
- Most data on treatment of GIST patients were derived from clinical studies, reflecting practice at mainly academic referral centers.
- The reGISTry, an observational, secure, Internet-based portal database, was designed to characterize evolving patterns of care for patients with GIST in both community and academic practice settings.
- The treatment of GIST is evolving, including in the community, as new therapies are introduced and additional data are collected on optimal treatment strategies.
- We report here on the findings of the reGISTry (September 17, 2009).

## OBJECTIVES

- To describe treatment and outcome patterns in patients with GIST treated with adjuvant imatinib, overall, and by patient and provider characteristics.
- To provide information regarding management of patients with GIST, as well as aggregate experiences of all physicians participating in the reGISTry.

## METHODS

- Enrolling Sites
  - More than 200 sites are expected to participate, with 105 sites active as of September 17, 2009.
  - Sites stratified by institution type: community based or academic center.
- Size / Duration
  - 1,800 patients will participate and be followed for up to seven years.
  - Enrollment initiated in November 2004 and is ongoing.
- Data Collection
  - Documentation of care -- no specified patient visits or interventions.
  - The study uses Electronic Data Capture (EDC) system. For more information concerning the study, please visit the reGISTry Website at [www.gistregistry.net](http://www.gistregistry.net).
- Statistical Analysis
  - Data analysis will be performed approximately every 6 months using descriptive statistics and summarizing changes over time.

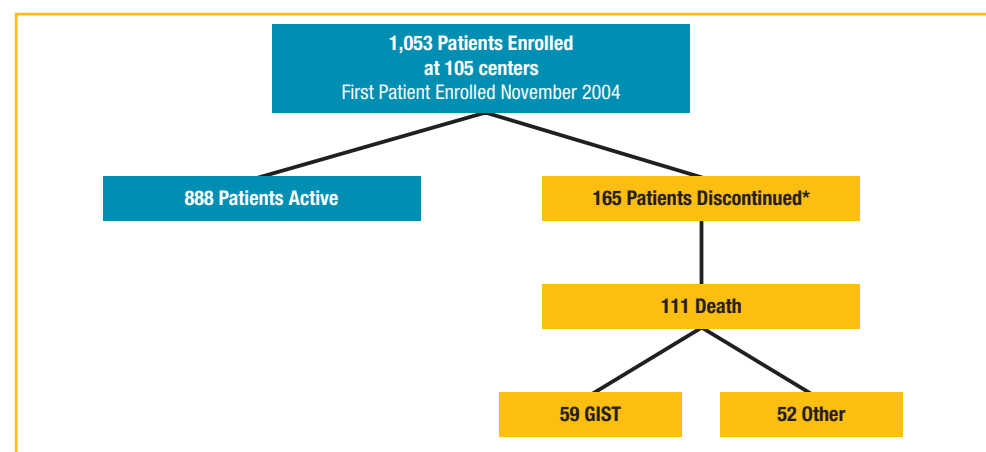
## Patient Data Being Collected

- Demographics
  - Date of birth, gender, ethnicity
- Diagnostic History
  - Date of GIST diagnosis, presenting signs, symptoms
  - Diagnostic tests performed and results
    - Imaging tests, lab tests, pathology, CD117 testing and special tests
  - Location, size, mitotic count of primary lesion
  - Location of metastatic lesions
  - Mutational analysis
- Family history
- Treatment History
  - First treatment:
    - Surgery, chemotherapy, targeted therapy, radiation, supportive care
      - Drugs, doses, duration, neoadjuvant/adjuvant treatment
    - Subsequent courses of therapy
      - Reason for change, dates of change
        - Criteria for evaluating response
    - Radiographic tests performed, results
  - Disease Management and Treatment History
    - Specialty of treating physician
    - Treatment history
    - Changes in patient status
      - Type of therapy received for progression, location of new lesions
      - Date, primary cause of death
    - Medical resource use
  - Safety
    - Serious Adverse Events related to Novartis products that led to change in GIST therapy.

## RESULTS

### Patient Characteristics

Figure 1. Patient Status



\*Other reasons for discontinuation include: patient transferred; administration problems; patient lost to follow-up.

- 84.3% of the patients ever enrolled in the reGISTry are still followed.
- The primary reason for imatinib discontinuation was death (67.3% of patient discontinuations); 28.5% of patients discontinued due to other reasons such as lost to follow up, administration problems, or being transferred to another treatment center.

Table 1. Patient Demographics

Institution Type Number of Patients	All Sites = 105 N=1,053 (100%)	Community Practices = 84 N=619 (59%)	Academic Institutions = 21 N=434 (41%)
Gender			
Male (%)	528 (50)	310 (50)	218 (50)
Female (%)	525 (50)	309 (50)	216 (50)
Median Age (years)	63 (15-92)	65 (17-92)	60 (15-92)
Race			
Caucasian	794 (75%)	473 (76%)	321 (74%)
African American	174 (17%)	95 (16%)	78 (18%)
Asian	28 (3%)	13 (2%)	15 (3%)
Hispanic	32 (3%)	19 (3%)	13 (3%)
Other/Unknown	25 (2%)	18 (3%)	7 (2%)
Referrals			
Treated where diagnosed	664 (63%)	383 (62%)	281 (65%)
Referred to tertiary care	389 (37%)	236 (38%)	153 (35%)

- More patients in the reGISTry are being treated in the community setting than in academic centers (619 vs 434).
- The majority of the patients are Caucasian regardless of where they are treated.
- No apparent difference exists in patient demographics when comparing those patients treated in the community versus academic center.

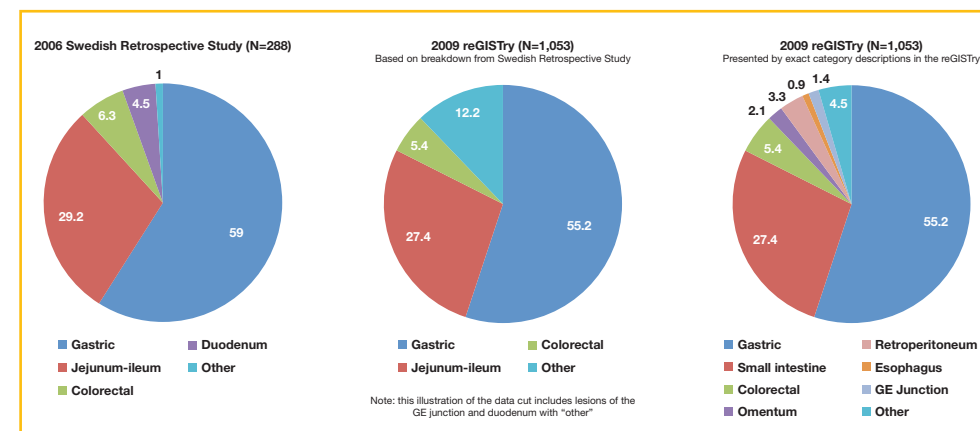
Table 2. Diagnosis – Cumulative Results Over Time

Parameter	2006 (N=228) N (%)	2007 (N=450) N (%)	2008 (N=753) N (%)	2009 (N=1,053) N (%)
GIST Stage				
Localized primary tumor	179 (78.5%)	365 (81.1%)	612 (81.3%)	868 (82.4%)
Metastatic disease	49 (18.9%)	85 (18.9%)	141 (18.7%)	185 (17.6%)
Biopsy Type				
Surgical	180 (78.9%)	330 (73.3%)	564 (74.9%)	789 (74.9%)
Endoscopic (FNA)	32 (14.0%)	93 (20.7%)	165 (21.9%)	231 (21.9%)
Interventional radiology	23 (10.1%)	47 (10.4%)	73 (9.7%)	108 (10.3%)
Imaging Methods Used				
CT Scan	137 (60.1%)	314 (69.8%)	552 (73.3%)	800 (76.0%)
Endoscopy	44 (19.3%)	88 (19.6%)	171 (22.7%)	259 (24.6%)
PET Scan	7 (3.1%)	22 (4.9%)	29 (3.9%)	40 (3.8%)
CT/PET Scan	4 (1.8%)	8 (1.8%)	15 (2%)	27 (2.6%)
Location of Metastatic Lesions	N=49	N=85	N=141	N=185
Liver	25 (51.0%)	54 (63.5%)	85 (60.3%)	118 (63.8%)
Peritoneum	9 (18.4%)	28 (32.9%)	56 (39.7%)	63 (34.1%)
Lymph Nodes	9 (18.4%)	9 (10.6%)	17 (12.1%)	17 (9.4%)
Other	15 (30.6%)	24 (28.2%)	37 (26.2%)	54 (29.2%)

FNA: fine needle aspiration; PET: positron emission tomography; CT: computed tomography.

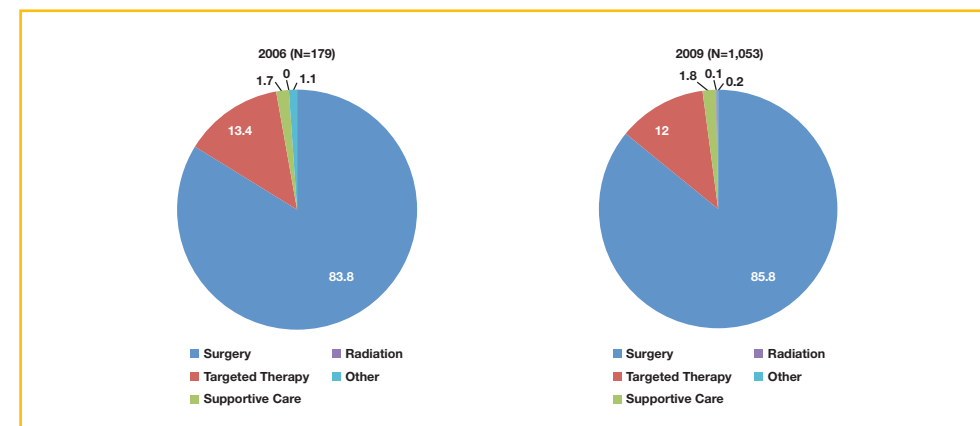
- Patients are diagnosed with localized primary tumor in the majority of the cases.
- CT scan appears to be the primary diagnostic imaging method.
- If patients are diagnosed with metastatic disease, the liver is the primary site of metastases.
- Surgical biopsy is the primary method of biopsy, compared to fine needle aspiration and interventional radiology.

Figure 2. Location of Primary Lesion



## TREATMENT OF GIST

Figure 3. First-line Treatment of Localized GIST: reGISTry Data



- Surgery remains the most common front-line intervention.
- There is little change in proportions of surgery, targeted therapy, supportive care and radiation from 2006 to 2009.

## ADJUVANT IMATINIB TREATMENT OF GIST

Table 3. Description of Adjuvant Patients Receiving Gleevec (N=208)

Location N (%)	Size N (%)	Mitotic Count N (%)	
Stomach	> 10 cm	> 10/50 HPF	37 (17.8%)
Small Intestine	6 – 10 cm	6 – 10/50 HPF	32 (15.9%)
Retropertoneum	2 – 5 cm	≤ 5/50 HPF	69 (33.1%)
Other	<2 cm	Unknown	70 (33.6%)

HPF: high powered field.

- 181/203 (87%) of patients received an initial imatinib dose of 400 mg QD.

Table 4. Adjuvant Imatinib Treatment Duration

Overall Mean Duration of Therapy = 366 days
Overall Mean Duration of Therapy = 495 days
Duration of adjuvant imatinib treatment by practice setting: Community practices mean 424 days [range 2 – 1970] Academic practices mean 348 days [16 – 1762] ( $P = 0.21$ )
Overall, 56% of patients were treated for longer than one year

Treatment Duration by Tumor Size	Median days (range)
>10 cm	361 (3 – 2246)
6-10 cm	368 (44 – 2836)
2-5 cm	360 (2 – 1509)
<2 cm	308 (16 – 666)
Unknown	582 (16 – 1970)
Treatment Duration by Tumor Location	Median days (range)
Stomach	366 (2 – 2276)
Small Intestine	366 (3 – 2836)
Treatment Duration by Mitotic Count	Median days (range)
>10/50 HPF (n=33)	351 (43 – 1509)
6-10/50 HPF (n=30)	384 (7 – 1569)
≤5/50 HPF (n=61)	361 (3 – 2276)
Unknown (n=67)	417 (2 – 2836)

HPF: high powered field.

## RESPONSE ASSESSMENT

- CT imaging by size, size/density (Not RECIST) is the most common method of evaluating response occurring in 632/743 (85%) instances.
- Even though PET utilization has increased since 2001 (reported previously), it was only used in 67/743 (9%) instances.

## TREATMENT OUTCOMES

Table 5. Time to Local or Distant Recurrence Following Surgery for Primary Disease

	2006 (N=150)	2007 (N=323)	2008 (N=548)	2009 (N=745)
Local Recurrence n (%)	4 (2.7%)	9 (2.8%)	17 (3.1%)	56 (7.5%)
Median (months)	13.9	16.6	25.3	48.1
Range (months)	12.5-73.6	3.4-118.5	0.4-118.5	12.8-151.3
Distant Recurrence n (%)	19 (12.7%)	55 (17.0%)	92 (16.8%)	75 (10.1%)
Median (months)	19.6	19.5	21.1	34.3
Range (months)	1.9-81.8	2-82.9	0.7-127.6	2.3-117.6

Table 6. Patients Receiving Adjuvant or No Adjuvant Therapy in Primary Localized Disease and Time to Progression

All Patients with Localized Primary Tumor Receiving Surgery (N=744)	Patients Receiving Adjuvant or No Adjuvant Therapy (N)		Time to Progression (Months)	
	Local Primary Tumor with Surgery and Adjuvant Therapy (N = 553)	Local Primary Tumor with Surgery and No Adjuvant Therapy (N = 191)	TTP with Adjuvant Therapy Months, median (n)	TTP Therapy with No Adjuvant Months, median (n)
Tumor Size				
>10 cm (n=196)	69 (35.2%)	127 (64.8%)	47.8 (11)	36.4 (38)
6-10 cm (n=188)	54 (28.7%)	134 (71.3%)	19.8 (5)	39.2 (24)
2-5 cm (n=225)	46 (20.4%)	179 (79.6%)	22.8 (6)	38.1 (14)
<2 cm (n=41)	6 (14.6%)	35 (85.4%)	N/A (0)	12.5 (3)
Unknown (n=94)	16 (17.0%)	78 (83.0%)	40.4 (4)	48.0 (26)
Mitotic Count				
>10/50 HPF (n=110)	35 (31.8%)	75 (68.2%)	26.9 (3)	30.8 (29)
6-10/50 HPF (n=72)	31 (43.1%)	41 (56.9%)	25.9 (5)	88.7 (7)
<5/50 HPF (n=282)	64 (22.7%)	218 (77.3%)	34.3 (4)	35.7 (19)
Unknown (n=280)	61 (21.8%)	219 (78.2%)	34.7 (14)	40.3 (50)

## CONCLUSIONS

- reGISTry provides a means to evaluate patient care trends in GIST over time in different care settings.
- Most patients in this registry presented with localized disease and were diagnosed operatively.
- Important factors for evaluating recurrence risk (tumor location, size and mitotic count) are being collected, but the reGISTry shows that decision-making for adjuvant treatment does not always incorporate these factors.
  - Some patients received adjuvant therapy without a known mitotic rate; however, this may be due overriding factors such as tumor location or size and time of assessment.
  - Additional effort is needed to ensure clinicians are obtaining necessary information to assess risk of recurrence.
- 87% of patients are treated with adjuvant imatinib which is initiated at a dose of 400 mg QD overall.
- Imatinib experience in the community and academic centers appears similar.
  - Academic centers enrolled more patients in the reGISTry than did community centers (619 vs 434).
- In reGISTry, patients remain on adjuvant therapy for approximately a year, which is consistent with the clinical trial experience.
- Duration of therapy did not appear to closely correlate with tumor size, site or mitotic rate.
- Time to progression and time to local and distant recurrence data continues to mature.
- Iterative data analyses over the next 2 years will allow for comparison of management patterns as advances in the understanding of GIST evolve.

## References

- DeMatteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumor: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2009;373:1097-1104.