



# The GOLD ReGISTry: a Global, Prospective, Observational Registry Collecting Longitudinal Data on Patients with Advanced and Localised Gastrointestinal Stromal Tumours



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**Abstract Background:** Gastrointestinal stromal tumours (GISTs) are the most common gastrointestinal sarcomas. This global, prospective registry followed patients with advanced or localised GIST (2007–2011).

**Methods:** Current and evolving diagnostics, treatments and outcome measures in patients with GIST were assessed. Eligible patients were diagnosed with advanced or localised GIST within 15 months of registry entry. No treatment plan was prescribed, and no visit schedule was mandated. Treating physicians recorded patient information, including tumour response, diagnostic methods, medications, surgeries performed, mutation status and adverse events

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leading to dose/medication changes. Survival outcomes were estimated using the Kaplan–Meier method. Other data were analysed using descriptive statistics.

**Results:** The registry included 1663 patients (advanced GIST,  $n = 1095$ ; localised GIST,  $n = 537$ ). Medications (e.g. tyrosine kinase inhibitor use and dosing), disease progression or recurrence and physician assessment of response to treatment in registry patients were consistent with controlled trials and prevailing clinical recommendations. In advanced GIST, estimated 30-month progression-free survival (PFS) (59.8%) and overall survival (OS) (82.7%) were higher than results from previously reported trials ( $\approx 40\%$  and  $\approx 70\%$ , respectively). Consistent with treatment guidelines, the most common initial treatments were imatinib for advanced GIST, and complete surgical resection for localised GIST. Computed tomography scans were the most common imaging technique used at diagnosis and follow-up. Mutation analysis was performed at diagnosis in only 15.3% and 14.5% of patients with advanced and localised GIST, respectively.

**Conclusions:** In this real-world GIST registry, patients with advanced GIST were treated with imatinib and patients with localised GIST received surgical resection, in accordance with prevailing clinical recommendations.

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## 1. Introduction

Gastrointestinal stromal tumours (GISTs) are rare, but represent the most common mesenchymal neoplasms of the alimentary canal [1,2]. They are derived from malignant transformation of the interstitial cells of Cajal, c-KIT-positive cells of neuroendocrine origin that function as the pacemaker in peristalsis [3]. The main drivers of GIST are somatic gain-of-function mutations in the tyrosine kinase KIT gene [1,4,5]. The most common sites of origin are the stomach (60%), jejunum and ileum (30%), duodenum (5%) and colorectum (<5%) [1].

Patients with GIST are categorised as having localised (resectable) or advanced (metastatic and/or locally advanced and unresectable) disease. In advanced GIST, inhibition of mutated c-KIT with imatinib, a tyrosine kinase inhibitor (TKI), has substantially improved long-term outcomes. In the preimatinib era, median progression-free survival (PFS) and overall survival (OS) were both <12 months [6]. With imatinib, median PFS and OS increased to >24 months and >55 months, respectively [7,8]. Sequential use of other TKIs (sunitinib and regorafenib) following development of resistance to imatinib has further improved long-term outcomes [7–12]. Surgical resection is the standard of care for localised, primary GISTs. Adjuvant imatinib following complete surgical resection prolongs recurrence-free survival (RFS) in patients with higher risk of recurrence [13,14]. The extent to which treatment recommendations for GIST [15–20] has been implemented in clinical practice, and their effects in the real-world setting, in a large patient cohort, has not been studied previously.

The GOLD ReGISTry is a 5-year global observational registry (April 2007 to October 2011) originally designed to collect longitudinal data on patients with

advanced GIST with the objective to assess the real-world use of current and evolving diagnostic techniques, treatment algorithms and outcomes in patients with advanced GIST. In July 2007, a protocol amendment allowed enrolment of patients with localised GIST after positive data from an interim analysis of the American College of Surgeons Oncology Group (ACOSOG) Z9001 trial were reported [21].

No patients from the United States (US) or United Kingdom (UK) were included in this registry because separate concurrent national registries were set up in these countries [22,23].

## 2. Patients and methods

### 2.1. General description and patient population

This 5-year global, multicenter, prospective, observational, non-interventional registry initially included only patients with advanced GIST (metastatic, unresectable or recurrence of previously resected disease). Patients with localised GIST could enrol after the protocol was amended in July 2007, following presentation of early data from ACOSOG Z9001 [21]. All patients were diagnosed within 15 months of registry entry. More details on entry criteria, registry design and analysis sets are available in [Supplementary Appendix A](#).

### 2.2. Objectives

Clinical effectiveness was evaluated by Kaplan–Meier estimates of OS, PFS and RFS. Tumour response was reported by the treating physician (satisfactory versus unsatisfactory). Diagnostic and treatment modalities (including any mutation analyses or surgical procedures) were described. Treatment duration, time from surgery to treatment, dose/regimen changes and reasons for

dose/regimen changes were documented. The development of other cancers and incidence of familial GIST were longitudinally assessed. Practice patterns were compared with the prevailing European Society of Medical Oncology (ESMO) recommendations [15–19].

The date at which eligible diagnosis was entered into the registry was used as the baseline for determining duration of response, duration of treatment and survival.

### 2.3. Ethics

This registry complied with the ethical principles of the Declaration of Helsinki, Good Pharmacovigilance Practice and applicable local regulations. Written and dated informed consent was obtained from each patient.

## 3. Results

### 3.1. Baseline characteristics

Median age and median time to registry entry since eligible GIST diagnosis were similar in the advanced and localised GIST groups (Table 1). The most common primary tumour sites were the small intestine and stomach, respectively. At diagnosis, CT scans were the most common imaging methods and biopsies were the most common methods for obtaining histologic samples. Of the 815 patients in the advanced group for whom risk level was assessed, 18.0% had metastatic disease. In the localised group, 484 patients had a risk assessment performed (22.1% low, 21.5% intermediate, and 44.8% high per modified Fletcher criteria).

### 3.2. Patient disposition

Of 1753 patients screened for participation in this registry, 1632 (93.1%) patients from 183 sites in 34 countries in Europe, Latin America, Asia and Canada were enrolled and met eligibility criteria. In the advanced ( $n = 1095$ ) and localised ( $n = 537$ ) GIST groups, 653 (59.6%) and 447 (83.2%) patients, respectively, completed the registry (ie, remained in follow-up until the final data cutoff); 432 (39.5%) and 81 (15.1%), respectively, discontinued participation (Supplementary Appendix B). In both groups, the most common reasons for discontinuation were death (262 and 28 patients, respectively) and loss to follow-up (132 and 43 patients, respectively).

### 3.3. Treatments at diagnosis and during the registry

In the advanced GIST group, most patients (96.3%) were treated with medication and/or surgery. Imatinib was the most common medication at diagnosis and during the registry period (Table 2). The most common

surgeries were complete resection and complete removal of metastatic lesions. Less common were partial resection, partial metastatic lesion removal and resection of local recurrent tumour.

In the advanced group, 450 patients received surgery. Prior to initial surgery, 132 (29.3%) patients received TKIs. Median time between initiating TKI medication and initial surgery was 11.40 months (range, 0.56–50.50). TKI medication was given after initial surgery in 387 (86.0%) patients. Median time between initial surgery and start of TKI medication was 1.12 months (range, 0.03–151.79).

In the localised GIST group, surgery was the most common initial treatment; the most common surgery was complete resection of the primary tumour. Imatinib was the initial medication for 204 (38.0%) patients at diagnosis (Table 2). During the registry period, of 217 patients who received medication, the most common medications were imatinib ( $n = 176$ , 81.1%) and sunitinib ( $n = 11$ , 5.1%).

In the localised group, 392 patients received surgery. For the 6 (1.5%) patients who received TKIs prior to initial surgery, median time between initiating TKI medication and initial surgery was 7.43 months (range 0.10–12.98). After initial surgery, 149 (38.0%) patients received TKIs; in this group, median time between surgery and start of TKI was 1.87 months (range 0.03–27.70).

### 3.4. Survival outcomes

Median OS was not reached in either group (Fig. 1; Supplementary Appendix C). Estimated 30-month OS rates were 82.7% (95% confidence interval (CI) 80.4–85.0) and 94.4% (95% CI 92.2–96.6) in the advanced and localised GIST groups, respectively. In the advanced GIST group, the median PFS was 40.8 months (95% CI 37.1–45.0) and the estimated 30-month PFS rate was 59.8% (95% CI 56.8–62.8). In localised GIST, RFS is usually measured starting at resection. Because only 353 of 537 patients had documented complete surgical resection, RFS was evaluated using date of surgery ( $n = 353$ ) and date of diagnosis ( $n = 537$ ) as baseline to determine whether RFS differed in patients with surgery. The median RFS was not reached regardless of which start date was used, though diagnosis typically predated surgery. Estimated 30-month RFS rates were 87.2% (95% CI 83.4–91.0) and 85.4% (95% CI 82.1–88.7), respectively.

### 3.5. Physician's opinion of response to initial treatment

CT scans were used most frequently to assess tumour response to initial treatment (67.8% and 48.8% in the advanced and localised GIST groups, respectively, Table 3). Physician's opinion of tumour response was satisfactory (SD or better) in 61.8% and 28.7% of

Table 1  
Baseline characteristics.

	Advanced GIST ( <i>n</i> = 1095)	Localised GIST ( <i>n</i> = 537)
Median age (range), y	59.0 (18–95)	57.0 (17–89)
Male, <i>n</i> (%)	638 (58.3)	262 (48.8)
Median time to registry entry since eligible GIST diagnosis (range), mo <sup>a</sup>	4.24 (0.03–15.05)	4.80 (0.03–14.95)
Location of GIST primary tumour, <i>n</i> (%)		
Oesophagus	13 (1.2)	2 (0.4)
Stomach	389 (35.5)	295 (54.9)
Small intestine	427 (39.0)	176 (32.8)
Colon	23 (2.1)	12 (2.2)
Appendix	3 (0.3)	1 (0.2)
Rectum	68 (6.2)	19 (3.5)
Peritoneum	60 (5.5)	8 (1.5)
Extra-gastrointestinal	54 (4.9)	12 (2.2)
Other	58 (5.3)	12 (2.2)
Risk assessment performed, <i>n</i> (%) <sup>b</sup>	815 (74.4)	484 (90.1)
Very low risk <sup>c</sup>	9 (1.1)	27 (5.6)
Low risk <sup>c</sup>	39 (4.8)	107 (22.1)
Intermediate risk <sup>c</sup>	95 (11.7)	104 (21.5)
High risk <sup>c</sup>	479 (58.8)	217 (44.8)
Metastatic disease <sup>c</sup>	147 (18.0)	1 (0.2)
Unable to assess due to lack of mitotic count <sup>c</sup>	46 (5.6)	28 (5.8)
Methods used to determine eligible diagnosis, <i>n</i> (%) <sup>d</sup>		
Unknown	6 (0.5)	14 (2.6)
Biopsy (total)	586 (53.5)	390 (72.6)
Surgical	315 (28.8)	339 (63.1)
Percutaneous	173 (15.8)	14 (2.6)
Endoscopic	102 (9.3)	48 (8.9)
Other	13 (1.2)	0
CT scan	799 (73.0)	312 (58.1)
Clinical evaluation	233 (21.3)	145 (27.0)
Ultrasound	212 (19.4)	87 (16.2)
Endoscopy	108 (9.9)	128 (23.8)
Laboratory values	92 (8.4)	92 (17.1)
MRI	78 (7.1)	12 (2.2)
Chest/abdominal X-ray	76 (6.9)	78 (14.5)
PET/CT fusion	67 (6.1)	8 (1.5)
FDG-PET	66 (6.0)	5 (0.9)
Endoscopic ultrasound	26 (2.4)	39 (7.3)
Laparoscopy	23 (2.1)	21 (3.9)
Other	53 (4.8)	52 (9.7)

CT, computed tomography; FDG, fluoro-deoxyglucose; GIST, gastrointestinal stromal tumour; MRI, magnetic resonance imaging; PET, positron emission tomography.

<sup>a</sup> Date of informed consent was used as registry entry.

<sup>b</sup> By size and/or mitotic count and/or metastasis for original GIST.

<sup>c</sup> The denominator for % is the number of patients for whom risk assessment was performed.

<sup>d</sup> Categories are not mutually exclusive.

patients, respectively (Table 4). In the localised group, an additional 41.3% had no progression after surgery. Unsatisfactory tumour response (i.e. lack of response) was reported in 10.0% and 1.5%, respectively.

### 3.6. Drug exposure and safety

The median overall exposure to any TKI for patients in the advanced (*n* = 994) and localised (*n* = 207) groups who received any TKI since eligible diagnosis was 31.49 months (range, 0.07–65.38) and 19.48 months (range, 0.26–53.13), respectively. Total time on TKI

treatment exceeded 36 months in 64.8% and 19.4%, respectively.

Safety data were collected as described in the registry protocol. Adverse events (AEs) were not solicited during the registry but serious AEs (SAEs) suspected to be related to a Novartis drug were recorded. Safety analyses included the cause of death and reasons for dose/regimen changes and/or not taking medications as prescribed.

For any medications received during registry, AEs leading to a dose/regimen change or a medication not taken as prescribed were reported in 124 (11.3%) and 17 (3.2%) patients in the modified advanced (*n* = 1096)

Table 2  
Treatments used at diagnosis and during the course of the registry.

	Advanced GIST (n = 1095)	Localised GIST (n = 537)
<i>Initial treatments for eligible diagnosis</i>		
Any surgeries or medication	1054 (96.3)	450 (83.8)
Any surgery	450 (41.1)	392 (73.0)
Complete resection of GIST	215 (47.8)	372 (94.9)
Partial resection of GIST	64 (14.2)	13 (3.3)
Resection of local recurrent tumour	39 (8.7)	2 (0.5)
Complete metastatic lesion removal	75 (16.7)	3 (0.8)
Partial metastatic lesion removal	54 (12.0)	0
Surgery to treat GIST-related complication	22 (4.9)	3 (0.8)
Surgery to prevent GIST-related complication	8 (1.8)	0
Other surgery	12 (2.7)	1 (0.3)
Surgery only	46 (4.2)	233 (43.4)
Any imatinib	970 (88.6)	204 (38.0)
Imatinib only	462 (42.2)	50 (9.3)
Surgery and imatinib	389 (35.5)	147 (27.4)
Any other TKI	236 (21.6)	18 (3.4)
No surgery or medication	41 (3.7)	87 (16.2)
<i>Use of medications during the course of the registry</i>		
No medication	87 (7.9)	320 (59.6)
Any medication	1008 (92.1)	217 (40.4)
<i>Of the patients who received any medication</i>		
Enrolled in Novartis clinical trial	57 (5.7)	41 (18.9)
Received imatinib in clinical trial	32 (3.2)	32 (14.7)
Enrolled in non-Novartis clinical trial	17 (1.7)	1 (0.5)
Non-clinical trial medication		
Imatinib	951 (94.3)	176 (81.1)
Sunitinib	215 (21.3)	11 (5.1)
Other non-Novartis drug <sup>a</sup>	34 (3.4)	10 (4.6)
Nilotinib	33 (3.3)	2 (0.9)
Chemotherapy	9 (0.9)	1 (0.5)
Dasatinib	2 (0.2)	1 (0.5)
Other Novartis drug	1 (0.1)	0

All data are presented as n (%).

GIST, gastrointestinal stromal tumour; TKI, tyrosine kinase inhibitor.

<sup>a</sup> The other non-Novartis drug is most likely regorafenib, but this information was not specifically collected.

and modified localised (n = 538) groups, respectively (Supplementary Appendix D). Of these, the most common AEs in the advanced group (each in ≤1.2% patients) were fatigue, peripheral oedema, rash, hand-foot syndrome and diarrhoea. In the localised GIST group, peripheral oedema (0.6%) and nausea (0.4%) were the only AEs reported in >1 patient. SAEs suspected as related to imatinib were rare, reported in 5 (0.5%) and 2 (0.4%) patients in the advanced and localised GIST groups, respectively. No individual SAE occurred in >1 patient in either group. Deaths were reported in 262 (23.9%) and 28 (5.2%) patients, respectively; 220 and 17 deaths, respectively, were due to disease progression.

### 3.7. Non-GIST malignancies and patient/family history of GIST

Before registry entry, non-GIST malignancies were reported in 6.7% and 6.0% of patients in the advanced

and localised GIST groups, respectively (Supplementary Appendix E). After registry entry, 2.3% and 1.3% of patients, respectively, were diagnosed with non-GIST malignancies. No non-GIST cancer type occurred in >1.5% of patients at diagnosis or during the registry. At diagnosis, 0.5% of patients in the advanced group and 0.9% of patients in the localised group had a history of neurofibromatosis. Few family members had GIST prior to registry entry (0.3% and 0.2%, respectively) or during registry period (0.2% and 0%, respectively).

### 3.8. Comparison of treatment patterns with clinical guidelines

Registry data were compared with ESMO recommendations in effect during registry [15–19]. Overall, most clinical practices (including first- and second-line treatment regimens, surgical procedures and disease monitoring) followed these recommendations (Table 5).



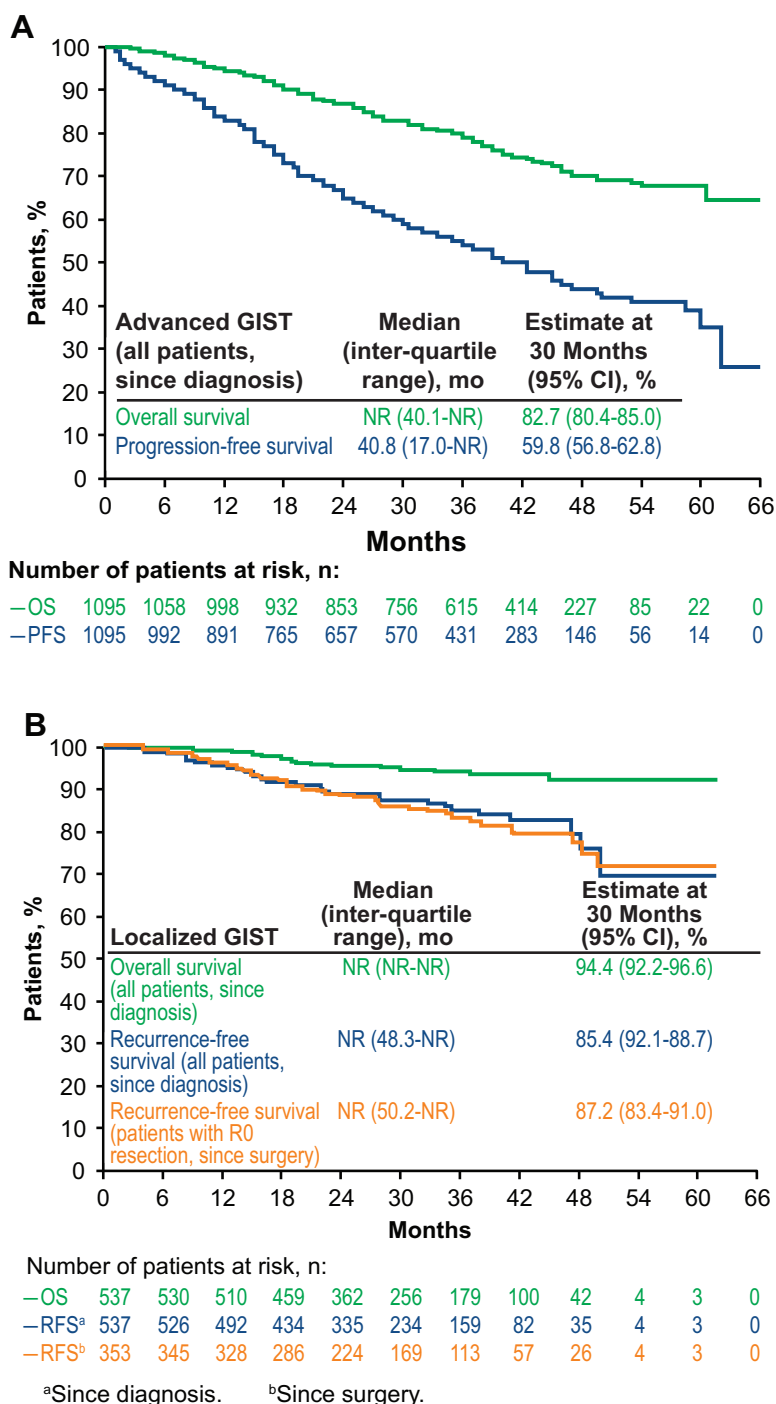


Fig. 1. Kaplan–Meier analysis of survival outcomes for the (A) advanced and (B) localised GIST groups.

Consistent with prevailing guidelines, mutation analysis was performed in <15% of patients at diagnosis in both the advanced and localised GIST groups (Table 6). *KIT* exon 11 mutation was the most common genotype occurring in ≈50% of patients in both groups. Additional comparisons of registry data with ESMO recommendations are presented in Supplementary Appendix F.

#### 4. Discussion

Patients included in clinical trials are selected and do not include all clinical presentations and situations observed in the real-world setting. For this reason, an analysis of the impact of treatment in unselected populations of patients is important to assess the benefit of a therapeutic strategy.

Table 3  
Methods to determine tumour response to initial treatment.

	Advanced GIST ( <i>n</i> = 1095)	Localised GIST ( <i>n</i> = 537)
CT scan	742 (67.8)	262 (48.8)
Clinical evaluation	268 (24.5)	199 (37.1)
Unknown/NA	210 (19.2)	146 (27.2)
Ultrasound	103 (9.4)	76 (14.2)
Laboratory values	87 (7.9)	60 (11.2)
FDG-PET	55 (5.0)	8 (1.5)
PET/CT fusion	48 (4.4)	12 (2.2)
MRI	39 (3.6)	4 (0.7)
Biopsy (total)	23 (2.1)	16 (3.0)
Surgical	18 (1.6)	15 (2.8)
Percutaneous	4 (0.4)	0
Endoscopic	1 (0.1)	1 (0.2)
Other	0	0
Chest/abdominal X-ray	18 (1.6)	26 (4.8)
Endoscopy	15 (1.4)	22 (4.1)
Endoscopic ultrasound	3 (0.3)	2 (0.4)
Laparoscopy	0	1 (0.2)
Other	11 (1.0)	20 (3.7)

All data are presented as *n* (%).

CT, computed tomography; FDG, fluoro-deoxyglucose; GIST, gastrointestinal stromal tumour; MRI, magnetic resonance imaging; NA, not available; PET, positron emission tomography.

The large patient population in the GOLD ReGISTry provides a large set of data on real-world treatment of GIST at the advent of the TKI era. In this registry, management of patients with GIST was consistent with ESMO recommendations [15–20]. The most common initial treatments were surgery for localised GIST and imatinib 400 mg/day for advanced GIST. However, no surgery was reported for ≈30% of patients with localised GIST as initial therapy, despite surgical resection being the standard of care for this population. This could have been due to the way data were collected upon enrolment (i.e. for some patients, surgeries may have been performed, but not designated as the treatment associated with the initial/eligible diagnosis of GIST). Few patients had mutation analysis performed

at diagnosis, consistent with the prevailing clinical practice prior to the release of the 2008 ESMO guidelines. Availability of mutation analysis data remains a major limitation in most places worldwide. Regardless, the proportion of patients with each mutation type was consistent with results from other registries and clinical trials [7,9,23–25]. Dosing of imatinib (the most commonly prescribed TKI in this registry and the only one indicated in the first-line or adjuvant treatment) and methods for monitoring tumour response were consistent with ESMO guidelines.

Registries from Poland, USA, Switzerland, UK, Sweden, Iceland, Spain and Taiwan have evaluated patients with GIST, both prior to the widespread use of imatinib [26–28] and more recently [22,23,29–32]. Most of these, except the Taiwanese registry [32], included fewer patients than the GOLD ReGISTry. These national registries included all patients with GIST in a given country, thus allowing calculations of the incidence of GIST for that country. In contrast, the GOLD ReGISTry was multinational, but not all patients with GIST in each country were enrolled; hence, epidemiological calculations cannot be performed. A nonprofit organisation (LifeRaft Group) also conducted a large, multinational registry (*n* = 1215) [25]. In all of these real-world studies, median age was similar, approximately 50% of patients were male, and *KIT* exon 11 mutations were the most prevalent GIST genotype (57–63%) [22,23,25–31]. These characteristics are consistent with those in the GOLD ReGISTry. Most of these registries did not report diagnostic methods or treatments prescribed. The US registry (*n* = 882) reported that 87% of patients with localised GIST and 50% of those with advanced GIST had surgeries [23]. These values are slightly higher than those reported in the GOLD ReGISTry (73.0% and 41.1%, respectively). Furthermore, our results indicate a higher proportion of patients with advanced disease were treated with TKIs as initial treatment than in the US registry (89%

Table 4  
Physician's opinion of tumour response.

Response to treatment	At initial treatment <sup>a</sup>		At least once during the registry <sup>b</sup>	
	Advanced GIST ( <i>n</i> = 1095)	Localised GIST ( <i>n</i> = 537)	Advanced GIST ( <i>n</i> = 1095)	Localised GIST ( <i>n</i> = 537)
Not applicable <sup>c</sup>	126 (11.5)	113 (21.0)	231 (21.1)	213 (39.7)
Not satisfactory (lack of response)	109 (10.0)	8 (1.5)	318 (29.0)	37 (6.9)
Stable disease or better	677 (61.8)	154 (28.7)	941 (85.9)	304 (56.6)
No progression of disease after surgery	N/A	222 (41.3)	N/A	278 (51.8)
Unable to assess	114 (10.4)	18 (3.4)	247 (22.6)	88 (16.4)
Unknown	69 (6.3)	18 (3.4)	0	0
Missing	0	4 (0.7)	0	0

All data are presented as *n* (%).

GIST, gastrointestinal stromal tumour.

<sup>a</sup> Treatment that has been entered as initial treatment for the eligible diagnosis according to the case report form; each category was counted only once per patient and values add up to 100% of patients.

<sup>b</sup> Tumour response any time during the registry. Values were not mutually exclusive, so the sum is >100%.

<sup>c</sup> Eligible diagnosis newly made and no treatments occurred prior to registry entry.

Table 5  
Comparison of registry data versus ESMO guidelines.

	Advanced GIST ( <i>n</i> = 1095)		Localised GIST ( <i>n</i> = 537)			
	<i>KIT</i> Exon 9 ( <i>n</i> = 18)	No <i>KIT</i> Exon 9 ( <i>n</i> = 1077)	Low risk ( <i>n</i> = 134)	Int. risk ( <i>n</i> = 104)	High risk ( <i>n</i> = 217)	Total ( <i>n</i> = 537)
First-line treatment (advanced)/adjuvant treatment (localised)	ESMO recommends imatinib 400 mg/d; 800 mg/d if <i>KIT</i> exon 9		ESMO recommends imatinib 400 mg/d for 3 years for patients with high risk <sup>a</sup>			
Imatinib 800 mg/d	0	26 (2.4)	0	0	0	0
Imatinib >400 to <800 mg/d	1 (5.6)	15 (1.4)	0	0	0	0
Imatinib 400 mg/d	17 (94.4)	895 (83.1)	4 (8.5)	15 (22.1)	72 (55.4)	119 (33.7)
Imatinib <400 mg/d	0	9 (0.8)	0	0	0	0
Sunitinib	0	14 (1.3)	0	0	0	0
Investigational product <sup>b</sup>	0	31 (2.9)	1 (1.1)	1 (1.5)	8 (6.2)	11 (3.1)
No medication	0	87 (8.1)	85 (90.4)	52 (76.5)	50 (38.5)	223 (63.2)
Median duration of imatinib treatment (range), d	N/A	0 (0–1484)	0 (0–1296)	312.5(0–1535)	0 (0–1535)	
Monitoring at any time since diagnosis	ESMO recommends CT scans; MRI and FDG-PET can be used in certain situations					
CT scan	18 (100)	1041 (96.7)	119 (88.8)	96 (92.3)	209 (96.3)	502 (93.5)
FDG-PET	7 (38.9)	129 (12.0)	6 (4.5)	10 (9.6)	13 (6.0)	32 (6.0)
MRI	2 (11.1)	126 (11.7)	7 (5.2)	5 (4.8)	14 (6.5)	32 (5.6)
Other <sup>c</sup>	14 (77.8)	805 (74.7)	122 (91.0)	84 (80.8)	193 (88.9)	472 (87.9)
Second-line treatment (progression [advanced]/ recurrence [localised])	ESMO recommends imatinib 800 mg/d if progression; sunitinib as second-line treatment		No specific guidelines in place for second-line adjuvant treatment			
Progression/recurrence	<i>n</i> = 17	<i>n</i> = 524;	<i>n</i> = 8;	<i>n</i> = 4;	<i>n</i> = 23	<i>n</i> = 49
Number progressed/recurred	15/17 (88.2)	325/524 (62.0)	2/94 (2.1) <sup>d</sup>	0/68	11/130	18/353
Number changed medication						
Imatinib >800 mg/d	0	1 (0.3)	0	0	0	0
Imatinib 800 mg/d	7 (46.7)	132 (40.6)	0	0	2 (18.2)	3 (16.7)
Imatinib >400 to <800 mg/d	2 (13.3)	36 (11.1)	0	0	0	0
Imatinib 400 mg/d	0	6 (1.8)	1 (50.0)	0	2 (18.2)	3 (16.7)
Imatinib <400 mg/d	0	30 (9.2)	0	0	3 (27.3)	3 (16.7)
Sunitinib	3 (20.0)	101 (31.1)	1 (50.0)	0	2 (18.2)	4 (22.2)
Investigational product <sup>b</sup>	3 (20.0)	19 (5.8)	0	0	2 (18.2)	5 (27.8)
No progression			N/A			
Number not progressed	<i>n</i> = 1	<i>n</i> = 553				
Number changed medication	0	48 (8.7)				
Imatinib 800 mg/d	0	5 (10.4)				
Imatinib >400 to <800 mg/d	0	0				
Imatinib 400 mg/d	0	2 (4.2)				
Imatinib <400 mg/d	0	34 (70.8)				
Sunitinib	0	4 (8.3)				
Investigational product <sup>b</sup>	0	3 (6.3)				



Surgery	ESMO does not recommend surgery	Surgical resection (R0) is the standard treatment			
Any surgery	450 (41.1)	100 (74.6)	76 (73.1)	147 (67.7)	392 (73.0)
Complete R0 resection	215 (47.8)	94 (70.1)	68 (65.4)	130 (59.9)	353 (65.7)
Mutational analysis					
Performed at original/eligible diagnosis	167 (15.3)	15 (11.2)	23(22.1)	38 (17.5)	78 (14.5)

All data are presented as *n* (%). CT, computed tomography; ESMO, European Society for Medical Oncology; FDG, fluoro-deoxyglucose; GIST, gastrointestinal stromal tumour; MRI, magnetic resonance imaging; PET, positron emission tomography; GIST, gastrointestinal stromal tumour.

<sup>a</sup> Registry data reflect treatment after complete resection, so *n* = 94/68/130.

<sup>b</sup> Investigational product is any product other than imatinib or sunitinib (e.g. nilotinib, regorafenib).

<sup>c</sup> 'Other' includes chest and abdominal X-ray, laparoscopy, endoscopy, endoscopic ultrasound, laboratory analyses, PET/CT fusion, ultrasound, and clinical evaluation.

<sup>d</sup> For the localised group, medication changes are reported regardless of progression status for all patients with complete R0 resection.

versus 47%). In both these registries, diagnosis and monitoring most frequently included CT scans. Estimated 30-month OS rates were similar in the GOLD ReGISTry and the LifeRaft registry ( $\approx 90\%$  for localised GIST and  $\approx 80\%$  for advanced GIST) [25]. In the Polish registry for advanced GIST, the 30-month OS rate was slightly lower ( $\approx 70\%$ ); however, median PFS (37.5 months) was similar to that of GOLD ReGISTry (40.8 months) [31].

Survival outcomes were higher in patients with advanced disease in the GOLD ReGISTry than in previous clinical trials of patients with advanced GIST. In registration studies, median PFS and OS were 18.9 months and 49.0 months, respectively, for patients with advanced GIST receiving imatinib 400 mg/d [33]. Estimated 30-month PFS and OS were approximately 40% and 70% in large clinical trials of imatinib (compared with 59.8% and 82.7%, respectively, in this registry) [7,9,24]. Median PFS for patients with advanced GIST in this registry was substantially higher than in the prospective BFR14 trial, which began enrolling patients in 2002 (40.8 months versus 29.7 months) [34,35]. However, it should be noted that clinical trials define baseline considering the time of study entry, not diagnosis. The survival results would likely be longer if the time of initial diagnosis were used as baseline. It is likely that more patients are treated earlier in the disease course and have less extensive disease than patients in the early 2000s. Because the advanced GIST group in this registry likely had less extensive, less prolonged disease than those enrolled in early clinical trials, it is not surprising that patients in the registry had a median PFS much longer than that reported in BFR14 [7–10]. Furthermore, the less stringent monitoring in the registry and less frequent follow-ups (at least twice per year) compared with controlled clinical trials may have contributed to the longer PFS results. Less frequent monitoring could allow more time to elapse before progression was recorded, but would not necessarily indicate that the progression event occurred later. Further, in some patients with advanced disease, diagnosis was reassigned after registry enrolment such that there were months between enrolment and eligible diagnosis. Because eligible diagnosis was used as baseline, this may have skewed the results to shorter PFS.

In patients with localised GIST, survival outcomes from the GOLD ReGISTry were similar to large clinical trials in this population. Here, estimated 30-month OS and RFS were 94.4% and 85.4%. In clinical trials, these values were approximately 96–98% and 83–87%, respectively [13,14]. These similarities may reflect that patients with localised disease entered the registry at or near the time of original diagnosis of GIST, which was similar to eligibility criteria for adjuvant clinical trials.

Results from the GOLD ReGISTry document that long-term outcomes for patients with GIST in the

Table 6  
Mutational analyses performed at original/eligible diagnosis.

	Advanced GIST ( <i>n</i> = 1095)			Localised GIST ( <i>n</i> = 537)	
	Original diagnosis	Eligible diagnosis	During registry	Original/eligible diagnosis	During registry
Mutational analysis performed	144 (13.2)	90 (8.2)	105 (9.6)	78 (14.5)	21 (3.9)
Results obtained <sup>a</sup>	131 (91.0)	84 (93.3)	92 (87.6)	72 (92.3)	18 (85.7)
<i>Of the patients with mutation analysis results</i>					
<i>KIT</i>	108 (75.0)	68 (75.6)	69 (65.7)	55 (70.5)	13 (61.9)
Exon 9	14 (9.7)	10 (11.1)	13 (12.4)	9 (11.5)	1 (4.8)
Exon 11	78 (54.2)	42 (46.7)	54 (51.4)	40 (51.3)	11 (52.4)
Exon 13	2 (1.4)	2 (2.2)	1 (1.0)	2 (2.6)	1 (4.8)
Exon 14	1 (0.7)	0	0	1 (1.3)	0
Exon 17	1 (0.7)	0	1 (1.0)	0	0
Other	12 (8.3)	13 (14.4)	0	3 (3.8)	0
<i>PDGFRα</i>	10 (6.9)	8 (8.9)	9 (8.6)	12 (15.4)	3 (14.3)
Exon 12	3 (2.1)	3 (3.3)	0	2 (2.6)	0
Exon 18	6 (4.2)	4 (4.4)	9 (8.6)	8 (10.3)	3 (14.3)
Other	1 (0.7)	1 (1.1)	0	2 (2.6)	0
Wild type	12 (8.3)	7 (7.8)	10 (9.5)	5 (6.4)	2 (9.5)
Double mutation	1 (0.7)	1 (1.1)	5 (4.8)	0	0

All data are presented as *n* (%).

GIST, gastrointestinal stromal tumour; PDGFRα, platelet-derived growth factor receptor alpha.

<sup>a</sup> The remaining mutation analyses were not evaluable.

real-world setting have improved substantially since TKIs entered the treatment landscape. Areas of ongoing clinical research involve determining the optimal duration of adjuvant treatment for localised GIST and evaluating novel agents targeting different molecular pathways to better control the disease.

#### Authors' contributions

CHB, MEB, JYB, MC, JG, YKK, TN, RCW, PR developed the study concept. CHB, MEB, JYB, PGC, MC, JG, YKK, TN, PR designed the study and were responsible for data acquisition. DP was responsible for ensuring quality control of data, algorithms and statistical analysis. CHB, JYB, PGC, MC, YKK, TN, DP, RCW, PR were responsible for data analysis and interpretation. CHB, MEB, JYB, JG, DP, TN, RCW, PR were responsible for drafting the manuscript, with writing support from Articulate Science, funded by Novartis. All authors were responsible for review and revision of the manuscript, and approval of the submitted version.

#### Earlier presentations

- Second annual summary of results presented by Matias Chacon at the 2010 Annual Meeting of American Society of Clinical Oncology (J Clin Oncol 28:15s, 2010 [suppl; abstr 10092]).
- Initial results presented by Peter Reichardt at the 2009 ASCO Gastrointestinal Cancers Symposium. Abstract 16.

#### Conflict of interest statement

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*Das Purkayastha*: Employee of Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA.

*Richard C. Woodman*: Employee of Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA.

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## Appendix A. Supplementary data

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