

RAPID COMMUNICATION

Treatment of patients with advanced gastrointestinal stromal tumor of small bowel: Implications of imatinib mesylate

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Key words: Gastrointestinal stromal tumor; Glivec; Patient survival; Kit gene mutation

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Abstract

AIM: To examine the impact of imatinib mesylate (Glivec) on patient survival and response and its safety, and the correlation of the response rate with the kit gene mutation status.

METHODS: Thirty-three of 74 (44.6%) small bowel gastrointestinal stromal tumor (GIST) patients who developed recurrence after curative resection and not treated with Glivec were classified as group A patients. Twenty-two advanced small bowel GIST patients treated with Glivec were classified as group B patients. Clinicopathological features, post-recurrence and overall survival rates were compared. Each tumor in group B patients was investigated for mutations of kit or platelet-derived growth factor alpha (PDGFRA). The mutation type was correlated with clinical outcomes. The anti-tumor effect and safety of Glivec in group B patients were also assessed.

RESULTS: Advanced small bowel GIST patients treated with Glivec had substantially longer post-recurrence survival and higher overall survival rates than those not treated with Glivec. A total of 15 patients had a partial response (PR) (67.8%). Activated mutations of c-kit were found in 16 of 19 tested patients and no PDGFRA mutant was identified. In 13 patients with GISTs harboring exon 11 kit mutations, the partial response rate (PR) was 69.3%, whereas two of three patients with tumors containing an exon 9 kit mutation had an overall response rate (ORR) of 66.7% (not significant).

CONCLUSION: Glivec significantly prolongs the post-recurrence and overall survival of Asian patients with advanced GISTs. Glivec induces a sustained objective response in more than half of Asian patients with

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are soft-tissue sarcomas primarily arising from mesenchymal tissue in the gastrointestinal (GI) tract and abdomen. They are rare neoplasms, accounting for 0.1%-3% of all gastrointestinal tract tumors^[1]. However, GISTs are the most common mesenchymal malignancy of the GI tract with the precise incidence unknown^[2]. Approximately 5000 GISTs are diagnosed annually in the USA, distributing equally in men and women. GISTs appear to be related the interstitial cells of Cajal of the mesenteric plexus^[3]. These cells are considered as GI pacemaker cells, from the interface between the automatic innervation of the bowel wall and its smooth muscle^[4,5]. GISTs express the cell-surface transmembrane receptor kit with a tyrosin kinase activity and are the protein product of the kit proto-oncogene. There are frequent gain-of-function mutations of kit in GISTs. These mutations result in constitutive activation of kit signaling, which leads to uncontrolled cell proliferation and resistance to apoptosis. It has been recently reported that kit activation occurs in all cases of GISTs, regardless of the mutation status of kit.

Surgical resection remains the mainstay of therapy for GIST. However, recurrence is common, the 5-year survival rate after complete resection ranges from 40% to 65%^[6-10]. Unresectable or metastatic GIST is a fatal disease that resists conventional chemotherapy. A recently study reported that the response rate to doxorubicin therapy is less than 5%^[11]. The effectiveness of radiation therapy for unresectable or metastatic GIST has not been proved.

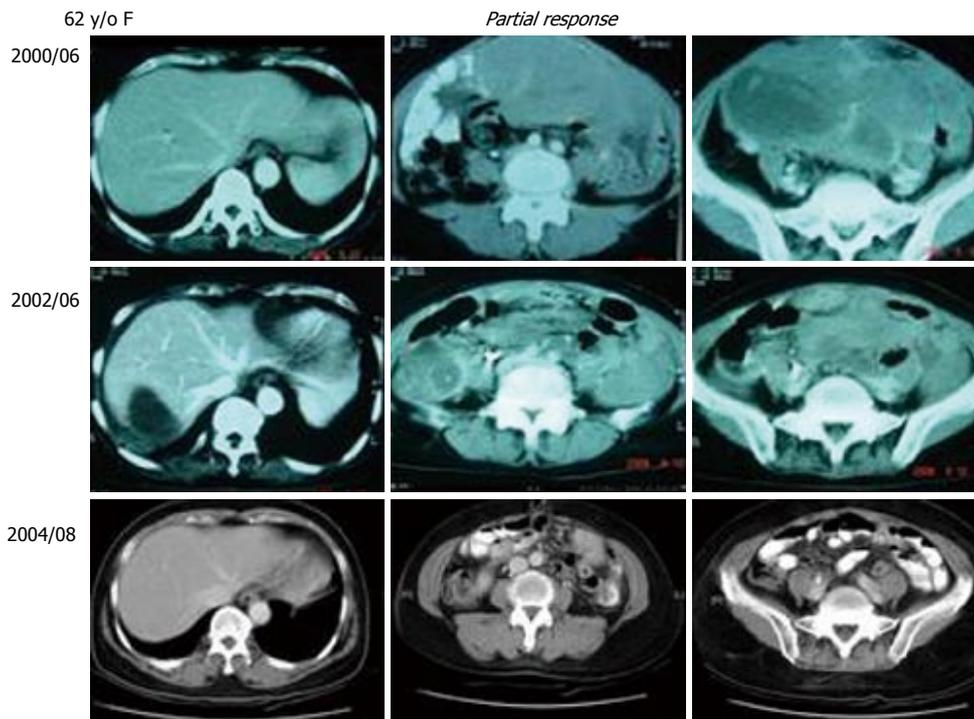


Figure 1 Sequential CT scans obtained in the same patient at base line (before treatment, upper row), middle row (2 year after Glivec treatment), and lower row (50 mo after Blivec treatment). The CT scans revealed partial response of the tumor at the same level.

The median length of survival is approximately 20 mo for patients with a metastatic GIST and 9 to 12 mo for patients with local recurrence^[3]. Before the development of Glivec, the outlook for patients with advanced GIST is extremely poor. A significantly large number of patients with initial resection of GIST eventually experience recurrence, for which there is no effective treatment.

Imatinib mesylate (formerly STI571, now referred to as Gleevec or Glivec) selectively inhibits certain protein tyrosin kinases, such as intracellular ABL kinase, chimeric BCR-ABL fusion oncoprotein of chronic myeloid leukemia, transmembrane receptor kit, and platelet-derived growth factor (PDGRF) receptors^[12-15]. Glivec induces a sustained objective response in more than half of patients in the West with advanced GISTs^[16]. However, the implication of Glivec on patient survival, patient response to and safety of Glivec for Asian patients with advanced GIST has not been elucidated. This study examined the impact of Glivec on patient survival and response and its safety, and the correlation of the response rate with the kit gene mutation status.

MATERIALS AND METHODS

Patients

From January 1983 to December 2002, 77 small bowel GIST patients with positive kit immunostaining underwent curative resection at the Department of Surgery, Chang Gung Memorial Hospital, Taiwan. Patients with other concurrent malignancies at presentation as well as those with incidental findings of tumors on laparotomy (most tumors were < 2 cm and had trace mitotic count) were excluded. Clinical presentation, operative findings, and long-term outcomes were retrospectively reviewed. Curative operation was defined as negative resection margin observed during histopathological examination.

Recurrent disease was defined as the presence of a histologically or radiographically identified tumor. Distant metastatic disease was defined as that occurring at structures noncontiguous with the primary tumor site. Regional intraperitoneal disease was deemed a local recurrence if it involved a recurrent solitary tumor or sarcomatosis.

During 2002 to June 2004, 22 histologically confirmed unresectable or metastatic small bowel GIST patients who expressed CD117 and CD34 (a marker of kit-receptor tyrosine kinase) were enrolled in this study. Criteria for inclusion were as follows: at least one measurable tumor; adequate hepatic, renal, and cardiac function; an adequate platelet count; and an Eastern Cooperative Oncology Group (ECOG) performance status of 3 or less. Patients could have previously received chemotherapeutic regimens (the last chemotherapy treatment must have been at least four weeks before study entry) and undergone radiotherapy, or surgery, or both. The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital and written informed consent for drug administration and the analysis of tumor-associated genetic alteration was obtained from each patient.

Study design

A prospective, non-randomized, and single center trial was conducted to evaluate the role of Glivec in inducing objective response in GIST patients. Patients were administered 400 mg of Glivec in 100 mg capsules, taken orally once daily with food. Patients had regular physical examinations and evaluations of performance status, body weight, complete blood count, and serum chemistry. The administration of each dose and any adverse events were recorded for each patient. Standard computed tomography (CT) was performed on each patient every three months to assess patient response (Figures 1A-C). Standard [18F]

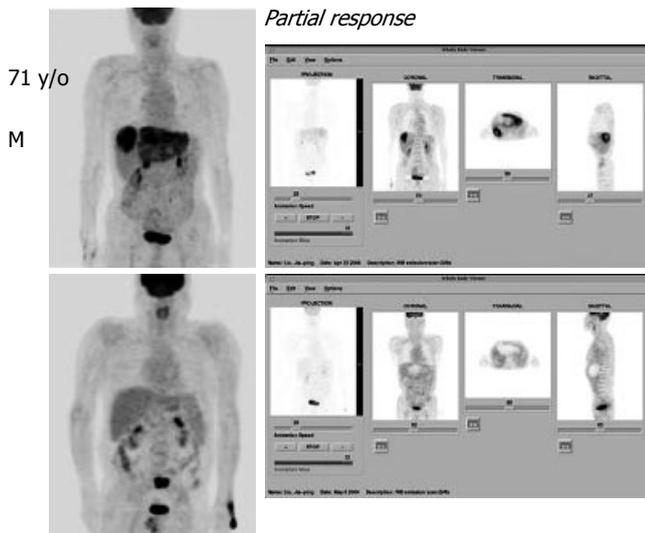


Figure 2 Sequential PET scans obtained in the same patient at base line (before treatment, upper row), and 1 mo after Glivec treatment (lower row). The PET scans revealed partial response of the tumor at the same level.

fluoro-2-deoxy-D-glucose positron-emission tomography (PET) scanning was performed on three patients to complement standard computed tomography (CT) and to assess changes in the metabolic profiles of the tumors (Figure 2).

Efficacy and safety evaluation

The response of the tumor to Glivec was evaluated after one month, three months, and every three months thereafter or whenever medical need was indicated. Assessments were performed according to the standard Southwest Oncology Group criteria and based solely on CT or PET^[17]. Responses were classified as follows: complete response (CR) (disappearance of all the disease that could be measured and evaluated), partial response (PR) (> 50% of the decrease in the sum of the products of the perpendicular diameters of all measurable lesions, the absence of progression, and the absence of new lesions), stationary disease (SD) (a response that did not qualify as a complete response, a partial response, or disease progression), and disease progression (DP) (> 50 per cent increase or an increase of 10 cm, whichever was smaller) in the sum of the products of the perpendicular diameter of all measurable lesions, worsening of a lesion that could be evaluated, the reappearance of any lesion or the presence of a new lesion, or failure of the patients to return for evaluation because of disease progression. Toxic effects were recorded in accordance with the National Cancer Institute Common Toxicity Criteria^[18].

Analysis of kit and PDGFRA mutations

Sections were prepared from formalin-fixed, paraffin-embedded pretreatment specimens trimmed to enrich tumor cells. Polymerase chain reaction amplification of genomic DNA for kit and PDGFRA was performed and amplification was analyzed for mutations as previously described^[19] (Figure 3).

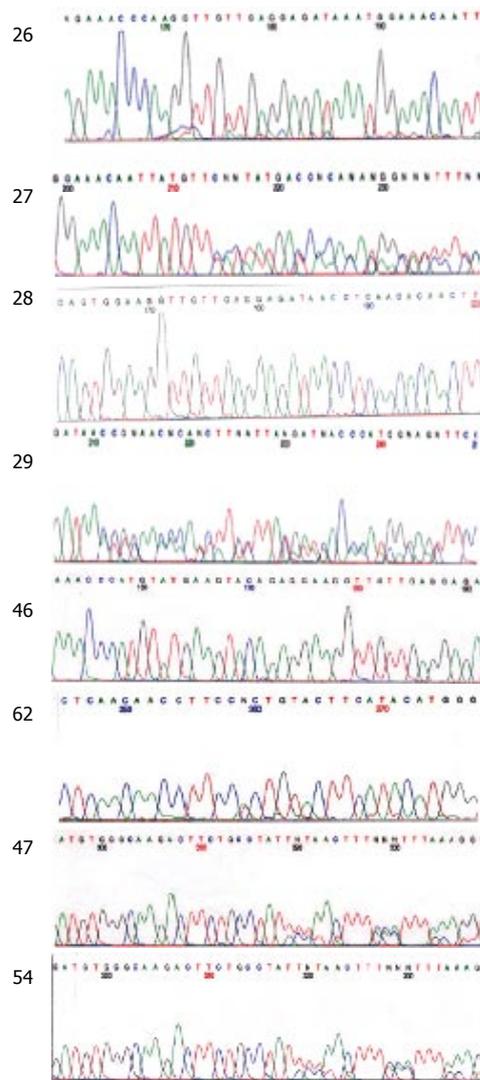


Figure 3 Mutation spectrum of the 8 small bowel GIST patients.

26, 27: Deletion mutation in exon 11; 28, 29: Deletion and insertion mutation in exon 11; 46, 62: Missense mutation in exon 11; 47, 54: Insertion mutation in exon 9.

Statistical analysis

All data were presented as percentages of patients or means with standard deviation. Numerical data were compared by an independent two-sample *t* test. Pearson chi-square test and Fisher's exact test were used for nominal variables. Survival rate was calculated and plots were constructed by the Kaplan-Meier method and compared between groups with a log-rank test. All statistical analyses were performed using SPSS computer software package (Version 10.0, Chicago, IL, USA). *P* < 0.05 was considered statistically significant.

RESULTS

Clinical features

Table 1 presents a summary of clinical features. A similar age distribution and gender ratio were observed in the two groups. The jejunum was the most common site for small bowel GISTs treated with or without Glivec. Liver was the most frequent site for metastasis of small bowel GISTs. There was no significant difference in tumor diameter between the two groups.

Table 1 Demographic data of 55 advanced and metastatic small bowel GIST patients treated with or without imatinib meslyate

	Non-Glivec (%) (n = 33)	Imatinib meslyate (%) (n = 22)	P
Age (yr)	56.5 ± 11.1	55.7 ± 15.4	0.803
Gender (M : F)	17 : 16	13 : 09	0.58
Location			
Duodenum	4 (12.1)	5 (22.7)	
Jejunum	22 (66.7)	8 (36.4)	
Ileum	7 (21.2)	6 (27.3)	
Multiple	0 (0)	3 (13.6)	0.05
Tumor size			
Mean/Median (cm)	10.3 ± 4.9/9.0	11.7 ± 5.1/10.5	0.315
Range (cm)	3.5-25	4-24	
Recurrence			0.022
Liver	28 (84.8)	11 (50)	
Peritoneum	10 (30.3)	10 (45.5)	
Retropertoneum	4 (12.1)	5 (22.7)	
Local	4 (12.1)	10 (45.5)	
Others	1 (0.3)	4 (18.2)	

M: Male; F: Female.

Table 2 Prognosis of 55 advanced and metastatic small bowel GIST patients treated with or without imatinib meslyate

	Non-Glivec (%) (n = 33)		Imatinib meslyate (%) (n = 22)				P
	Re-resection (n = 6)	C/T (n = 5)	Conservative treatment (n = 22)	CR (n = 0)	PR (n = 15)	SD (n = 4)	PD (n = 3)
PRS (m) (median/mean)		6.7/14.7			-/72.6		0.00001
Mean	36.2	4.8	9.6		75.6	31.6	
Median	15.7	3.7	5.9		-	24.7	
95% CI of mean	7.5-65.0	2.3-7.3	6.1-13.0		67.5-87.0	22.0-41.2	
Log-rank (p)		0.048			0.462		
OS (m) (median/mean)		33.6/49.2			137.7/128.9		0.00001
Mean	73.1	28.5	48.2		140.1	53.2	
Median	47.5	23.5	33.2		137.7	50.9	
95% CI of mean	27.0-119.3	18.7-38.4	30.3-66.1		136.7-143.3	50.0-56.4	
Log-rank		0.189			0.083		

CI: Confidence interval; PRS: Post recurrence survival; OS: Overall survival; CR: Complete response; PR: Partial response; SD: Stationary disease; PD: Progression of disease.

Treatment and outcomes

The median time of post-recurrent survival was 6.7 mo (range 1.2-90 mo). Although surgical re-resection is a better option for recurrent disease, complete re-resection for recurrent disease was only performed for 6 patients. The median time of post-recurrence survival in these patients was 15.7 mo. Chemotherapy (doxorubicin [adriamycin] and dacarbazine [DTIC]) was administered to 5 patients with median survival of 3.7 mo. Twenty-two patients with recurrence were given supportive treatments such as analgesics or nutritional supplements (median survival of 5.9 mo). Re-resection significantly prolonged post-recurrence patient survival when compared with the patients treated

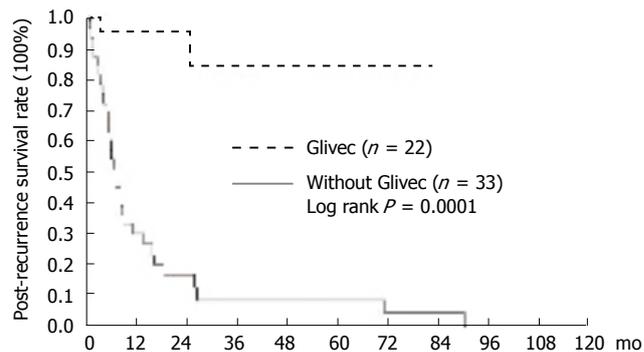


Figure 4 Post-recurrence survival rate of 55 small bowel GIST patients treated with and without Glivec.

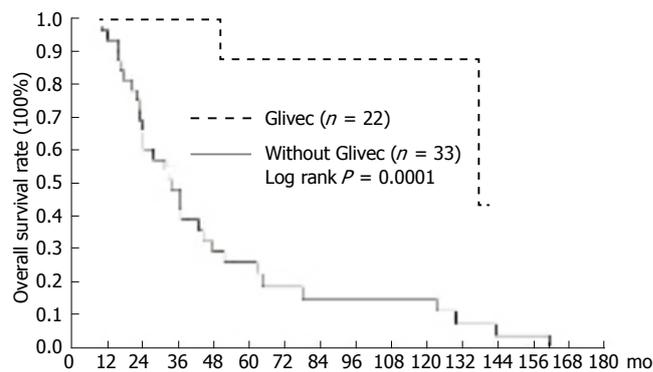


Figure 5 Overall survival rate of 55 small bowel GIST patients treated with or without Glivec.

with chemotherapy and conservative treatment ($P = 0.00481$), but did not improve overall survival rates ($P = 0.1887$). Glivec was administered to patients with unresectable or metastatic (advanced) small bowel GISTs from 2000. Twenty-two patients with advanced stages of the disease were given 400 mg Glivec per day. Advanced small bowel GIST patients treated with Glivec had significantly longer post-recurrence survival and overall survival than those not treated with Glivec ($P = 0.0001$) (Table 2) (Figures 4 and 5). The median follow-up time was 36.3 mo, range 8 mo to 142.4 mo. Although edema was common (14/22; 60.7%), therapy with Glivec was well tolerated. Overall, 15 patients (68.2%) had a partial response (PR), 4 stationary disease (SD) (18.2 %), 3 progressive disease (PD) (13.6%) (Table 3).

Spectrum of mutations in 22 small bowel GIST patients

Tumor specimens suitable for genetic analysis were available from 19 (86.4%) of the 22 small bowel GIST patients (Figures 3A-D and Table 4). Overall, 16 (72.7%) of the 22 examined GISTs had activated mutations of kit exons 9, 11, 13, or exon 17. No GIST had an activated mutation in more than one kit. Three of 19 GISTs expressed exon 9 mutation, 13 had exon 11 mutation, and three patients had no mutation of kit. No PDGFRA mutant isoforms were found. All the three GISTs had kit exon 9 mutation and displayed in-frame duplication of nucleotides, resulting in insertion of alanine (A) and tyrosine (Y) at condons 502 and 503. Among 13 GIST

Table 3 Antitumor response and mutation status of 22 advanced and metastatic small bowel GIST patients treated with imatinib mesylate

	CR	PR	SD	PD	P
Exon 9 (n = 3)	0	2	0	1	0.486
Exon 11 (n = 13)	0	9	2	2	
No mutation (n = 3)	0	3	0	0	
Insufficient specimen (n = 3)	0	1	2	0	
	Exon 9 (n = 3)		Exon 11 (n = 13)		1.0
PR, n (%)	2 (66.7)		9 (69.2)		
SD + PD, n (%)	1 (33.3)		4 (30.8)		

PR: Partial response; SD: Stationary disease; PD: Progression of disease.

Table 4 Mutation patterns of 22 advanced and metastatic small bowel GIST patients treated with imatinib mesylate

Case (n)	Mutation pattern
2	Deletion mutation at codon 551-556 in exon 11
4	Deletion mutation at codon 557-561 in exon 11
8	Deletion mutation at codon 550-5 in exon 11
12	Deletion mutation at codon 563-576 in exon 11
13	Deletion mutation at codon 575-576 in exon 11
19	Deletion mutation at codon 569-575 in the exon 11
24	Deletion mutation at of codon 555-572 in exon 11
1	Deletion and insertion mutations at codons 563-572 in exon 11
15	Deletion and insertion mutations at codons 557-8 in the exon 11
22	Deletion and insertion mutations at codon 563-574 in exon 11
3	Missense mutation at codon 556 in exon 11
18	Missense mutation at codon 576 in the exon 11
21	Missense mutation at codon 557 in exon 11
7	Insertion mutation at codon 502-3 AY(alanine and tyrosin) in exon 9
9	Insertion mutation at codon 502-3 AY(alanine and tyrosin) in exon 9
17	Insertion mutation at codon 502-3 AY(alanine and tyrosin) in exon 9
10	No mutation
14	No mutation
20	No mutation

patients who had kit exon 11 mutations, 3 exhibited insertion/deletion, 7 showed deletion, and 3 demonstrated missense mutations (Table 4). Three of 19 tested GIST patients had no detectable kit mutation (kit wild-type) and no PDGFRA mutation. In 13 patients with GISTs harboring kit exon 11 mutations, the partial response rate (PR) was 69.3%, whereas two of three patients with tumors containing an exon 9 kit mutation had an ORR rate of 66.7% (Table 3, not significant).

DISCUSSION

The demographic features, tumor locations, and clinical features for Asian small bowel GIST patients are similar to those identified in other series^[3,10,20-22]. Since the symptoms of small bowel GIST are vague, early diagnosis is not always easy and tumor sizes are usually large at diagnosis^[3,10,20-22]. Before the introduction of Glivec, poor responses to radiation and chemotherapy have made surgery the only realistic treatment to cure the primary lesion^[3,10,23-25]. A substantial number of patients with initial resection of GISTs eventually experience recurrence.

The liver is the most frequent site for recurrence. There has been no effective treatment for advanced GISTs and the outlook for patients is extremely poor. As shown in this study, patients with recurrence who underwent further surgery with curative intention had a significant longer post-recurrence survival than those treated with chemotherapy or conservative treatment. However, the overall survival rates for both groups were similar. After treatment with Glivec, advanced small bowel GIST patients had significant longer post-recurrence and overall survival.

Therapeutic responses to targeted inhibition of activated tyrosine kinases have been demonstrated in certain types of leukemia, sarcoma, and breast cancer^[19]. The mechanisms of kinase activation vary considerably among these cancers, but study of the influence of these mechanisms on drug response has been limited^[19]. GISTs in particular, present a variety of genomic mutations across two different receptor tyrosine kinase genes. The kit or PDGFRA mutation in Asian clinically advanced small bowel GIST patients was examined in this study. Most small bowel GISTs expressed kit mutation (16/19, 84.2%). The kit kinase oncoproteins were intrinsically sensitive to Glivec, accounting for the excellent overall clinical response to Glivec, and coincident with results obtained by Heinrich *et al*^[19]. Similar to that in report by demetri *et al*^[16], the PR rate for Glivec in this study was 68.2%.

Gain-of-function mutations of PDGFRA has been recently discovered in GISTs^[26] and studies have reported that PDGFRA and kit mutations are mutually exclusive^[19]. However, no PDGFRA mutations were detectable in this series. More cases should be studied to clarify the racial differences regarding the incidence of PDGFRA mutation in GIST patients. A subset of GIST tumors in this study lacked detectable kit or PDGFRA mutations. Although such GISTs lack apparent genomic mutations, they can express phosphorylated kit or PDGFRA proteins that likely contribute to tumor proliferation or survival^[19]. Contrary to the observation of Heinrich *et al*^[26], GISTs lacking a detectable kinase mutation had a similar PR rate for Glivec to tumor with an exon 11 mutation or an exon 9 mutation (100% *vs* 69.2% *vs* 66.7%, $P = 0.527$).

In contrast to Heinrich *et al*^[26], the PR rate did not differ between the groups of patients whose GISTs had kit exon 9 and exon 11 mutation (66.7% *vs* 69.2%), suggesting that the kit oncoproteins encoded by exons 9 and 11 are equally sensitive to Glivec *in vitro*^[19].

In conclusion, Glivec significantly prolongs the post-recurrence and overall survival of Asian patients with advanced GISTs. Glivec induces a sustained objective response in more than half of Asian patients with advanced small bowel GISTs. Activated mutations of kit exon 11 are detectable in the vast majority of GISTs. There is no difference in the PR rate for patients whose GISTs have KIT exon 9 and exon 11 mutations.

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