EJC SUPPLEMENTS 6, NO. 1 (2008) 1–14

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Systemic treatment of patients with gastrointestinal stromal tumor: Current status and future opportunities

George D. Demetri[a,*], *Heikki Joensuu*[b]

[a]*Ludwig Center at Dana-Farber/Harvard Cancer Center, Boston, MA, USA* [b]*Helsinki University Central Hospital, Helsinki, Finland*

ARTICLE INFO

Keywords:
Gastrointestinal stromal tumor
Outcome
Mutational status
Tyrosine kinase inhibitor
Imatinib
Sunitinib
Nilotinib
Adjuvant therapy
Neoadjuvant therapy

ABSTRACT

Imatinib mesylate is considered the standard first-line systemic treatment for patients with advanced gastrointestinal stromal tumor (GIST). Results from recent research have expanded the knowledge of tyrosine kinase inhibitors in management of GIST. In the setting of unresectable and metastatic GIST, long-term follow-up of the B2222 study showed that imatinib 400 and 600 mg/d produced objective responses in 68% of patients and clinical benefit in 84%; it also extended median survival from 19 months in historical controls to 57 months. The MetaGIST analysis in two large phase 3 trials consisting of more than 1600 patients with metastatic and/or unresectable GIST showed that imatinib 800 mg/d compared with the standard 400-mg/d dose conferred a progression-free survival advantage in patients with *KIT* exon 9 mutations but not in other subpopulations. The higher starting dose does not significantly improve overall survival. The BFR14 trial demonstrated that interrupting imatinib is associated with a high risk of rapid disease progression. For patients with imatinib-intolerant or imatinib-resistant GIST, sunitinib or a variety of investigational agents, including the next-generation kinase inhibitor nilotinib, may be viable options for achieving disease control. In the setting of primary localized GIST, function-sparing surgical resection is the standard treatment approach, but some patients may be at substantial risk of disease recurrence and metastasis depending on tumor size, mitotic count, and possibly other factors. Initial results from ACOSOG Z9001 indicate that adjuvant imatinib for 1 year prolongs recurrence-free survival following surgical resection of larger (at least 3 cm) KIT-expressing GIST. Other ongoing studies are further exploring the role of imatinib in both adjuvant and neoadjuvant therapy. Recent updates to clinical practice guidelines and recommendations now incorporate some of these new findings.

1. Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract, occurring most frequently in the stomach (50–70%) and small intestine (25–30%), and less frequently in the colon (10%), omentum/mesentery (7%), and esophagus (5%).[1–3] During the past decade, the diagnosis of GISTs appears to have increased.[3,4] A Norwegian study evaluated trends in mesenchymal tumors over 30 years, from 1974 to 2003, and found that the incidence of GISTs more than tripled from the first to the third decade, from 5.8 per million to 19 per million.[4] Several recent population-based studies indicate that GISTs

*Corresponding author. George D. Demetri, MD. Ludwig Center at Dana-Farber Cancer Institute and Harvard Medical School, 44 Binney Street, Dana Building D1212, Boston, MA 02115, USA. Tel.: +1 617 632 3985; fax: +1 617 632 3408.
E-mail address: gdemetri@partners.org, george_demetri@dfci.harvard.edu (G.D. Demetri).

occur at an annual incidence of 6 to 15 per million in European and US populations.[5–9] However, possible precursor lesions – which have been termed *microscopic GISTs* and *GIST tumorlets* – appear to be much more common in the general adult population. GIST tumorlets ranging in size from 1 to 10 mm and having histologic features consistent with GISTs were detected in 22 of 98 consecutive autopsies (22.5%) of individuals over 50 years of age.[10] These lesions were found in the proximal parts of the stomach, but not in the antrum or intestines. Similarly, microscopic GISTs were detected in the upper portion of the stomach in 35 of 100 patients (35%) diagnosed with gastric cancer.[11] The high prevalence of these lesions suggests that few progress rapidly into clinical GISTs with malignant potential, even though many contain the same oncogenic mutations found in larger GISTs. The secondary signals that are responsible for malignant transformation of GIST cells remain obscure.

GISTs may be distinguished from other tumors, including leiomyomas, leiomyosarcomas, and schwannomas, on the basis of their characteristic immunohistochemical profile and underlying genotype in the proper histopathological context. Approximately 95% of GISTs are positive for KIT (CD117) – the receptor for stem cell factor (SCF) – whereas 60–70% are positive for CD34 and 30–40% for smooth muscle actin.[1–3] Other markers are found only rarely, including S-100 protein in 5%, desmin in 1–2%, and keratin in 1–2%. Under normal conditions, SCF binds to the extracellular domain of KIT, thereby promoting KIT dimerization and enabling lateral interactions between the juxtamembrane domains of the two KIT molecules.[12] These changes result in tyrosine kinase activation and, consequently, to stimulation of downstream signaling pathways and cellular responses.

A majority of GISTs have activating mutations in the *KIT* gene, most frequently caused by mutations in *KIT* exon 11, which encodes the juxtamembrane domain, less frequently in *KIT* exon 9, which encodes the proximal part of the extracellular domain, and rarely in *KIT* exon 13 or 17, which encode the tyrosine kinase I domain and activation loop, respectively.[2,3,13] Mutations in *KIT* exon 11 seem to promote KIT dimerization in the absence of SCF, whereas those in *KIT* exon 9 are thought to disrupt an antidimerization motif in the extracellular domain.[2] Both cause constitutive activation of the KIT tyrosine kinase in the absence of SCF, thereby driving oncogenic signaling and neoplastic transformation of the cell. Approximately 5–7% of GISTs have activating mutations in *PDGFRA*, the gene encoding a receptor for platelet-derived growth factor alpha (PDGFRα), which results in constitutive activation of PDGFRα tyrosine kinase activity in the absence of its ligand.[3,13] The remaining GISTs have no detectable *KIT* or *PDGFRA* mutations and are termed wild-type GISTs.

The clinical outcome of patients with advanced GISTs has been improved substantially by the development of imatinib – a small-molecule inhibitor of several related tyrosine kinases, including KIT and PDGFRα.[14,15] GISTs are not responsive to conventional cytotoxic chemotherapy: reported response rates are generally <5%, and median survival in advanced disease is only 14–19 months.[3,6,16,17] A retrospective analysis of 119 patients with metastatic GIST diagnosed before July 1998 – before the advent of the imatinib era – found median survival of 19 months, with 2-year and 5-year survival rates of 41% and 25%, respectively.[18] The first report of the effectiveness of imatinib in metastatic GIST was published in 2001, showing that the drug caused substantial tumor shrinkage and disappearance of some liver metastases in a patient with progressive disease who had failed prior chemotherapy and thalidomide/interferon-alfa therapy.[19] Since that time, clinical trials have shown that imatinib produces clinical benefit in most patients with unresectable or metastatic GIST and extends median survival from 19 months observed in historical controls to 57 months.[20–23] Imatinib is now uniformly recognized as the standard of care for advanced GIST,[1,3] and has received regulatory approval for the treatment of unresectable or metastatic GIST.

On September 23, 2007, a satellite symposium was held in conjunction with the European CanCer Organisation (ECCO) 14 meeting in Barcelona, Spain, to discuss the state of the art of knowledge and research related to extending the survival of patients with GIST. This supplement discusses the proceedings of the satellite symposium and places the presented data within the context of recent updates to practice guidelines and recommendations.

2. Long-term efficacy of imatinib in the unresectable or metastatic GIST setting

Imatinib received approval for use in patients with unresectable or metastatic GIST on the basis of results from the B2222 trial.[20] In this phase 2 open-label, randomized, multicenter study, 147 patients with unresectable or metastatic GIST were randomly assigned to receive imatinib 400 or 600 mg/d. Patients who progressed on the 400-mg/d dose and remained in otherwise good clinical condition were allowed to increase imatinib to 600 mg/d. B2222 was initially designed as a 36-month core study, but a 4-year extension phase was added to explore the long-term efficacy of imatinib after a significant proportion of patients were seen to benefit from treatment. Patients who completed the core study were eligible to enter the extension phase if they continued to have clinical benefit from imatinib and had no significant safety issues. Overall, 67 patients (46%) completed the core study, and 56 patients (38% of the initial cohort) entered the extension phase.

The long-term efficacy of imatinib was evaluated after patients had been treated for up to 71 months.[23] Response rates, median progression-free survival (PFS), and median overall survival (OS) were essentially identical between the imatinib 400-mg/d and 600-mg/d treatment arms. Overall, the objective response rate was 68.1% (95% confidence interval [CI]: 59.8–75.5%), which consisted of 2 patients (1.4%) with complete responses and 98 patients (66.7%) with partial responses. An additional 23 patients (15.6%) achieved stable disease, most for more than 1 year. The response rate of 68.1% is higher than the rate of 53.7% reported initially in B2222 after a median follow-up of 9.4 months.[20] This difference reflects the fact that 25% of patients achieved objective responses after 5.3–39 months of imatinib therapy.[23] Despite tumor size being an independent prognostic predictor for GIST, patients with smaller and larger tumors had comparable response rates to imatinib. Thus, objective response rates with imatinib may increase cumulatively with continued therapy and longer follow-up, independent of tumor size.

Median survival was 57 months in both treatment arms and for the pooled study population.[23] Patients who achieved objective responses or stable disease had comparable survival, with both having substantially longer survival than those who initially progressed on imatinib (5-year survival: 55% vs 9%). Mutational analysis was performed for 128 patients (87% of the study cohort): the majority had mutations in *KIT* exon 11 (67%) or exon 9 (18%), with mutations in *KIT* exons 13 (2%) and 17 (1%) and in *PDGFRA* (5%) seen less frequently. Nine patients (7%) did not have detectable mutations in either *KIT* or *PDGFRA*. Patients with *KIT* exon 11 mutations had longer median OS than those with *KIT* exon 9 mutations (63 vs 44 months), with significantly shorter median survival seen in patients with other or no mutations (26 months; $P = 0.005$). In the multivariate analysis, prognostic factors associated with improved survival included female gender (hazard ratio [HR] = 0.49; $P = 0.0093$) and presence of a *KIT* exon 11 mutation (HR = 0.40; $P = 0.0004$), and those associated with poorer survival included elevated albumin (Common Toxicity Criteria [CTC] grade $\geqslant 1$: HR = 2.35; $P = 0.0007$) and neutrophil ($\geqslant 4.5 \times 10^9$/L: HR = 2.25; $P = 0.0023$) levels at baseline. When the multivariate analysis was conducted after dividing the survival time into two periods (0–30 months and 30–72 months), the impact of the *KIT* exon 11 mutation on OS was seen primarily in the early time period, whereas the impact of gender was evident during the later time period.

Imatinib remained well tolerated during long-term therapy, with no patient withdrawing from the extension study due to an adverse event.[23] Overall, 41 patients (28% of the original cohort) were still receiving long-term imatinib therapy in the extension study as of the data cutoff point in May 2006. These findings demonstrate that imatinib can control advanced GIST in a large proportion of patients for over 5 years. Due to these results, the Glivec team at Novartis has committed to a further 3-year extension of this study, and currently has enrolled over 40 patients in the extended follow-up.

3. Personalizing imatinib therapy based on molecular subtype of GIST: MetaGIST analysis

Data from B2222 showed no difference in response or survival between the 400-mg/d and 600-mg/d treatment arms, although this study was not powered to address this question.[20,23] In the initial phase 1 and 2 studies, the clinical activity of imatinib in patients with advanced GIST was demonstrated at doses ranging from 400 to 1000 mg/d.[20,21,24] The efficacy and safety of standard-dose (400 mg/d) and high-dose (800 mg/d) imatinib were subsequently compared in two adequately powered, similarly designed phase 3 randomized, intergroup, international trials: EORTC 62005 conducted in Europe and Australia[25] and S0033 conducted in the USA and Canada.[22] In these studies, patients with unresectable or metastatic GIST expressing KIT were randomly assigned to receive imatinib 400 or 800 mg/d until disease progression. Patients allocated to the 400-mg/d treatment arm were offered the option to cross over to 800 mg/d at the time of disease progression.

Although the design of EORTC 62005 and S0033 was similar, these studies differed in their primary end points (PFS in EORTC 62005 and OS in S0033) and in various demographic and clinical characteristics of their patient populations. The MetaGIST analysis was a prospectively planned meta-analysis of these two studies and was designed to build prognostic models for PFS and OS and to characterize patients who may benefit from high-dose imatinib therapy.[26] As presented at ASCO 2007, the meta-analysis demonstrated that imatinib 800 mg/d produced a small but significant improvement in PFS relative to imatinib 400 mg/d, although median OS did not differ.[26] A multivariate analysis was also conducted on independent prognostic factors that adversely affected both PFS and OS for patients treated with standard-dose or high-dose imatinib.[26]

Patients with disease progression on the initial 400-mg/d dose of imatinib were eligible to cross over to 800-mg/d therapy in both studies. Cross-over data from study 62005 were analyzed after a median follow-up of 25 months.[27] A total of 133 of 241 patients (55%) crossed over to imatinib 800 mg/d within 2 months of documented disease progression.

The risk reduction in overall PFS seen with high-dose versus standard-dose imatinib in the phase 3 EORTC-Australasian–Italian consortium trial led to a search for subpopulations that might derive greater benefit from starting imatinib therapy at 800 mg/d. Only one

Metastatic GIST with *KIT* exon 9 mutation

A 57-year-old previously healthy man has a 9-cm GIST surgically resected from the small intestine in June 2003. The tumor expresses KIT (+++ on immunohistochemistry), and exhibits a high mitotic rate (15 per 50 high power fields [HPF]). Fifteen percent of nuclei are positive for Ki-67 immunostaining. Two years later, an abdominal computed tomography scan reveals multiple metastases, and a needle biopsy confirms metastatic GIST. Mutational analysis reveals an insertion mutation in *KIT* exon 9. Mutations in *KIT* exon 9 occur in approximately 10% of all GISTs and are particularly common in tumors originating in the small intestine and in those with high mitotic counts. [1]

Should patients with KIT *exon 9 mutations be started on high-dose imatinib therapy?*
Standard-dose imatinib (400 mg/d) is very effective in GISTs with the more common *KIT* exon 11 mutation, whereas patients with the *KIT* exon 9 mutation have less favorable responses to standard-dose imatinib. [23,26,28] Nevertheless, high-dose imatinib (800 mg/d) may be effective. The strongest evidence supporting initial high-dose therapy in this setting comes from the MetaGIST analysis, which included patients with *KIT* exon 9 mutations who participated in the phase 3 multinational EORTC 60025 and S0033 studies. [26] Starting imatinib therapy at 800 mg/d produced significantly longer median PFS and higher 3-year PFS than the standard 400-mg/d dose in the subpopulation with *KIT* exon 9 mutations. Despite the improvement in PFS, the MetaGIST analysis did not find a significant survival advantage between imatinib dose levels, although median OS tended to be somewhat longer with imatinib 800 mg/d than 400 mg/d in this subpopulation.

factor was found to significantly affect the relative benefit of high-dose versus standard-dose imatinib: *KIT* exon 9 mutational status. [28] This analysis indicated that initiating imatinib therapy at 800 mg/d in patients with *KIT* exon 9 mutations improves PFS but does not significantly prolong OS.

Cross-over analysis of the phase 3 EORTC 60025 study demonstrated that imatinib dose escalation from 400 to 800 mg/d was well tolerated. [27] Anemia and fatigue were more likely to be worse after cross-over ($P = 0.015$ and $P = 0.00001$, respectively), but neutropenia was likely to be slightly less severe ($P = 0.002$). The hemoglobin level declined by about 10% during the first 8 weeks after cross-over before stabilizing, consistent with experience during initial 400-mg/d imatinib therapy. All other toxicities did not differ significantly in severity before and after cross-over. Only 17% of patients required a dose reduction 6 months after cross-over. In elderly patients, who are more susceptible to adverse events, gradual dose escalation to 800 mg/d may be advisable. Thus, in GIST patients who progress on imatinib 400 mg/d, crossover from 400 to 800 mg/d is feasible, particularly in patients able to tolerate the standard dose.

4. Benefits of continuing imatinib therapy without interruption in management of advanced GIST

The optimal duration of imatinib therapy in responding patients with advanced GIST is unknown. The BFR14 trial is a prospective multicenter phase 3 study initiated in June 2002 to compare continuous versus interrupted imatinib therapy in patients with advanced or metastatic GIST expressing KIT. [29–31] A total of 338 patients were enrolled from May 2002 to April 2007. In the initial study design, 58 patients free of disease progression after 1 year of imatinib therapy were randomly assigned to continue imatinib 400 mg/d (n = 26) or to stop treatment and then resume it at disease progression (STOP arm) (n = 32). [29] The primary end point was PFS, whereas OS and response to imatinib readministration in the STOP arm were evaluated as secondary end points.

Median PFS as calculated from the date of randomization was significantly longer in the group with continuous imatinib than in those in the STOP arm (18.0 vs 6.1 months, $P < 0.0001$) [31] (Figure 1). In the STOP arm, 1-year PFS was 25% (95% CI: 10–40%) after 1 year of interrupting imatinib therapy. Median PFS was poor in the STOP arm regardless of whether patients did or did not have residual disease at the time of randomization (5.6 and 8.9 months, respectively). In the group that stopped imatinib, treatment was reintroduced after a median of 6.0 months (95% CI: 3.5–9.5 months), and tumor control (either objective response or stable disease) was achieved in 92% of cases. Median survival has not yet been reached, but was not significantly different between continuous imatinib and interrupted therapy ($P = 0.61$) (Figure 2). The trial was terminated prematurely due to the significantly higher rate of progression in the discontinuation arm, and patients in the STOP arm were readministered imatinib.

In an effort to determine whether a longer duration of imatinib therapy affects PFS after discontinuation, a cohort of 50 patients who were progression free after 3 years of therapy were randomly assigned to either continuous or interrupted imatinib therapy. [32] At 11-month median follow-up after randomization, continuous imatinib therapy produced significantly higher 1-year PFS than interrupted therapy. Imatinib

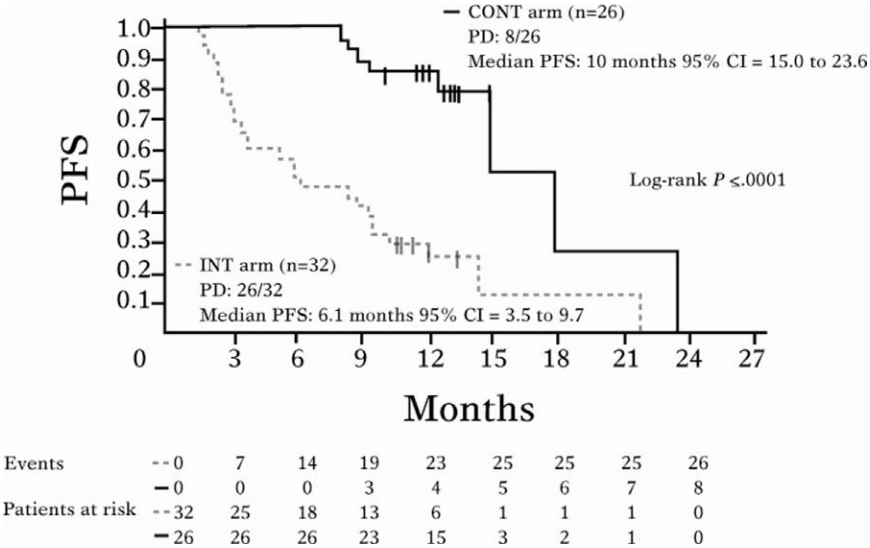

Fig. 1 – Comparison of continuous versus interrupted imatinib therapy on PFS in patients with advanced GIST – 1-year randomization cohort in BFR14 trial. Reproduced with permission from Blay JY, Le Cesne A, Ray-Coquard I, *et al.* Prospective multicentric randomized phase III study of imatinib in patients with advanced gastrointestinal stromal tumors comparing interruption versus continuation of treatment beyond 1 year: the French Sarcoma Group. *J Clin Oncol* 2007;25:1107–13 [31].

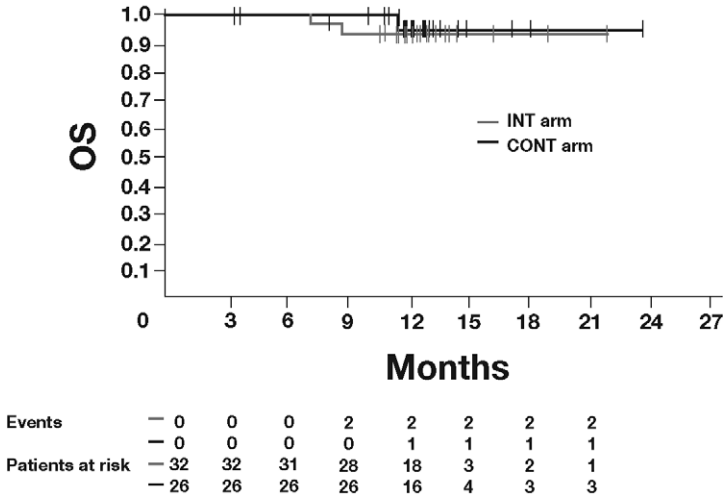

Fig. 2 – Comparison of continuous versus interrupted imatinib therapy on OS in patients with advanced GIST – 1-year randomization cohort in BFR14 trial. Reproduced with permission from Blay JY, Le Cesne A, Ray-Coquard I, *et al.* Prospective multicentric randomized phase III study of imatinib in patients with advanced gastrointestinal stromal tumors comparing interruption versus continuation of treatment beyond 1 year: the French Sarcoma Group. *J Clin Oncol* 2007;25:1107–13 [31].

was restarted in patients in the STOP arm with disease progression, producing responses in all evaluable patients at last follow-up.

The interruption of imatinib in responding patients after 1 or 3 years of therapy resulted in similarly rapid progression of disease. These results indicate that interruption of imatinib in patients achieving clinical benefit results in a high risk of rapid progression of advanced GIST regardless of the pattern of response to imatinib. Interruption leads to a substantial reduction in PFS and cannot be recommended in routine clinical practice. Restarting imatinib at the same 400-mg/d dose at the time of disease progression produces a high rate of tumor control. Although interrupting imatinib profoundly reduces PFS, its impact on OS after 3 years of treatment remains to be determined. A new randomization has been proposed to evaluate patients who do not have progressive disease after 5 years of imatinib therapy.

5. Options in imatinib-intolerant and imatinib-resistant GIST

Although imatinib is the most effective therapy available for patients with advanced GIST, there are some

Table 1 – Management of advanced GIST that progresses during imatinib therapy

- Surgery may be effective, when only one (or few) growing metastasis is detected by computed tomography or MR imaging; such metastases may contain second *KIT* mutation, causing imatinib resistance
- Check for compliance with taking imatinib
- Check for comedication: high (up to 800–1000 mg a day) imatinib doses may be needed when enzyme-inducing antiepileptic drugs are also administered
- About 7% of patients will respond and 30% will have stable disease after imatinib dose escalation from 400 to 800 mg a day
- Sunitinib
- Participation in a clinical trial

patients who may not respond initially, others who may not tolerate the drug, and still others who may respond initially but have disease recurrence that cannot be managed with dose escalation. The fundamental management principles of advanced GIST that has progressed on imatinib are summarized in Table 1.

5.1. *Surgery*

The impact of surgery in patients with advanced GIST who are being treated with imatinib or other tyrosine kinase inhibitors depends on the extent of disease before surgery. This point is illustrated by a study of 69 consecutive patients who underwent surgery for advanced GIST – nearly all of whom were receiving either imatinib or sunitinib.[33] Patients were categorized as having stable disease, limited disease progression, or generalized disease progression based on the extent of disease before surgery. After a median follow-up of 14.6 months, response status was significantly associated with PFS and OS (both $P < 0.0001$): 1-year PFS was 80%, 33%, and 0% in patients with stable disease, limited progression, and generalized progression before surgery, respectively, and 1-year OS was 95%, 86%, and 0%, respectively. Other studies also showed that patients with disease progression on imatinib did not achieve major benefit from surgery.[34–36] Taken together, these studies indicate that during tyrosine kinase inhibitor therapy, surgery has little to offer in the setting of generalized disease progression. However, palliative surgery may benefit selected patients with generalized progression, such as those with bleeding or obstructive metastases. According to the 2007 National Comprehensive Cancer Network (NCCN) practice guidelines, surgery may be carried out in recurrent or metastatic GIST when disease is stable or shrinking on tyrosine kinase inhibitor therapy and complete gross resection is possible, or when isolated clones progress on such therapy after initially responding while other disease sites remain stable.[3,37] Since the benefit of surgery in these patients is not definitive, a randomized study is being planned to address this question.

5.2. *Sunitinib*

Sunitinib is approved worldwide for use in second-line treatment of advanced GISTs,[38] which is based on data from a randomized, double-blind, placebo-controlled, multinational phase 3 study.[39] A total of 312 patients with unresectable, imatinib-resistant GIST were randomly assigned in a 2:1 ratio to sunitinib (50 mg/d for 4 weeks followed by 2 weeks off treatment) or placebo. The study was terminated early when a planned interim analysis showed that sunitinib prolonged median time to tumor progression (primary study end point) relative to placebo (27.3 vs 6.4 weeks; $P < 0.0001$). Similarly, sunitinib prolonged median PFS (24.1 vs 6.0 weeks; $P < 0.0001$), with 16% of patients in the sunitinib group remaining progression free for at least 6 months compared with 1% in the placebo group. Sunitinib produced partial responses as "best reported response during study participation" in 7% and stable disease in 58%, compared with rates of 0% and 48%, respectively, in the placebo group.

Adverse events were noted in both the sunitinib arm and the placebo arm of this trial, reflecting the fact that patients with advanced GIST often are very symptomatic following failure of imatinib. The presence of the placebo data allows rigorous assessment of adverse events due to drug versus those associated with the clinical disease status of the patients. Fatigue was the most common adverse event observed with sunitinib relative to placebo in the phase 3 study (34% vs 22%; grade 3: 5% vs 2%).[39] Other adverse events that occurred more frequently with sunitinib than placebo included diarrhea (29% vs 8%), hand–foot syndrome (14% vs 2%), hypertension (10% vs 2%), neutropenia (51% vs 4%), and thrombocytopenia (40% vs 4%). Hypothyroidism – which commonly manifests and is classified as fatigue – also occurs frequently with sunitinib, particularly after prolonged dosing. In a cohort of 42 GIST patients treated for a median of 47 weeks with sunitinib, 26 (62%) had abnormal serum thyroid stimulating hormone concentrations and 15 (36%) developed persistent, primary hypothyroidism.[40]

Similarly, in a series of renal cell cancer patients treated with sunitinib, 56 of the 66 patients (85%) had one or more abnormality in their thyroid function test results, consistent with hypothyroidism, and 47 of the 56 patients

Table 2 – Investigational agents for GIST

Agent	Mechanism	Phase	Ongoing studies
Nilotinib	KIT and PDGFRα kinases	III	Nilotinib vs best supportive care in patients who failed imatinib and sunitinib (open-label with extension)
Everolimus	mTOR inhibitor	II/III	Everolimus + imatinib in patients progressing on imatinib 400 mg/d
Sorafenib	Multiple kinase inhibitor	II	Sorafenib in patients progressing on imatinib or sunitinib (open-label)
Vatalanib (PTK787/ZK222584)	KIT, PDGFR, and VEGFR-1, -2 and -3 kinases	II	Vatalanib in patients progressing on imatinib or intolerant of imatinib
AZD2171	RTK inhibitor (VEGF)	II	AZD2171 in patients resistant to or intolerant of imatinib using PET responses (open-label)
IPI-504	Hsp90 inhibitor	I	Safety and pharmacokinetics in patients with unresectable or metastatic GIST

Resistance or intolerance to tyrosine kinase inhibitor therapy

Liver and surgical scar metastases are identified in a 34-year-old woman who had had several epithelioid GISTs removed from her stomach 15 years earlier. Mutational analysis does not identify any *KIT* or *PDGFRA* mutations. The patient starts imatinib 400 mg/d in March 2002, resulting in stabilization of the liver metastases and disappearance of the surgical scar metastasis. In June 2005, the imatinib dose is escalated to 600 mg/d due to progression of a liver metastasis, again resulting in disease stabilization. Further dose escalation is needed in May 2006 due to progressive disease, resulting in resolution of ascites and abdominal pain. Both dose escalations are well tolerated. In February 2007, the patient is switched to sunitinib at a dose of 50 mg/d for 4 weeks followed by a 2-week break again due to progressive disease. Consideration is given in August 2007 to switch to third-line therapy due to adverse events (lethargy and mucosal inflammation) as well as evidence of disease progression.

How should a patient be treated who progresses on sunitinib or is intolerant to it?
A variety of experimental agents are being studied in advanced GIST, which may be options within a clinical trial framework (Table 2). These agents may bind to mutated KIT or PDGFRα receptor tyrosine kinases in a different manner from imatinib and sunitinib, may demonstrate greater tissue penetration, or may target other cell signaling pathways, resulting in a potential for response even when administered as third or later line of systemic therapy. Selected patients may benefit from palliative surgery, radiation therapy, or arterial embolization. Anecdotally, rechallenge with imatinib might benefit some patients despite prior progression during imatinib treatment.

(84%) with abnormal thyroid function tests had signs and/or symptoms possibly related to hypothyroidism.[41] The risk of hypothyroidism increased with duration of sunitinib therapy, suggesting that regular surveillance of thyroid function is needed. Sunitinib may also be associated with cardiac adverse events in certain patients.[42] In an effort to better manage the adverse events associated with sunitinib, altered treatment schedules are being explored, including administration of lower doses given continuously on a daily basis rather than according to the currently approved "4 weeks on, 2 weeks off" schedule.

5.3. *Future agents in development: nilotinib*

A variety of new agents are being evaluated for treatment of GIST that has progressed on imatinib, including nilotinib, everolimus, dasatinib, sorafenib, AZD2171, IPI-504, and PTK787/ZK222584 (Table 2).

Nilotinib is a next-generation inhibitor of selected tyrosine kinases, including KIT, PDGFR, and BCR-ABL. Nilotinib achieves 7- to 10-fold higher intracellular concentrations than imatinib in GIST cell lines,[43] inhibits proliferation of imatinib-sensitive GIST cells, and maintains activity in some resistant GIST cell lines.

Nilotinib administered either alone or in combination with imatinib was evaluated in an open-label, multicenter, phase 1 study of patients with unresectable or metastatic GIST who had radiologically confirmed disease progression on imatinib 800 mg/d.[44] PFS was generally comparable in the groups that received nilotinib alone or in combination with imatinib. Nilotinib given alone or in combination with imatinib was generally well tolerated. The safety profile of nilotinib was generally similar in imatinib-resistant compared with imatinib-intolerant patients. The results of this study demonstrate that nilotinib alone or in combination with imatinib has promising activity in imatinib-resistant patients with advanced GIST, including patients who progressed on sunitinib and other tyrosine kinase inhibitors. Nilotinib is currently being compared with best supportive care including the investigator's choice

of treatment in an ongoing open-label, phase 3 study of patients following documented prior progression despite sequential therapy with imatinib and sunitinib.

6. Adjuvant imatinib therapy following surgical removal of localized primary GIST

Surgery is the treatment of choice for patients with localized primary GIST, but disease often recurs even after complete resection with wide margins.[3] Median time to recurrence after complete resection is 1.5–2 years.[3,45,46] Several groups are currently investigating imatinib as adjuvant therapy for the treatment of KIT-expressing primary GIST after surgical resection.

In ACOSOG Z9000, a single-arm, open-label, phase 2, multicenter study, 106 evaluable patients underwent complete gross resection of a KIT-expressing primary GIST that was at high risk of recurrence (tumor size $\geqslant$10 cm, tumor rupture, or <5 peritoneal metastases). Patients received imatinib 400 mg daily for 1 year starting at a median of 59 days (range 25–84) after operation. The primary end point was overall survival.

ACOSOG Z9001 is a phase 3 Intergroup trial of adjuvant imatinib.[47] A total of 708 patients with primary GIST $\geqslant$3 cm and expressing KIT who underwent complete gross resection were randomly assigned to receive imatinib 400 mg/d or placebo for 1 year starting within 84 days of surgery. The primary end point was recurrence-free survival (RFS), and secondary end points were OS and safety. After a median follow-up of 1.2 years, imatinib significantly improved 1-year RFS compared with placebo. The data monitoring committee overseeing the trial recommended that the results from an interim analysis be made public after the study met its primary end point of increasing RFS. Treatment was unblinded at the time of disease recurrence; patients in the placebo group were offered imatinib 400 mg/d.

The evidence of RFS benefit with adjuvant imatinib therapy in ACOSOG Z9001 is supported by a single-center pilot study, in which 23 consecutive patients with high-risk GIST were treated with imatinib for 1 year after surgical resection and compared with historic control of 48 patients from previous population-based series who had undergone surgery alone.[48] After a mean follow-up of more than 3 years in both groups, only 1 of the 23 patients (4%) in the adjuvant imatinib group had disease recurrence compared with 32 of the 48 historic control patients (67%). Similarly, an open-label, single-arm, multicenter phase 2 study conducted by the China Gastrointestinal Cooperative Group was presented at ASCO 2007.[49] Patients with KIT-expressing GIST that was either $\geqslant$5 cm or $\geqslant$5 mitoses per 50 HPF started imatinib 400 mg/d within 4 weeks of complete surgical resection. Preliminary RFS was reported for patients who completed at least 12 months of imatinib. Only 2 relapses were documented among the 51 patients included in the intention-to-treat-analysis.[49] Taken together, these studies suggest that adjuvant imatinib for 1 year prolongs RFS in patients at high risk of recurrent disease and metastases following complete surgical resection of the primary GIST.

Although an early advantage in relapse-free survival has been demonstrated by the ACOSOG Z9001 study, the European Society for Medical Oncology (ESMO) consensus group considered imatinib adjuvant therapy in GIST to be investigational (personal communication, Paolo Casali, MD). "The evidence that was provided by the ACOSOG Z9001 study was very interesting but preliminary", said Dr. Paolo G. Casali, Chair of the ESMO Sarcoma Working Group, "It still remains to be seen whether the improved RFS will translate into a survival benefit." The end point considered by the ESMO Sarcoma Working Group to be most critical in the assessment of the efficacy of adjuvant therapy is OS. RFS and time to secondary resistance are valuable secondary end points. Though many believe that adjuvant therapy is beneficial to patients with high-risk GISTs, longer follow-up is needed to determine the effect of adjuvant imatinib therapy on long-term survival. Identification of patients with high-risk GIST could be carried out by the NIH consensus criteria of Fletcher *et al.*[50] as well as tumor site (small bowel, rectum) on an individualized basis in consultation with the patient.

According to consensus recommendations from the National Institutes of Health (NIH) risk stratification by Fletcher *et al.*,[50] patient prognosis can be stratified into 4 risk groups (very low, low, intermediate, and high) on the basis of tumor size and mitotic count.[50] RFS was associated with risk group in several cohorts with GISTs,[51] and 5-year OS was associated with tumor size in a cohort of 200 GIST patients treated during the pre-imatinib era.[45] Moreover, two large patient series from the Armed Forces Institute of Pathology (AFIP) demonstrated that tumor size and mitotic count predict metastatic potential and outcome of gastric and small intestinal GIST.[52,53] In the AFIP series of 1765 gastric GISTs, 86% of the tumors >10 cm with a mitotic count >5 per 50 HPF metastasized compared with <3% of tumors <10 cm with <5 mitoses per 50 HPF.[53] The metastatic rate of tumors that were either >10 cm with <5 mitoses per 50 HPF, or 2–5 cm with >5 mitoses per 50 HPF differed depending on location: it was relatively low (12–16%) for gastric GIST, but generally much higher (>50%) for small intestinal tumors.[52] Other factors associated with poorer outcomes were coagulative necrosis, ulceration, mucosal invasion, gastric GISTs with a location in the fundus or gastroesophageal junction, and small intestinal GISTs with diffuse nuclear atypia and epithelioid cytology. Because surgery alone may not control high-risk GIST, ongoing trials are exploring whether adjuvant imatinib therapy will improve outcomes in this setting.

To identify the patients with the highest-risk GISTs who would be most suitable for an adjuvant imatinib trial, several groups have developed modifications to the NIH risk stratification consensus criteria.[50] One modification reassigned the risk stratification groups to discern patients with the highest risk of recurrence. The modified criteria combined NIH "very low" and "low" risk into one category, "risk level I," redesignated the intermediate-risk GISTs as "risk level II" and divided the high-risk into "risk level III" and "risk level IV". Patients who fall in the risk level IV category have the highest risk of recurrence and should be the top priority for genetic analysis to assess the suitability of postoperative adjuvant imatinib therapy.[54] At the 2007 Gastrointestinal Cancers Symposium, Gold and colleagues presented a graphical calculating device that they developed to predict recurrence after resection of primary gastrointestinal stromal tumor (GIST) without adjuvant treatment.[55] They found that the system was more predictive of recurrence than tumor size and mitotic index alone. Another variation was to expand the prognostic factors for recurrence risk. Takahashi *et al.* discovered that in addition to the standard tumor size and mitotic rate, disease-free survival was also affected by peritoneal dissemination, metastasis, invasion, and tumor rupture. Patients with at least one of these factors had an unfavorable outcome and were therefore potential candidates for adjuvant therapy. This modified Fletcher's system could distinguish patients that are potential candidates for adjuvant therapy from those who require no therapy other than surgery.[56]

Several other studies analyzing the utility of adjuvant imatinib are currently underway.[3] The Scandinavian/German (SSG XVIII/AIO) Trial of Adjuvant Imatinib is an open-label, randomized, prospective, multicenter study of short-duration (1 year) versus long-duration (3 years) adjuvant imatinib in patients with surgically removed GIST and high-risk status (i.e., tumor size >10 cm; mitotic count >10 per 50 HPF; or tumor size >5 cm and mitotic count >5 per 50 HPF).[57] The primary end point is RFS, with OS, GIST-specific survival, and safety as secondary end points. Approximately 345 patients are planned to participate. EORTC 62024 is an open-label, randomized, prospective, multicenter trial of adjuvant imatinib for 24 months versus no treatment in intermediate- and high-risk patients with completely resected KIT-positive GIST.[58] This trial is planned to include 760 patients and will evaluate OS as the primary end point, with RFS and safety as secondary end points.

Imatinib is also currently under clinical investigation for use in the neoadjuvant setting for patients with large primary tumors. Neoadjuvant imatinib may offer several benefits. Particularly in cases of rectal GISTs, neoadjuvant imatinib may improve the operability of unresectable or marginally resectable GISTs to enable less extensive surgical resections and preserve organs. Neoadjuvant treatment with imatinib may reduce surgery-related morbidity and blood loss and may provide treatment of any undetectable metastases. The study RTOG-S-0132, now closed, is an open-label, multicenter, phase 2 study of neoadjuvant imatinib therapy in patients with potentially resectable primary tumors $\geqslant$5 cm or potentially resectable recurrent or metastatic tumors $\geqslant$2 cm (N = 63).[59] Patients received neoadjuvant imatinib 600 mg/d for up to 10 weeks, and following restaging, surgical candidates underwent complete resection followed by adjuvant imatinib 600 mg/d for 2 years. Key end points include PFS, response rate, and safety during neoadjuvant therapy and RFS during postoperative therapy. Phase 2 studies addressing preoperative neoadjuvant administration of imatinib as treatment of locally advanced GIST are also being conducted in Canada and Germany.

7. Updates on clinical practice guidelines/recommendations

7.1. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines

A task force composed of NCCN faculty and other key experts from the USA, Europe, and Australia met in December 2006 to update and expand existing NCCN guidelines for GIST.[3] The updated practice guidelines recognize imatinib as the standard of care for first-line management of recurrent or metastatic GIST (Table 3).

In this setting, imatinib should be administered at an initial dose of 400 mg/d. This dose was recommended by the task force, because higher doses have not consistently shown a major difference in overall survival but carry a higher risk of severe toxicity. If molecular diagnosis is available demonstrating the presence of *KIT* exon 9 mutations, NCCN guidelines support the use of imatinib at 800 mg/d as a category 2B recommendation pending the full analyses of the MetaGIST project, which were not available at the time the task force met. As reported at ASCO 2007, the pooled MetaGIST analyses demonstrated that imatinib 800 mg/d produced significantly longer PFS than 400 mg/d in patients with *KIT* exon 9 mutations, though OS was not extended at the time of analysis.[26]

The NCCN guidelines indicate that dose escalation may be appropriate for patients started on imatinib 400 mg/d who have disease progression confirmed by appropriate imaging studies, but only if it occurs after more than 2 months of imatinib therapy.[3] For patients with limited disease progression, several options are offered: continuing imatinib at the same dose, increasing the dose of imatinib, or switching to sunitinib. Before changing the imatinib dose or switching to sunitinib, compliance to imatinib therapy should be assessed and confirmed. Surgery may be indicated for isolated metastases progressing on tyrosine kinase inhibitor therapy

Neoadjuvant imatinib for primary GIST

A 60-year-old man has pain in the left arm and shoulder while on a business trip in November 2006, and 10 days later he falls unconscious. He is found to have black stools and a blood hemoglobin level of 6.6 g/dL. Gastroscopy reveals a 10-cm gastric tumor, which is confirmed as GIST by needle biopsy. On immunohistochemistry, the tumor stains strongly for KIT (+++) and is also positive for the Bcl-2 oncogene and vimentin, but negative for desmin and S-100. Approximately 25% of the nuclei stain positive for Ki-67. The performance status of the patient is good (World Health Organization [WHO] performance status [PS] 1).

Should this patient be treated with imatinib prior to surgical resection?
Evidence supporting neoadjuvant imatinib is based on several case reports. [60,61] A 68-year-old woman with multiple local recurrences of a rectal GIST presented with 4 adjacent masses in the retrovaginal septum and no distant metastases. [61] The patient was treated with imatinib 400 mg/d in order to avoid a permanent colostomy. Imatinib reduced the total tumor mass by 83% over a 12-month period, thereby allowing complete surgical resection by coloanal anastamosis. No KIT-immunostaining cells were found on histopathologic examination of the excised tumor. In another case study, a 57-year-old man with a large primary GIST extending from pelvis to diaphragm rapidly responded to imatinib and continued to have rapid tumor shrinkage and symptomatic relief over the course of 6 months. [60] The tumor then began to enlarge, but appeared to consist mostly of fluid. The patient then underwent surgery, with evacuation of intratumoral fluid facilitating surgical resection of a compressed tumor mass.

Should adjuvant therapy be continued after surgical resection?
The answer to this question is not yet known. The first patient continued imatinib therapy for 2 years and remained free of disease recurrence. The second patient was instructed to continue imatinib but failed to do so, presenting 2 months later with rapidly progressive disease. The patient was restarted on imatinib 800 mg/d, resulting in definite regression of the liver metastases. After additional surgery, the patient remained recurrence free on continued imatinib therapy.

Table 3 – Summary of recent updates of NCCN practice guidelines and recommendations in GIST [3]

Unresectable or metastatic GIST	
First-line therapy	*Imatinib*
Starting dose	400 mg/d
KIT exon 9 patients	800 mg/d [a]
Options on limited progression	Continue imatinib dose Escalate imatinib dose Surgery Switch to sunitinib
Options on generalized progression	Escalate imatinib dose Switch to sunitinib
Options on progression on sunitinib	Investigational agent in clinical trial
Primary localized GIST	
First-line therapy	*Surgery*
Adjuvant imatinib	No specific recommendation
Neoadjuvant imatinib	Physician discretion; evaluate for surgery at each imaging assessment

[a] Some NCCN task force members recommended imatinib 800 mg/d pending results of MetaGIST.

after initial response. [3] For patients with generalized progression who have reasonable performance status (WHO PS 0–2), the imatinib dose can be increased as tolerated or the patient switched to sunitinib. In general, patients should remain on tyrosine kinase inhibitors for as long as possible until they no longer receive any clinical benefit. For patients who become resistant to imatinib and sunitinib, consideration should be given to enrolling in a clinical trial testing novel approaches to controlling GIST.

The guidelines consider neoadjuvant imatinib as "a matter of surgical and medical discretion". Many very

large GISTs are considered unresectable due to risk of unacceptable morbidity, and therefore imatinib may be used in first-line therapy until the tumor becomes resectable and the risk of surgical morbidity becomes acceptable. In this setting, neoadjuvant imatinib may need to be administered for as long as 6–12 months. At each imaging assessment, patients should be reevaluated regarding their candidacy for surgery, because it may not always be necessary to wait until a maximal response to neoadjuvant therapy has been reached.

No specific recommendations are made in NCCN guidelines regarding adjuvant imatinib therapy.[3] The guidelines recognize that "although no data support the adjuvant use of imatinib in primary completely resected GIST, some physicians administer adjuvant imatinib outside of a clinical trial".

7.2. ESMO, Canadian, and Japanese recommendations

The European Society of Medical Oncology (ESMO) held a consensus meeting on the clinical management of GIST in Lugano, Switzerland, on October 20, 2007. The objectives of this international consensus meeting were to describe the optimal management procedures for patients with GIST in localized and advanced stages and to discuss future research issues. The consensus statement is expected to be published in early 2008. Publication of the Canadian guidelines and the Japanese recommendations for the treatment of GIST is also planned for early 2008.

8. Conclusions

New clinical results and long-term analyses of very mature data and clinical experience continue to illustrate the importance of molecular targeted therapy with tyrosine kinase inhibitors in the management of GIST. A recent analysis of the extension study of B2222 demonstrated that the efficacy of imatinib is maintained during long-term treatment of patients with unresectable or metastatic GIST.[23] Imatinib produced objective responses in 68% of patients and clinical benefit in 84%. This response rate is higher than initially reported, as 25% of the patients responded to imatinib after 5.3–39 months of therapy. Median OS was 57 months, which appears at least 3 times longer than the survival rates seen for this population in the pre-imatinib era. Five-year survival rates were significantly higher for patients with objective responses or stable disease than for those who had initial disease progression (55% vs 9%). Thus, imatinib controls advanced GIST for more than 5 years in a significant proportion of patients.

The MetaGIST project demonstrates that high-dose imatinib (800 mg/d) compared with standard-dose imatinib (400 mg/d) prolongs PFS in patients with *KIT* exon 9 mutations, although OS is not significantly improved.[26] These results provide a rationale for administering imatinib at 800 mg/d in the subset of GIST patients with *KIT* exon 9 mutations. The initial imatinib dose of 400 mg/d remains a very reasonable starting dose for all other subtypes of GIST patients. Although the optimal duration of imatinib therapy in advanced GIST remains unknown, the BFR14 trial demonstrates that interrupting imatinib is associated with an unacceptably high risk of rapid disease progression.[32]

For patients with imatinib-intolerant or imatinib-resistant GIST, several options are available. Surgery may benefit selected patients who have bleeding or obstructing metastases, but otherwise it cannot be recommended for patients with generalized progression of GIST.[33] Surgery may be an option for patients with stable disease or limited disease progression whose tumors can be resected. Sunitinib is an option for second-line treatment once all options with imatinib have been exhausted,[38,39] or alternatively, a variety of investigational agents may be considered within the framework of a clinical trial.

Patients whose primary GIST can be completely resected are at risk of disease recurrence and metastasis depending on the tumor size, mitotic count, and possibly other factors. Initial results from ACOSOG Z9001 indicate that adjuvant imatinib therapy for 1 year prolongs RFS following surgical resection of KIT-expressing localized primary GIST tumors at least 3 cm in maximal dimension.[47] Ongoing studies are exploring whether a longer duration of adjuvant imatinib will further improve RFS in high-risk patients and whether adjuvant therapy will also prolong OS in intermediate- and high-risk patients. Several case reports indicate that neoadjuvant imatinib may be an option for patients with very large GIST that may initially be unresectable.[60,61] The value of neoadjuvant imatinib is also currently being explored in prospective clinical trials.

Recent updates to clinical practice guidelines/recommendations incorporate some of these new findings, recognizing the need for continuous, long-term imatinib therapy in advanced disease, the potential value of high-dose imatinib in patients with *KIT* exon 9 mutations, and potential value of adjuvant imatinib in higher-risk patients.[3] The availability of new clinical information about imatinib and the development of new targeted therapies offer the promise to further extend survival of patients with GIST.

Acknowledgements

Dr. George Demetri has received research funds from the following sources: The Virginia and Daniel K. Ludwig Trust for Cancer Research, the Rubenstein Foundation, the Katz Foundation, the Quick Family Fund for Cancer

Research, the Stutman GIST Cancer Research Fund, Paul's Posse and Leslie's Links.

Prof. Heikki Joensuu has received research funds from the Academy of Finland, Cancer Society of Finland, Sigrid Juselius Foundation, and Helsinki University Research Funds.

Financial disclosure statements

Dr. George Demetri has disclosed working as a consultant for, has received research funding from, and has provided uncompensated expert testimony for Novartis, Pfizer, and Infinity. He has also received honoraria from Novartis and Pfizer.

Prof. Heikki Joensuu has disclosed receiving honoraria from and has served as a speaker and advisory board member for Novartis.

References

1. Blackstein ME, Blay JY, Corless C, *et al.* Gastrointestinal stromal tumours: consensus statement on diagnosis and treatment. *Can J Gastroenterol* 2006;20:157–63.
2. Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. *J Clin Oncol* 2004;22:3813–25.
3. Demetri GD, Benjamin RS, Blanke CD, *et al.* NCCN Task Force Report: Management of patients with gastrointestinal stromal tumor (GIST) – update of the NCCN Clinical Practice Guidelines. *J Natl Compr Canc Netw* 2007;5(Suppl 2):S1–29.
4. Steigen SE, Eide TJ. Trends in incidence and survival of mesenchymal neoplasm of the digestive tract within a defined population of northern Norway. *Apmis* 2006;114: 192–200.
5. Goettsch WG, Bos SD, Breekveldt-Postma N, Casparie M, Herings RM, Hogendoorn PC. Incidence of gastrointestinal stromal tumours is underestimated: results of a nation-wide study. *Eur J Cancer* 2005;41:2868–72.
6. Nilsson B, Bumming P, Meis-Kindblom JM, *et al.* Gastrointestinal stromal tumors: The incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era. *Cancer* 2005;103:821–9.
7. Rubio J, Marcos-Gragera R, Ortiz MR, *et al.* Population-based incidence and survival of gastrointestinal stromal tumours (GIST) in Girona, Spain. *Eur J Cancer* 2007;43:144–8.
8. Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1458 cases from 1992 to 2000. *Am J Gastroenterol* 2005;100:162–8.
9. Tryggvason G, Gislason HG, Magnusson MK, Jonasson JG. Gastrointestinal stromal tumors in Iceland, 1990–2003: the Icelandic GIST study, a population-based incidence and pathologic risk stratification study. *Int J Cancer* 2005;117:289–93.
10. Agaimy A, Wunsch PH, Hofstaedter F, *et al.* Minute gastric sclerosing stromal tumors (GIST tumorlets) are common in adults and frequently show c-KIT mutations. *Am J Surg Pathol* 2007;31:113–20.
11. Kawanowa K, Sakuma Y, Sakurai S, *et al.* High incidence of microscopic gastrointestinal stromal tumors in the stomach. *Hum Pathol* 2006;37:1527–35.
12. Yuzawa S, Opatowsky Y, Zhang Z, Mandiyan V, Lax I, Schlessinger J. Structural basis for activation of the receptor tyrosine kinase KIT by stem cell factor. *Cell* 2007;130:323–34.
13. Heinrich MC, Corless CL, Duensing A, *et al.* PDGFRA activating mutations in gastrointestinal stromal tumors. *Science* 2003;299:708–10.
14. Buchdunger E, Cioffi CL, Law N, *et al.* Abl protein-tyrosine kinase inhibitor STI571 inhibits in vitro signal transduction mediated by c-kit and platelet-derived growth factor receptors. *J Pharmacol Exp Ther* 2000;295:139–45.
15. Heinrich MC, Griffith DJ, Druker BJ, Wait CL, Ott KA, Zigler AJ. Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor. *Blood* 2000;96:925–32.
16. Edmonson JH, Marks RS, Buckner JC, Mahoney MR. Contrast of response to dacarbazine, mitomycin, doxorubicin, and cisplatin (DMAP) plus GM-CSF between patients with advanced malignant gastrointestinal stromal tumors and patients with other advanced leiomyosarcomas. *Cancer Invest* 2002;20:605–12.
17. Ryan DP, Puchalski T, Supko JG, *et al.* A phase II and pharmacokinetic study of ecteinascidin 743 in patients with gastrointestinal stromal tumors. *Oncologist* 2002;7:531–8.
18. Gold JS, van der Zwan SM, Gonen M, *et al.* Outcome of metastatic GIST in the era before tyrosine kinase inhibitors. *Ann Surg Oncol* 2007;14:134–42.
19. Joensuu H, Roberts PJ, Sarlomo-Rikala M, *et al.* Effect of the tyrosine kinase inhibitor STI571 in a patient with metastatic gastrointestinal stromal tumor. *N Engl J Med* 2001;344:1052–6.
20. Demetri GD, von Mehren M, Blanke CD, *et al.* Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2002;347:472–80.
21. Verweij J, van Oosterom A, Blay J-Y, *et al.* Imatinib mesylate (STI-571 Glivec®, Gleevec) is an active agent for gastrointestinal stromal tumours, but does not yield responses in other soft-tissue sarcomas that are unselected for a molecular target. Results from an EORTC Soft Tissue and Bone Sarcoma Group phase II study. *Eur J Cancer* 2003;39:2006–11.
22. Rankin C, Von Mehren M, Blanke C, *et al.* Dose effect of imatinib (IM) in patients (pts) with metastatic GIST – Phase III Sarcoma Group Study S0033 [ASCO abstract 9005]. *Proc Am Soc Clin Oncol* 2004;22:815.
23. Blanke CD, Demetri GD, Von Mehren M, *et al.* Long-term results from a randomized phase II trial of standard versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. *J Clin Oncol*, in press.
24. van Oosterom AT, Judson I, Verweij J, *et al.* Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. *Lancet* 2001;358:1421–3.
25. Verweij J, Casali PG, Zalcberg J, *et al.* Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet* 2004;364:1127–34.

26. Van Glabbeke M, Owzar K, Rankin CJ, Simes J, Crowley J; GIST Meta-analysis Group (MetaGIST). Comparison of two doses of imatinib for the treatment of gastrointestinal stromal tumors (GIST): a meta-analysis based on 1,640 patients (pts) [ASCO abstract 10004]. *J Clin Oncol* 2007;25(18S):546s.
27. Zalcberg JR, Verweij J, Casali PG, *et al.* Outcome of patients with advanced gastro-intestinal stromal tumours crossing over to a daily imatinib dose of 800 mg after progression on 400 mg. *Eur J Cancer* 2005;41:1751–7.
28. Debiec-Rychter M, Sciot R, Le Cesne A, *et al.* KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. *Eur J Cancer* 2006;42:1093–103.
29. Blay J-Y, Berthaud P, Perol D, *et al.* Continuous vs intermittent imatinib treatment in advanced GIST after one year: a prospective randomized phase III trial of the French Sarcoma Group [ASCO abstract 9006]. *Proc Am Soc Clin Oncol* 2004;23:815.
30. Rios M, Lecesne A, Bui B, *et al.* Interruption of imatinib (IM) in GIST patients with advanced disease after one year of treatment: updated results of the prospective French Sarcoma randomized phase III trial on long term survival [ASCO abstract 10016]. *J Clin Oncol* 2007;25(18S):549s.
31. Blay JY, Le Cesne A, Ray-Coquard I, *et al.* Prospective multicentric randomized phase III study of imatinib in patients with advanced gastrointestinal stromal tumors comparing interruption versus continuation of treatment beyond 1 year: The French Sarcoma Group. *J Clin Oncol* 2007;25:1107–13.
32. Le Cesne A, Ray-Coquard I, Bui B, *et al.* Continuous versus interruption of imatinib (IM) in responding patients with advanced GIST after 3 years of treatment: A prospective randomized phase III trial of the French Sarcoma Group [ASCO abstract 10005]. *J Clin Oncol* 2007;25(18S):546s.
33. Raut CP, Posner M, Desai J, *et al.* Surgical management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitors. *J Clin Oncol* 2006;24:2325–31.
34. Bonvalot S, Eldweny H, Pechoux CL, *et al.* Impact of surgery on advanced gastrointestinal stromal tumors (GIST) in the imatinib era. *Ann Surg Oncol* 2006;13:1596–603.
35. Gronchi A, Fiore M, Bertulli R, *et al.* Surgery of residual disease following imatinib mesylate in advanced gastrointestinal stromal tumors (GIST) [ASCO abstract 9038]. *J Clin Oncol* 2005;23:825s.
36. Rutkowski P, Nowecki Z, Nyckowski P, *et al.* Surgical treatment of patients with initially inoperable and/or metastatic gastrointestinal stromal tumors (GIST) during therapy with imatinib mesylate. *J Surg Oncol* 2006;93:304–11.
37. Desai J, Shankar S, Heinrich MC, *et al.* Clonal evolution of resistance to imatinib in patients with metastatic gastrointestinal stromal tumors. *Clin Cancer Res* 2007;13: 5398–405.
38. Goodman VL, Rock EP, Dagher R, *et al.* Approval summary: sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma. *Clin Cancer Res* 2007;13:1367–73.
39. Demetri GD, van Oosterom AT, Garrett CR, *et al.* Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet* 2006;368:1329–38.
40. Desai J, Yassa L, Marqusee E, *et al.* Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. *Ann Intern Med* 2006;145:660–4.
41. Rini BI, Tamaskar I, Shaheen P, *et al.* Hypothyroidism in patients with metastatic renal cell carcinoma treated with sunitinib. *J Natl Cancer Inst* 2007;99:81–3.
42. Schmidinger M, Vogl UM, Schukro C, *et al.* Cardiac involvement in patients with sorafenib or sunitinib treatment for metastatic renal cell carcinoma [ASCO abstract 5110]. *J Clin Oncol* 2007;25(18S):262s.
43. Prenen H, Guetens G, de Boeck G, *et al.* Cellular uptake of the tyrosine kinase inhibitors imatinib and AMN107 in gastrointestinal stromal tumor cell lines. *Pharmacology* 2006;77:11–6.
44. Von Mehren M, Reichardt P, Casali P, *et al.* A phase I study of nilotinib alone and in combination with imatinib (IM) in patients (pts) with imatinib-resistant gastrointestinal stromal tumors (GIST) – study update [ASCO abstract 10023]. *J Clin Oncol* 2007;25(18S):550s.
45. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg* 2000;231:51–8.
46. Ng EH, Pollock RE, Romsdahl MM. Prognostic implications of patterns of failure for gastrointestinal leiomyosarcomas. *Cancer* 1992;69:1334–41.
47. DeMatteo R, Owzar K, Maki R, *et al.*, and the American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant GIST Study Team. Adjuvant imatinib mesylate increases recurrence free survival (RFS) in patients with completely resected localized primary gastrointestinal stromal tumor (GIST): North American Intergroup Phase III trial ACOSOG Z9001 [ASCO abstract 10079]. In: 43rd Annual Meeting of the American Society of Clinical Oncology June 1–5, 2007; Chicago, IL.
48. Nilsson B, Sjolund K, Kindblom LG, *et al.* Adjuvant imatinib treatment improves recurrence-free survival in patients with high-risk gastrointestinal stromal tumours (GIST). *Br J Cancer* 2007;96:1656–8.
49. Zhan WH, China Gastrointestinal Cooperative Group. Efficacy and safety of adjuvant post-surgical therapy with imatinib in patients with high risk of relapsing GIST [ASCO abstract 10045]. *J Clin Oncol* 2007;25(18S): 556s.
50. Fletcher CDM, Berman JJ, Gorstein F, *et al.* Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Hum Pathol* 2002;33:459–65.
51. Singer S, Rubin BP, Lux ML, *et al.* Prognostic value of KIT mutation type, mitotic activity, and histologic subtype in gastrointestinal stromal tumors. *J Clin Oncol* 2002;20: 3898–905.
52. Miettinen M, Makhlouf H, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. *Am J Surg Pathol* 2006;30:477–89.
53. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. *Am J Surg Pathol* 2005;29:52–68.
54. Huang HY, Li CF, Huang WW, *et al.* A modification of NIH consensus criteria to better distinguish the highly

lethal subset of primary localized gastrointestinal stromal tumors: a subdivision of the original high-risk group on the basis of outcome. *Surgery* 2007;141:748–56.
55. Gold JS, Gönen MI, Maki RG, *et al*. A nomogram to predict recurrence after resection of primary gastrointestinal stromal tumor (GIST) [abstract 55]. In: Gastrointestinal Cancers Symposium; January 19–21, 2007; Orlando, FL.
56. Takahashi T, Nakajima K, Nishitani A, *et al*. An enhanced risk-group stratification system for more practical prognostication of clinically malignant gastrointestinal stromal tumors. *Int J Clin Oncol* 2007;12:369–74.
57. Scandinavian Sarcoma Group. Study comparing 12 months versus 36 months of imatinib in the treatment of gastrointestinal stromal tumor (GIST). SSGXVIII/AIO. http://www.clinicaltrials.gov/ct/show/NCT00116935?order=1. Accessed October 25, 2007.
58. European Organization for Research and Treatment of Cancer. Imatinib mesylate or observation only in treating patients who have undergone surgery for localized gastrointestinal stromal tumor. EORTC-62024. http://www.clinicaltrials.gov/ct/show/NCT00103168?order=1. Accessed October 25, 2007.
59. RTOG S-0132 protocol. A phase II trial of neoadjuvant/adjuvant STI-571 (Gleevec NSC #716051) for primary and recurrent operable malignant GIST expressing the KIT receptor tyrosine kinase (CD117). www.rtog.org/members/protocols/s0132/s0132.pdf. Accessed October 3, 2007.
60. Benjamin RS, Blanke CD, Blay JY, Bonvalot S, Eisenberg B. Management of gastrointestinal stromal tumors in the imatinib era: selected case studies. *Oncologist* 2006; 11:9–20.
61. Salazar M, Barata A, Andre S, *et al*. First report of a complete pathological response of a pelvic GIST treated with imatinib as neoadjuvant therapy. *Gut* 2006;55:585–6.