Perspective on Updated Treatment Guidelines for Patients With Gastrointestinal Stromal Tumors

Jean-Yves Blay, MD, PhD¹; Margaret von Mehren, MD²; and Martin E. Blackstein, MD, PhD³

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract and present predominantly in middle-aged and older individuals. Historically, the outlook for patients with GISTs was very poor because of the general lack of efficacy of conventional chemotherapy and the often limited surgical options. However, the recognition of the role of mutations of the v-kit Hardy/Zuckerman 4 feline sarcoma viral oncogene homolog *KIT* and the platelet derived growth factor receptor alpha gene *PDGFRα* in the development of GISTs led to the evaluation of potential antitumor effects of the tyrosine kinase inhibitors imatinib and, more recently, sunitinib. Consequently, these molecularly targeted therapies were introduced into clinical practice, and the outcome for patients with GISTs improved considerably. In the last few years, the European Society of Medical Oncology, the National Comprehensive Cancer Network, and the Canadian Advisory Committee on GIST each published a major set of guidelines or practice recommendations for the management of patients with GIST. In the current review, the latest recommendations from each organization are summarized in terms of diagnosis and risk assessment, tumor staging, surgical and/or drug treatment of primary resectable and recurrent metastatic disease, and patient follow-up and assessment. In addition, areas of consensus and points of divergence among the guidelines are highlighted along with any unresolved issues. *Cancer* 2010;116:5126–37. © 2010 American Cancer Society

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Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract and have characteristic histologic features with either spindle cell, epithelioid, or occasionally pleomorphic mesenchymal morphology.^{1–3} GISTs also share phenotypic characteristics with the intestinal pacemaker cells, known as interstitial cells of Cajal (ICCs), and are thought to arise from a common cell precursor.⁴ Immunohistochemical analysis has demonstrated that nearly all GISTs (~95%) express v-kit Hardy/Zuckerman 4 feline sarcoma viral oncogene homolog (KIT) protein (cluster of differentiation 117 [CD117]), a transmembrane tyrosine kinase receptor for stem cell factor.^{1,5} Other markers identified on immunohistochemistry include “discovered on GIST 1” (DOG1) (present in 87% of GISTs), protein kinase C theta (~80%), CD34 (60%-70%), and smooth muscle actin (30%-40%). Some GISTs, although a far lower proportion, also demonstrate immunopositivity for S-100 protein (5%), desmin (1%-2%), and keratin (1%-2%).^{1,5–8} The characteristic immunohistochemical profile of GISTs also can be used to differentiate them from smooth muscle tumors (ie, true leiomyomas and leiomyosarcomas) and schwannomas.^{1,5–7}

Although GISTs are relatively rare tumors, reporting has increased dramatically since the early 1990s as a result of increased awareness of this tumor type, thus leading to appropriate pathologic diagnoses. In an analysis of the National Cancer Institute’s Surveillance Epidemiology and End Results (SEER) registry, Tran and colleagues identified 1458 patients with GIST who were diagnosed between 1992 and 2000 in the United States and reported an age-adjusted yearly incidence rate of 0.68 per 100,000 population.⁹ Population-based studies in other Western countries, including Iceland and Sweden, have reported an annual incidence of GISTs of approximately 1.1 to 1.5 per 100,000 population.^{10,11}

In recent years, several organizations, including the European Society for Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN), and the Canadian Advisory Committee on GISTs, have published guidelines

Corresponding author: Jean-Yves Blay, MD, PhD, Centre Leon Berard, 28, rue Laennec, 69008 Lyon France; Fax: (011) 33478782757; blay@lyon.fnclcc.fr

¹Leon Berard Center, Claude Bernard University, Lyon, France; ²Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania; ³The Mount Sinai and Princess Margaret Hospitals, University of Toronto, Toronto, Ontario, Canada

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or practice recommendations for the management of patients with GISTs.^{1,12-14} In addition, other guidelines have been developed with the goal of providing recommendations for GIST management in specific countries (ie, Switzerland and Japan).^{15,16} In the current review, we provide a summary of the latest recommendations from ESMO, NCCN, and the Canadian Advisory Committee on GISTs and identify areas of consensus, points of divergence, and unresolved issues.

Disease Background

Characterization of the causal molecular event responsible for the neoplastic transformation that results in GISTs was made possible by the identification of gain-of-function mutations in the *KIT* proto-oncogene in 1998.¹⁷ *KIT* encodes the KIT protein, which serves as the transmembrane receptor for stem cell factor. Similar but mutually exclusive mutations also were identified subsequently in the platelet-derived growth factor receptor α (*PDGFR α*) gene in a small subset of GISTs.¹⁸ Mutations in *KIT* and *PDGFR α* are associated with specific clinicopathologic phenotypes. For example, GISTs with *KIT* exon 9 mutations, which are present in approximately 10% to 15% of patients with GIST, frequently are located in the small bowel, whereas *PDGFR α* -mutations (approximately 5% of GISTs) are more common in epithelioid gastric GISTs.^{8,19} However, not all GISTs harbor mutations of the *KIT* and *PDGFR α* genes, and approximately 10% to 15% of GISTs lack such mutations.^{8,20}

Notably, mutations in *KIT* or *PDGFR α* cause constitutive activation of the tyrosine kinase activity of the KIT and PDGFR α receptors, respectively.¹⁸ Recognition of the importance of *KIT* and *PDGFR α* mutations in the development of GISTs subsequently led to the rationally based evaluation of the potential antitumor effect of imatinib, a tyrosine kinase inhibitor (TKI) with activity against KIT receptors and PDGFR α as well as the breakpoint cluster region/v-abl Abelson murine leukemia viral oncogene homolog (bcr/abl).²¹

Clinical Presentation

GISTs occur predominantly in middle-aged and older individuals and rarely in individuals aged <40 years.²² In an analysis of SEER registry data, the mean age at diagnosis of GIST was 63 years, and it was 66 to 69 years in 2 European population-based studies.⁹⁻¹¹ GISTs occur with similar frequency in men and women, although some studies suggest a slight predominance among men.^{3,23,24} GISTs commonly present in the stomach

(40%-60%) and small intestine (30%-35%) and present less frequently in the colon/rectum (5%-16%) and esophagus ($\leq 1\%$).^{2,3,8,23} In patients who have germline KIT mutations, multifocal proliferations of benign, KIT-positive ICC cells are common. These growths most likely represent the earliest stage of GIST development.

Diagnosis

According to the ESMO, NCCN, and Canadian guidelines, the accurate diagnosis of GIST should be based on tumor morphology and immunohistochemistry (Table 1).^{1,12-14} Therefore, biopsy or surgical excision of a nodule is needed for pathologic analysis.

The NCCN and ESMO guidelines indicate that nodules ≥ 2 cm should be excised and biopsied, whereas the Canadian guidelines indicate that even small GISTs <1 cm should be excised because of the risk of metastasis.^{1,12,13} The NCCN guidelines do state that the 2/cm cutoff is somewhat arbitrary, although reasonable, and suggest that the proper management of small GISTs (<2 cm) discovered incidentally remains controversial.¹

For smaller nodules (≤ 2 cm), the ESMO recognizes that biopsy is difficult and recommends endoscopic ultrasound and then follow-up, reserving excision only for esophageal, gastric, and duodenal nodules that increase in size. Conversely, the standard approach to nodules >2 cm is biopsy/excision. Rectal nodules should be excised regardless of size. When endoscopic assessment is not possible, excision is the standard approach.¹³ If metastatic disease is obvious at presentation, then a biopsy of a metastatic focus may be sufficient for diagnostic purposes, although resection of the primary tumor may be recommended for the prevention of complications or for the palliation of symptoms.¹³

The Canadian guidelines provide more specific recommendations regarding pathologic assessment than the other guidelines, advising descriptive inclusion of tumor morphology, cellularity, degree of cytologic atypia, and tumor size and features of aggressiveness, including necrosis, invasiveness, marginal status, and mitotic index.¹²

An immunohistochemical panel that includes KIT, CD34, smooth muscle actin, S-100 protein, desmin, and vimentin also is recommended; however, specific recommendations for immunohistochemistry are not listed in the ESMO or NCCN guidelines.^{1,12-14} Although most GISTs are KIT-positive, a small percentage ($\sim 5\%$) are KIT-negative. In such patients and in patients with an unclear diagnosis, each set of guidelines recommends

Table 1. Table 1. Comparison of Recommendations for the Diagnosis, Staging, and Risk Assessment of Gastrointestinal Stromal Tumors According to the European Society for Medical Oncology, the National Comprehensive Cancer Network, and the Canadian Advisory Committee on Gastrointestinal Stromal Tumors Guidelines

Variable	ESMO (Casali 2009 ¹³)	NCCN (NCCN 2009 ¹⁴)	Canadian (Blackstein 2006 ¹²)
Diagnosis: Biopsy	Excise and biopsy all nodules >2 cm; recognize that biopsy is difficult for nodules ≤2 cm and recommend endoscopic ultrasound with follow-up (reserve excision only for esophageal, gastric, and duodenal nodules that increase in size but excise all rectal nodules regardless of size); excision should be standard approach when endoscopic ultrasound not appropriate	Excise and biopsy all nodules ≥2 cm	Excise and biopsy all nodules, including those <1 cm; include description of tumor morphology, cellularity, degree of cytologic atypia, tumor size, and features of aggressiveness, including necrosis, invasiveness, marginal status, and mitotic index
Diagnosis: Immunohistochemistry	No specific recommendations; mutational analysis for KIT-negative GIST	No specific recommendations; mutational analysis for KIT-negative GIST	Immunohistochemical panel comprising KIT, CD34, smooth muscle actin, S-100 protein, desmin, and vimentin; mutational analysis for KIT-negative GIST
Staging: Risk factors	Tumor size, mitotic count, and tumor site; no mention of mutational status	Tumor size, mitotic count, and tumor site; no mention of mutational status	Tumor size and mitotic count only; no mention of mutational status
Staging: Imaging	Contrast-enhanced CT of pelvis and abdomen; MRI as an alternative and preferred for rectal GISTs	Contrast-enhanced CT and occasionally MRI (recognize value of FDG-PET/CT)	Combination of CT and PET scanning (CT scanning for small tumors found incidentally)

ESMO indicates European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; KIT, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; GIST, gastrointestinal stromal tumor; CD34, cluster of differentiation molecule 34 (a cell surface glycoprotein); CT, computerized tomography; MRI, magnetic resonance imaging; FDG, [¹⁸F]2-fluoro-2-deoxy-D-glucose; PET, positron emission tomography.

mutational analysis for confirming a diagnosis of GIST.^{1,12-14}

Staging

According to the consensus of a GIST workshop by the National Institutes of Health in 2001, the risk of aggressive clinical behavior should be stratified on the basis of tumor size and mitotic count; this approach is recommended in the Canadian guidelines for risk assessment.^{5,12} However, the ESMO and NCCN guidelines recognize that a more recent classification that includes tumor site has better prognostic value (Table 1). This is based on the observation that gastric GISTs are associated with a better prognosis than small intestinal or rectal GISTs of the same size and mitotic count.^{1,3,13,14} In addition, tumor rupture (whether spontaneous or at the time of surgical resection) is identified by the ESMO as an adverse prognostic factor because of its association with peritoneal contamination.¹³

According to Lasota and Miettinen, mutational status may also affect prognosis based on patients with GIST who were treated before the era of TKI therapy.²⁵ For example, gastric *KIT* exon 11 deletions are associated with more aggressive disease than exon 11 substitutions, although the same is not true for intestinal GISTs. In addition, tumors with homozygous *KIT* exon 11 mutations almost always have an aggressive course regardless of location. It was believed initially that *KIT* exon 9 mutations conferred aggressive clinical behavior because of their predominance in the small intestine, but they do not appear to result in more aggressive tumors than in exon 11 mutations, which are identified mostly in gastric tumors. In contrast, *KIT* exon 13 mutations, although rare, appear to be more aggressive than the average gastric GIST with other *KIT* mutations.²⁵ *PDGFRα* mutations, as a rule, have a low mitotic rate and confer a favorable prognosis.²⁵ However, despite these findings, mutational status, per se is not included in the prognostic assessment recommended by any of the guidelines.

Imaging is a diagnostic tool that is useful for confirming, characterizing, and staging GISTs. The ESMO guidelines indicate that contrast-enhanced computerized tomography (CT) scanning of the pelvis and abdomen is the imaging of choice for staging, because it takes into account the finding that most relapses occur in the peritoneum and liver (Table 1). Magnetic resonance imaging (MRI) is an alternative and is preferred for the staging of rectal GISTs.¹³ The NCCN guidelines recommend contrast-enhanced CT and, occasionally, MRI as the

Table 2. Comparison of Treatment Recommendations for Gastrointestinal Stromal Tumors According to the European Society for Medical Oncology, the National Comprehensive Cancer Network, and the Canadian Advisory Committee on Gastrointestinal Stromal Tumors Guidelines

Treatment Setting		ESMO (Casali 2009)¹³	NCCN (NCCN 2009)¹⁴	Canadian (Blackstein 2006)¹²
Primary resectable disease	First-line treatment	Surgery	Surgery	Surgery
	Adjuvant imatinib	Option for patients at high risk of relapse	Option for patients at high risk of relapse	Not recommended as standard therapy and suggest enrolling high-risk patients in a clinical trial of adjuvant imatinib
Recurrent or metastatic disease				
First-line treatment	Standard imatinib dose	Imatinib 400 mg/d	Imatinib 400 mg/d	Imatinib 400 mg/d
	Patients with KIT exon 9	Yes (400 mg/d)	Yes (400 mg/d)	Yes (400 mg/d)
	Imatinib dose escalation	Increase imatinib dose to 800 mg/d	Increase imatinib dose to 800 mg/d	Increase imatinib dose to 800 mg/d (also recommended for PDGFR α D842V mutations)
		For patients with tumor progression	For patients with tumor progression	For previous imatinib responders with progression who develop secondary resistance
Neoadjuvant imatinib therapy		Recommended for patients for whom R0 surgery is not feasible or for those patients who are candidates for less mutilating cytoreductive surgery	Recommended for patients with marginally resectable tumors or for resectable GISTs with a risk of significant morbidity	Consider when surgery could result in significant morbidity or loss of organ function; consider surgery 4 to 12 mo after maximal tumor shrinkage
Second-line treatment		Continue imatinib therapy at the same dose or at an increased dose, if tolerated, in patients with limited progressive disease; switch to sunitinib if progression on or intolerance to imatinib; also consider clinical trial of a new therapy or combination therapies	Continue imatinib therapy at the same dose or at an increased dose, if tolerated, in patients with limited progressive disease; consider sunitinib or enrollment in a clinical trial	No specific recommendations after imatinib failure; consider experimental regimen in a clinical trial

ESMO indicates European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; KIT, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; PDGFR α , platelet-derived growth factor receptor alpha; D842V, replacement of valine (V) for aspartic acid (D) at amino acid 842 of PDGFR α ; R0, complete surgical resection; GISTs, gastrointestinal stromal tumors.

Table 3. Summary of Studies Evaluating the Efficacy of Imatinib for the Postsurgical Adjuvant Treatment of Patients With Resectable Gastrointestinal Stromal Tumors

Study and Design	Treatment	Patients ^a	Efficacy
ACOSOG Z9001 trial (Dematteo 2009 ²⁸); phase 3, R, DB, ongoing study	Im 400 mg/d × 1 y vs PI ^b	Tumor size ≥3 cm; N = 713 (evaluable) ^c	RFS (primary endpoint): 1 y, Im 98% vs PI 83% (<i>P</i> = .0001; HR, 0.35; 95% CI, 0.22-0.53); OS: no significant difference between Im or PI
ACOSOG Z9000 trial (Dematteo 2008 ²⁹); phase 2, MC, OL	Im 400 mg/d × 1 yr	High-risk relapse (tumor size ≥10 cm, tumor rupture, or <5 peritoneal metastases); N = 107 (evaluable)	OS (primary endpoint): 1 y 99%, 2 y 97%, 3 y 97%; RFS: 2 y 94%, 2 y 73%, 3 y 61%
MC, OL (Zhan 2007 ³⁰)	Im 400 mg/d × ≥1 y	High-risk relapse (tumor size ≥5 cm or ≥5/50 HPF); N = 51 (evaluable)	Relapse or metastases rate (primary endpoint): 3.92% of patients; median DFS, 385 d
EORTC 62024 (EORTC 2009 ³¹); ongoing phase 3, MC, R, OL	Im 400 mg/d × 2 y vs no further treatment	High-risk relapse (tumor >10 cm or mitotic rate >10/50 HPF or tumor >5 cm AND mitotic rate >5/50 HPF) or intermediate-risk of relapse (tumor <5 cm AND mitotic rate 6-10/50 HPF or tumor 5-10 cm AND mitotic rate <5/50 HPF)	Time to secondary resistance (primary endpoint): results awaited
SSG XVIII/AIO (SGS 2009 ³²); ongoing phase 3, MC, R, OL	Im 400 mg/d × 1 y or 3 y	High-risk relapse (tumor >10 cm or mitotic rate >10/50 HPF or tumor >5 cm AND mitotic rate >5/50 HPF)	RFS (primary endpoint): results awaited

ACOSOG indicates American College of Surgeons Oncology Group; R, randomized; DB, double blind; Im, imatinib; PI, placebo; RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival; MC, multicenter; OL, open label; HPF, high-power fields; DFS, disease-free survival; EORTC, European Organization for Research and Treatment of Cancer; SGS, Scandinavian Sarcoma Group; XVIII/AIO, Scandinavian and German Intergroup Trial.

^a All patients underwent a complete resection of v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT)-positive tumor.

^b Upon recurrence, treatment was unblinded, and patients were crossed over to Im if they were receiving PI or the Im dose was increased to 800 mg/day if they already were receiving Im.

^c Patients to be followed for up to 10 years.

imaging modality of choice for initial evaluation and also recognize that [¹⁸F]2-fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET)/CT can be useful in staging.^{1,14} According to the Canadian guidelines, the optimal imaging approach should use a combination of CT and PET scanning, because it can delineate lesions more appropriately, particularly in early stage disease. CT scanning or endoscopic ultrasound is recommended for small tumors that are identified incidentally.¹²

Treatment

Resectable GISTs

Surgery is the cornerstone of treatment for primary resectable GISTs when there is no evidence of metastases (Table 2).^{1,12-14} However, despite complete (R0) surgical resection, some patients are at a high risk of disease recurrence that will result in an aggressive clinical course. Five-year recurrence-free and disease-free survival rates of 49% and 65%, respectively, have been reported for patients undergoing complete resection.^{26,27}

The results from several studies suggest that adjuvant imatinib is useful in some high-risk patients after surgical resection (Table 3). The phase 3 American College of Surgeons Oncology Group (ACOSOG) Z9001 trial is a large, randomized, double-blind study of patients with KIT-expressing GISTs ≥3 cm in size; results from this study based on 682 treated patients indicated that adjuvant imatinib 400 mg daily significantly improved 1-year recurrence-free survival compared with placebo.²⁸ In the phase 2 ACOSOG Z9000 open-label study of patients with GISTs at high risk of recurrence (tumor size ≥10 cm, tumor rupture, or <5 peritoneal metastases) who received imatinib 400 mg daily for 1 year; the 3-year survival rate was 97%, and the 3-year recurrence-free survival rate was 61%—both of which were superior to similar data reported in historic controls.²⁹ In an open-label, multicenter trial conducted in 16 hospitals in China, low rates of recurrence also were reported in patients with GISTs ≥5 cm in size or with mitotic counts ≥5 per 50 high-power fields (HPF) after treatment with adjuvant imatinib for ≥1 year.³⁰ Results

also are awaited with interest from 2 other phase 3 studies that are evaluating imatinib in the adjuvant setting—European Organization for Research and Treatment of Cancer (EORTC) trial 62024 and Scandinavian Sarcoma Group (SSG) Intergroup trial SSG XVIII/AIO (Table 3).^{31,32}

Although the ESMO guidelines mention the preliminary ACOSOG Z9001 data, they highlight the finding that, currently, there are no overall survival data for imatinib. According to the ESMO, there is no global consensus on the use of imatinib as adjuvant therapy for localized GIST, although it may be used for 1 year as adjuvant therapy in patients at high risk of relapse.¹³ Similarly, the NCCN guidelines recommend adjuvant imatinib or observation for patients who are at significant risk of recurrence after undergoing complete resection.¹⁴ The Canadian guidelines, which were released before the ACOSOG Z9001 trial results were made public, do not recommend adjuvant imatinib as standard therapy in this setting and suggest that high-risk patients should be considered for inclusion in a clinical trial of adjuvant imatinib.¹² On the basis of the data from the phase 3 ACOSOG Z9001 trial, imatinib (400 mg daily) has been approved recently by the US Food and Drug Administration (FDA) for the adjuvant treatment of adult patients after complete surgical removal of KIT (CD117)-positive GISTs.³³ After the recent Swiss and European approvals in this setting, more worldwide approvals are expected.

Recurrent or metastatic disease

In the past, treatment options for patients with recurrent or metastatic disease were limited because of the generally poor response of GISTs to conventional chemotherapy and radiotherapy. However, currently, based on data from clinical studies that evaluated imatinib in this patient group, a median survival after diagnosis of 4 to 5 years can be expected (Table 4). Initial results from the phase 2 B2222 trial indicated that imatinib at doses of 400 mg or 600 mg daily induced sustained objective responses in patients with advanced GISTs, and similar results were achieved at the 2 dose levels (partial response rate, 53.7%; stable disease rate, 27.9%).³⁴ Subsequent long-term follow-up of data from that study demonstrated that imatinib extended survival to a median of 57 months, and similar benefits were achieved in patients who had objective responses and patients who had stable disease.³⁵

The S0033 and EORTC 62005 studies were 2 phase 3, multicenter, randomized trials that compared standard-dose imatinib (400 mg daily) with high-dose imatinib

(800 mg daily) in patients with advanced or metastatic GIST, allowing patients who progressed on the standard dose to cross over to the high dose.^{36,37} The initial report from the EORTC 62005 study suggested that high-dose imatinib prolonged progression-free survival (PFS) compared with the standard dose; however, on longer follow-up (median, 40 months), PFS for the 2 dose levels was similar.³⁸ Furthermore, the S0033 study did not identify any significant difference in outcome between the 2 imatinib dose levels.³⁶ MetaGIST was a prospectively planned meta-analysis designed to determine whether the imatinib dose influenced outcome in certain patient subgroups. The analysis was based on 1640 patients who participated in the S0033 and EORTC 62005 studies.³⁹ After a median follow-up of 45 months, the results demonstrated that high-dose imatinib provided a small but significant advantage in PFS compared with the standard dose in the entire cohort. Overall survival was identical with the 2 doses. However, in the subset of patients who had *KIT* exon 9 mutations, high-dose imatinib conferred a significantly substantial benefit in terms of PFS compared with the standard dose along with a trend toward improved overall survival in this subgroup with the 800/mg daily dose.³⁹

The ESMO, NCCN, and Canadian guidelines all recognize that imatinib is the standard of care for patients with recurrent, unresectable, and metastatic GISTs. The ESMO recommends using imatinib at a dose of 400 mg daily except in patients who have *KIT* exon 9 mutations, for whom the recommended starting dose is 800 mg daily. Patients who have tumor progression on 400 mg daily should have their imatinib dose increased to 800 mg daily, which may be particularly useful in patients who have exon 9 mutations.¹³

The NCCN guidelines also recommend prescribing imatinib at a dose of 400 mg daily and increasing the starting dose to 800 mg daily in patients with exon 9 mutations. Dose escalation to 800 mg daily is considered appropriate for patients who have disease progression on the standard dose.¹⁴ The Canadian guidelines specify prescription of imatinib at a standard dose of 400 mg daily but suggest considering a starting dose of 800 mg daily for patients who have *KIT* exon 9 mutations or the *PDGFRα* D842V mutation (replacement of valine [V] for aspartic acid [D] at amino acid 842 of *PDGFRα*) for recurrent or metastatic disease. They also suggest that dose escalation to 800 mg daily should be considered in previous responders who have progression or who develop secondary resistance.¹²

Table 4. Summary of Studies Evaluating the Efficacy of Imatinib for the Treatment of Recurrent or Metastatic Gastrointestinal Stromal Tumors

Study and Design	Treatment	Patients	Efficacy
B2222 trial (Blanke 2008 ³⁵); phase 2, MC, R, OL	Im 400 or 600 mg/d ^a	Advanced unresectable or metastatic GIST; KIT +ve; ECOG PS ≤3; ≥1 measurable tumor not previously treated with chemotherapy or embolization; N = 147 (evaluable)	Median FU 9.6 mo (combined data for both doses) ^b ; all patients: CR (0%), PR (53.7%), SD (27.9%), PD (13.6%); estimated 1-y OS, 88%; median FU 63 mo (combined data for both doses) ^b : CR (1.4%), PR (66.7%), SD (15.6%), PD (11.6%); median OS, 57 mo
S0033 trial (Blanke 2008 ³⁶); phase 3, MC, R, OL	Im 400 mg qd or bid ^a	Metastatic or surgically unresectable disease; KIT +ve; Zubrod PS, 0-3; N = 694	Median FU 4.5 y ^b : median PFS (primary endpoint), 18 mo (400 mg), 20 mo (800 mg); median OS (primary endpoint): 55 mo (400 mg), 51 mo (800 mg); 400 mg: CR (5%), PR (40%), SD (25%), PD (12%); 800 mg: CR (3%), PR (42%), SD (22%), PD (10%)
EORTC 62005 trial (Verweij 2004, ³⁷ Casali 2005 ³⁸); phase 3, MC, R	Im 400 mg qd or bid ^a	Advanced or metastatic disease; KIT +ve; WHO PS <4; N = 946	Median FU 25.3 mo: PFS (primary endpoint): 44% (400 mg) vs 50% (800 mg); HR, 0.82; 95% CI, 0.69-0.98; <i>P</i> = .026; median FU 40 mo (combined data for both doses) ^b : median PFS, 22 mo; 3-y OS, 59%; 3-y PFS, 33%
MetaGIST (Van Glabbeke 2007 ³⁹); meta-analysis of S0033 and EORTC 62005 trials	Im 400 mg qd or bid ^a	The same as S0033 and EORTC 62005; N = 1640	Median FU 45 mo: Im 800 mg small but significant advantage vs Im 400 mg for PFS; OS comparable for both doses; KIT exon 9 mutations, Im 800 mg benefit for PFS and OS vs Im 400 mg

MC indicates multicenter; R, randomized; OL, open label; Im, imatinib; GIST, gastrointestinal stromal tumor; KIT, v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; +ve, positive; ECOG, Eastern Cooperative Oncology Group; PS, performance status; FU, follow-up; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OS, overall survival; qd, once daily; bid, twice daily; PFS, progression-free survival; EORTC, European Organization for Research and Treatment of Cancer; WHO, World Health Organization; HR, hazard ratio; MetaGIST, GIST Meta-Analysis Group.

KIT v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog

^aPatients were crossed over to the higher Im dose if they progressed on the lower dose.

^bThere was no significant difference between the 2 dose groups for any endpoint.

Neoadjuvant therapy

Surgical resection may become feasible in some patients with previously unresectable GISTs after treatment with imatinib. This is highlighted by several reported series that illustrate experience with neoadjuvant imatinib therapy at various medical centers.⁴⁰⁻⁴⁶ For example, Andtbacka and colleagues reported that patients with recurrent or metastatic GIST who had a partial radiographic tumor response to neoadjuvant imatinib therapy (n = 11) had a significantly higher complete resection rate compared with patients who had progressive disease (n = 24; resection rate, 91% vs 4%; *P* < .001).⁴⁰

Neoadjuvant imatinib is recommended in the ESMO guidelines in patients for whom R0 surgery is not feasible and for those patients who are candidates for less mutilating cytoreductive surgery.¹³ The NCCN guidelines recommend neoadjuvant imatinib for marginally

resectable tumors and for resectable GISTs with a risk of significant morbidity.¹⁴ According to the Canadian guidelines, neoadjuvant imatinib should be considered if surgery could result in significant morbidity or loss of organ function, and subsequent surgery may be considered 4 months to 12 months later after maximal tumor shrinkage.¹²

Second-Line Treatment of Advanced GISTs

After disease progression on high-dose imatinib or the development of imatinib intolerance, there is evidence to suggest that switching to the TKI sunitinib may be warranted. Sunitinib has activity against KIT and PDGFR α as well as other pathways that may be relevant in GIST, such as vascular endothelial growth factor receptor.^{47,48} In a phase 3 randomized trial, sunitinib administered at a dose of 50 mg daily in a 4-week/on/2-week/off

cycle significantly prolonged the time to progression compared with placebo in patients with advanced GISTs who were resistant or intolerant to imatinib (27.3 weeks vs 6.4 weeks; $P < .0001$).⁴⁹ Continuous daily dosing with sunitinib 37.5 mg daily reportedly is active and compares favorably with the 4-week/on/2-week/off cycle.⁵⁰ Sunitinib also appears to be active against secondary mutations that affect the adenosine triphosphate (ATP) binding site but not against secondary mutations that affect the KIT activation loop, both of which are resistant to imatinib.^{51,52} On the basis of these findings, sunitinib was approved by the FDA in 2006 for the second-line treatment of patients with GISTs whose disease has progressed or who are unable to tolerate treatment with imatinib.⁵³

Nilotinib is a second-generation TKI that achieves higher intracellular concentrations in GISTs than imatinib, suggesting that it has potential activity in certain imatinib-resistant cell lines.⁵⁴ In support of this, nilotinib alone or in combination with imatinib demonstrated promising clinical activity in patients with advanced GISTs who had progressed on imatinib in a phase 1 study.⁵⁵ Recently, a phase 3 registrational trial of third-line nilotinib in patients with GIST who failed both imatinib and sunitinib was completed.⁵⁶ In that trial, 248 patients were randomized to receive either nilotinib (400 mg twice daily) or best supportive care, which may or may not have included a TKI of the investigator's choice; patients were allowed to cross over to nilotinib upon progression. Also, a phase 3 randomized trial comparing nilotinib 800 mg daily with imatinib 800 mg daily for the first-line treatment of patients with advanced and/or metastatic GISTs has been initiated.⁵⁷ Some other agents that are under investigation for the treatment of GISTs include masitinib, dasatinib, and sorafenib.

Masitinib, a TKI against wild/type c-KIT and its activated forms—PDGFR α , PDGFR β , Lyn kinase/focal adhesion kinase, and fibroblast growth factor receptor 3—has been evaluated in a phase 1 dose-escalation study in patients with GISTs.⁵⁸ The maximum tolerated dose was not reached in that study; however, 12 mg/kg daily was considered the maximal recommended dose in long-term treatment, and masitinib exhibited clinical activity.⁵⁹ A phase 2 trial of single-agent masitinib in imatinib-naïve patients who have inoperable, locally advanced, or metastatic GIST is underway. Preliminary results have produced a disease control rate of 97%, a median PFS of 44 months, a 2-year PFS rate of 60%, a 3-year overall survival rate of 90%, and fairly well tolerated side effects.

With respect to the second-line treatment of GISTs, both the ESMO and NCCN guidelines support the continued use of imatinib at the same dose or at an increased dose, as tolerated, in patients with limited progressive disease.^{13,14} After failure on imatinib, both the ESMO and the NCCN support the use of sunitinib in patients who progress on imatinib or who are intolerant to imatinib and suggest that, after failure, patients should be considered for a clinical trial.^{13,14} In contrast, the Canadian guidelines do not make any specific recommendations after imatinib failure, suggesting consideration of an experimental regimen in a clinical trial. Perhaps this is because sunitinib was approved for the treatment of GIST only in 2006.¹²

Follow-Up: Response to Therapy and Monitoring

The optimal management of GISTs requires a multimodality approach with contributions from medical oncologists, surgical oncologists, radiologists, and pathologists—both during the initial management and during follow-up.¹ In terms of follow-up after surgical resection of the primary tumor, patients should be monitored for disease recurrence or metastatic disease at periodic intervals. The ESMO does not provide specific recommendations for follow-up after resection—noting that follow-up schedules differ by institution—but the ESMO does suggest that the risk assessment performed after surgery may help determine the optimal frequency of follow-up monitoring.¹³ Very/low-risk tumors may not warrant routine follow-up.¹³ The NCCN guidelines recommend follow-up by abdominal/pelvic CT scans every 3 to 6 months but suggest that less frequent follow-up is appropriate for patients with very/low-risk disease.¹⁴ A follow-up CT scan every 3 to 6 months for a minimum of 5 years after resection is recommended in the Canadian guidelines.¹²

For those patients who have advanced disease, regular monitoring should be undertaken to assess response to treatment with imatinib and subsequent lines of therapy. Significantly, response assessments based solely on changes in tumor size, such as Response Evaluation Criteria in Solid Tumors (RECIST) or the Southwest Oncology Group criteria, are recognized now as insufficient for evaluating response to TKIs, because stable disease also should be considered a sign of tumor efficacy in these patients.^{60,61} The criteria reported by Choi and colleagues include an evaluation of the density of the metastases in addition to an evaluation of tumor size, and these criteria will need to be integrated into subsequent clinical trials.⁶⁰

On CT scans, tumors that respond to imatinib generally have the disappearance of enhancing nodules and tumor vessels, increased tumor homogeneity, and decreased tumor density irrespective of changes in tumor size. These changes may reflect ongoing tumor necrosis, intratumoral hemorrhage, or myxoid degeneration.⁶⁰ Furthermore, Choi and colleagues demonstrated that changes in tumor size and density were correlated with treatment responses on FDG-PET images; and, based on these findings, they proposed new criteria for assessing treatment responses according to changes in tumor size or density.^{60,62} According to these criteria, a partial response is defined as a decrease in tumor size $\geq 10\%$ or a decrease in tumor density $\geq 15\%$ without any new lesions or obvious progression of nonmeasurable lesions.⁶² Moreover, at 2 months, the Choi criteria were able to distinguish time to progression and disease-specific survival between good and poor responders, whereas RECIST were not.^{62,63}

For patients who are active treatment for advanced GISTs, the ESMO guidelines recommend considering both tumor size and density on CT scans or consistent changes on MRI studies in the response assessment. FDG-PET is recommended when an early response to treatment is needed and in patients for whom the response assessment by CT is unclear.¹³ According to the NCCN guidelines, follow-up monitoring by CT with or without PET should be undertaken within 3 months of initiating TKI therapy. The NCCN also recognizes the benefit of the Choi criteria over RECIST but indicates that further studies are needed to validate this approach.^{1,14} In the Canadian guidelines, CT and FDG-PET studies every 3 months are recommended as the preferred methods for assessing treatment responses and should be performed using RECIST in combination with qualitative changes in tumor characteristics (eg, density) and morphology.¹²

There also is evidence to indicate that the clinical benefit of imatinib in patients with progressive GISTs, according to RECIST or the Choi criteria, correlates with exposure to adequate drug blood levels, suggesting that monitoring blood levels may be useful in patients with suboptimal response. For example, in the B2222 study, measurement of trough blood levels after 1 month of imatinib therapy revealed a statistically significant lower median time to progression in patients with the lowest quartile of trough imatinib levels compared with other quartiles.⁶⁴ However, despite these findings, assessment of imatinib blood levels has yet to be incorporated into any of the guidelines.

Treatment compliance is important for achieving and maintaining responses and, thus, should be verified in all patients who do not have suboptimal responses. The BFR14 study demonstrated that patients who interrupted imatinib after 1 or 3 years had high rates of disease recurrence compared with patients who continued imatinib therapy without interruption.⁶⁵⁻⁶⁷ After 1 year of tumor control on imatinib at 400 mg daily, dose interruption resulted in disease progression in 85% of patients compared with 31% of patients who were receiving continuous therapy.⁶⁷ Similarly, among patients who were free from progression on imatinib 400 mg daily for 3 years, subsequent interruption of therapy was associated with a 1-year PFS rate of 32% compared with 92% among patients who were receiving continuous imatinib therapy.⁶⁷ In this respect, all 3 sets of guidelines recommend the administration of imatinib therapy indefinitely until there is evidence of disease progression.

In conclusion, GISTs are relatively rare tumors that require a multimodal approach to management. Three sets of major guidelines on the management of GISTs have been published over the last several years; and, although some points of divergence do exist, the guidelines offer similar recommendations in a variety of areas. It should be noted, however, that as this review is being written, the 2009 Canadian GIST guidelines are being finalized; thus, recommendations that have been discussed herein ultimately may change.

With respect to the diagnosis of GISTs, the guidelines agree that immunohistochemistry and morphology play crucial roles in the use of mutational analysis if the diagnosis is unclear. Surgery remains the mainstay of treatment and is recommended for primary resectable disease (tumors ≥ 2 cm); this should be followed by stratification for risk from an aggressive clinical course based on tumor size, mitotic count, and location. It is noteworthy that the introduction of imatinib into clinical practice has significantly improved the clinical outcome of patients with metastatic or advanced GIST and is reflected in the guideline recommendations, which endorse imatinib at a dose of 400 mg daily as first-line therapy for patients with recurrent and metastatic GISTs and the continuation of therapy without interruption until disease progression. Dose escalation to 800 mg daily is recommended on disease progression.

Despite the publication of comprehensive guidelines on the management of patients with GISTs, several issues remain unresolved. These include the need for better definition of the role of mutational status in risk stratification;

however, currently, mutational status is not included in the risk stratification in any guidelines. Indeed, the prognostic implication of mutations may require re-evaluation in the era of TKI therapy, because the likelihood of response to currently available therapies may dramatically change the prognosis from that observed before the standard use of TKIs. Furthermore, although the guidelines (NCCN and ESMO) agree that, in patients with localized GIST, adjuvant imatinib can be used for up to 1 year after resection in high-risk patients, additional evidence is needed to support the role of imatinib in the adjuvant setting—for example, defining which patient subgroups warrant such treatment.

Case series offer supportive evidence for the use of neoadjuvant imatinib in patients with unresectable disease. Patients may become surgical candidates when they respond to imatinib, but clinical studies still are needed to establish the role of neoadjuvant therapy and to identify appropriate patient characteristics. Similarly, second-line treatment after imatinib needs to be clarified; because, although sunitinib currently is approved in this setting, several other options are being evaluated in clinical studies. It is noteworthy that a more accurate and earlier assessment of response to treatment should help to address many of the unresolved issues relating to the management of patients with GISTs. In this respect, the Choi criteria offer promise in assessing treatment responses to the TKIs imatinib and sunitinib, and further studies are needed urgently to validate these criteria and to demonstrate their value in routine clinical practice.

CONFLICT OF INTEREST DISCLOSURES

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