Gastrointestinal Stromal Tumors

Leah Strickland, MD, G. Douglas Letson, MD, and Carlos A. Muro-Cacho, MD, PhD

Background: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. A relationship to the interstitial cells of Cajal (ICCs) has been proposed, and expression of CD117, the c-kit receptor present in ICCs, has been suggested as a marker for GISTs.

Methods: The English literature has been reviewed with an emphasis on histogenetic features, especially the potential relationship of GISTs to ICCs.

Results: GISTs are most common in the stomach (70%), followed by small intestine (20%), colon and rectum (5%), and esophagus (<5%). GISTs commonly have activating mutations in exon 11 (or rarely exon 9 and exon 13) of the KIT gene that encodes a tyrosine kinase receptor for the stem cell factor or mast cell growth factor.

Conclusions: Malignant potential is best estimated by the simultaneous evaluation of several clinical parameters. The only absolute criterion for malignancy is tumor spread beyond the organ of origin at the time of diagnosis. The remarkable clinical response of tumors that express c-kit to treatment with the tyrosine kinase inhibitor STI571 is a triumph of molecular pharmacology.

Introduction

Gastrointestinal stromal tumors (GISTs) are rare neoplasms thought to arise from mesenchymal cells of the gastrointestinal tract. The histogenesis, classification, diagnostic criteria, and biological behavior of GISTs have been the subject of much controversy. Stout1 believed that these tumors derived from smooth muscle and that a high mitotic rate was the best predictor of malignancy. In recent years, however, it has become clear that GISTs show remarkable cellular variability and histopathologic appearance and that GIST cells may be able to differentiate towards a variety of cell types or may be undifferentiated. Furthermore, their malignant potential is often difficult to predict and is best estimated by the simultaneous evaluation of several parameters such as size, location in the gut, invasion of adjacent organs, mucosal invasion, degree of cellularity, cellular architecture, mitotic count, nuclear pleomorphism, necrosis, and proliferation.
rate.\textsuperscript{23} GISTs differ clinically and pathogenetically from true leiomyosarcomas (rare in the gastrointestinal tract), leiomyomas, schwannomas, and gastrointestinal autonomic nerve tumors. In an effort to integrate numerous studies into a practical operational scheme, several histogenetic classifications of GISTs have been proposed (Tables 1 and 2).\textsuperscript{4,5} A relationship to the interstitial cells of Cajal has been recently proposed.\textsuperscript{6,8}

**Interstitial Cells of Cajal and the c-kit Protooncogene**

The interstitial cells of Cajal (ICCs) form a complex cellular network within the muscle wall of the gut where they function as a muscular pacemaker system controlling gut motility.\textsuperscript{9} Expression of the c-kit protooncogene is essential for the slow wave activity of ICCs and for the development of the ICC system. Although not limited to this cell type, c-kit expression is widely recognized as a molecular marker of ICCs.\textsuperscript{10-12} The c-kit receptor (KIT/SCF-R) encodes a tyrosine kinase that is dimerized and activated upon ligand stimulation, leading to autophosphorylation as well as phosphorylation of a number of signal transduction molecules. Ultimately, this process results in cellular responses such as cell division, actin reorganization, and chemotaxis. Mutant c-kit tyrosine kinase receptors are constitutively activated in the absence of its ligand, the stem cell factor. Naturally occurring mutations in the receptor gene, as well as in that of its ligand (the steel locus), cause defects in migration, differentiation, and proliferation of melanogenic, gametogenic, and hematopoietic stem cells. Furthermore, stable transfection of the mutant c-kit cDNAs into murine lymphoid cells induces malignant transformation.\textsuperscript{13-15}

In one study,\textsuperscript{16} GISTs were reported to express the c-kit receptor, as did ICCs in the adjacent nonneoplastic gastrointestinal wall, while conventional gastrointestinal leiomyomas and leiomyosarcomas did not. Furthermore, gain-of-function c-kit mutations have been reported in several GISTs, and mutations in the exon 11 of the c-kit protooncogene have been found in 65% of both sporadic and familiar forms of GISTs.\textsuperscript{17-21} These mutations may be responsible, at least in part, for GIST metastatic capabilities.\textsuperscript{18,22,23} In 1995, Miettinen et al.\textsuperscript{24} reported that the c-kit receptor is coexpressed with CD34, a sialylated transmembrane glycoprotein found in mesenchymal cells, both in GIST and in a ramifying network of tumor cells that surrounds the Auerbach’s ganglia and is reminiscent of the ICC system. This finding supports the hypothesis that either GIST is a tumor of ICCs or it originates from stem cells that differentiate toward a pacemaker cell phenotype. The name “gastrointestinal pacemaker cell tumor” has been proposed for this subset of neoplasms.\textsuperscript{25,26} However, confocal optical sections of normal intestinal muscle have shown

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**Table 1. — Histogenetic Classification of Gastrointestinal Stromal Tumors (Suster*)**

<table>
<thead>
<tr>
<th>Differentiation Features</th>
<th>Lineage</th>
<th>Tumor Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well developed</td>
<td>Smooth muscle</td>
<td>Leiomyma/leiomyosarcoma, Schwannoma/neurofibroma/ganglioneuroma</td>
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<tr>
<td></td>
<td>Neural</td>
<td></td>
</tr>
<tr>
<td>Primitive or incomplete</td>
<td>Myoid</td>
<td>Gastrointestinal stromal tumors (GIST)</td>
</tr>
<tr>
<td></td>
<td>Neural</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Autonomic nerve/ganglionic (plexoma)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mixed neural/myoid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Undifferentiated</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>Myoid</td>
<td>Gastrointestinal stromal sarcomas</td>
</tr>
<tr>
<td></td>
<td>Neural</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Autonomic nerve/ganglionic differentiation (GANT)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mixed neural/myoid differentiation</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. — Histogenetic Classification of Gastrointestinal Stromal Tumors (Rosai†)**

<table>
<thead>
<tr>
<th>Differentiation</th>
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<tbody>
<tr>
<td>Smooth muscle type</td>
</tr>
<tr>
<td>Epithelioid</td>
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</table>

| Neural type | GANT |
| Smooth muscle-neural type | GIST, combined differentiation |
| Uncommitted | GIST, NOS |

GANT = gastrointestinal autonomic nerve tumor  
GIST = gastrointestinal stromal tumor  
NOS = not otherwise specified
that CD34 and c-kit are expressed by closely adjacent but not overlapping cell populations. The CD34-positive cells coexpress the fibroblast marker prolyl 4-hydroxylase and are distinct from smooth muscle cells, glial cells, and macrophages. The c-kit-positive ICCs, however, do not express CD34. Furthermore, ultrastructural studies have demonstrated that the fibroblast-like cells are located in the proximity of ICCs at all levels of the intestine and may be actually be an integral part of the ICC bundles. These findings challenge an ICC origin of GISTs and seem to suggest that c-kit somatic mutations are not markers of cell of origin but have a major role in GIST oncogenesis, a position recently supported by the fact that CD117, the c-kit protooncogene product, is in fact a more specific marker for GISTs than for CD34. Other tumors, such as angiosarcoma, melanoma, small cell carcinoma, seminoma, or Ewing’s sarcoma, may express the c-kit product but only rarely enter into the differential diagnosis.

**Immunohistochemical Features of GISTs**

Fixation, tissue preparation methods, and variations in reagents and staining techniques account, in part, for the reported phenotypic heterogeneity in GISTs. However, true histogenetic variability has been recently recognized and may explain the differences in percentages assigned to each differentiation lineage in several large series. Thus, Hurllmann et al observed smooth muscle differentiation in 30% of the cases, neural differentiation in 10%, dual smooth muscle and neural differentiation in 3%, and no obvious differentiation in 40%. The majority of the tumors in a series reported by Saul et al, however, showed smooth muscle differentiation. Smooth muscle differentiation seems to be more common in esophageal and colonic tumors. In contrast, only 50% of benign and 70% of malignant gas-

dritic tumors and 40% of benign and 10% of malignant small-bowel tumors show smooth muscle differentiation.

In tumors with neural differentiation, vimentin is expressed in 95% of tumors, neuron-specific enolase is expressed in 50%-100%, synaptophysin in 100%, neurofilament protein in 10%, S-100 protein in 20%-60%, vasointestinal peptide in 20%-40%, and CD34 in 60%. Chromogranin, cytokeratin, glial fibrillary acidic protein, scrotonin, and desmin are typically not expressed. Tumors with smooth muscle differentiation do not express neuron-specific enolase, synaptophysin, chromogranin, glial fibrillary acidic protein, or protein gene product 9.5. They express lineage-specific markers with the following frequencies: muscle-specific antigen (HHF-35) - 68%, smooth muscle actin (SMA) - 57%, and desmin - up to 50% (Fig 1). In 50% of cases, desmin is absent while SMA expression is maintained, and in 40% of cases, muscle markers are coexpressed with S-100, suggesting dual differentiation. A small percentage of tumors show prominent S-100 expression, and half of these coexpress desmin and/or SMA. Expression of only S-100 is rare, although small numbers of S-100 positive cells, probably representing entrapped Schwann cells, are not unusual.

A type of GIST showing neural differentiation is the gastrointestinal autonomic nerve tumor (GANT). Originally designated as “plexoma” or “plexosarcoma,” GANTs are uncommon stromal tumors with morpho-
logic features resembling the cell processes of the enteric autonomic plexus\textsuperscript{40} that occasionally develops in the context of von Recklinghausen’s disease.\textsuperscript{41} GANTs are typically epithelioid or spindle cell neoplasms and usually of low histologic grade.\textsuperscript{42,43} They typically express S-100, neuron-specific enolase, vimentin, and synaptophysin, and they are CD34 negative.\textsuperscript{44} GANTs can be distinguished from other GISTs only on the basis of their unique ultrastructural features.\textsuperscript{45-47} Thus, ultrastructural demonstration of neural differentiation is required for its definitive diagnosis.

The typical GIST, as recognized today, expresses CD117 and CD34 and rarely SMA.\textsuperscript{48} Vimentin expression seems to be a constant feature. In up to 40% of tumors, vimentin is the only marker detected (undifferentiated or null-phenotype GIST). However, 80% of these cases have been shown to coexpress CD34. CD117 expression in the absence of desmin seems to differentiate GISTs from smooth muscle tumors that are typically desmin and SMA positive and CD34 and CD117 negative.\textsuperscript{45,46,48}

Immunophenotypic differences in relationship with anatomical location have been reported. Thus, retroperitoneal leiomyosarcomas seem to frequently express CD34, most esophageal and rectal tumors express CD34 and lack SMA, and GISTs of the small intestine express CD34 and SMA in equal proportions.\textsuperscript{48} It has been suggested that expression of several markers of a given lineage correlates with a more favorable prognosis.

**Ultrastructural Features**

GANTs show synapse-like structures with dense core neurosecretory granules measuring 100-200 nm, endocytosomal vesicles measuring 40-60 nm, interdigitating cytoplasmic processes without basement membranes, and interstitial skeinoid fibers. These features suggest an origin in the myenteric nerve plexus (Fig 2). Ultrastructurally, myogenic differentiation is characterized by scattered mitochondria and prominent Golgi apparatus, strands of rough endoplasmic reticulum, focal accumulation of intracytoplasmic microfilaments with occasional focal condensations, subplasmalemmal attachment plaques and immature cell junctions, focal extracellular basal lamina material, and surface-oriented micropinocytotic activity.\textsuperscript{46}

**Histopathology**

The following architectural growth patterns have been observed: fascicular, storiform, palisading, diffuse

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Immunohistochemistry</th>
<th>Electron Microscopy</th>
</tr>
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<tbody>
<tr>
<td>Smooth Muscle</td>
<td>Markers</td>
<td>Major criteria: parallel arrays of intracytoplasmic actin microfilaments</td>
</tr>
<tr>
<td></td>
<td>HHF-35 (MSA)</td>
<td>Minor criteria: interspersed dense bodies, plasmalemmal attachment plaques, micropinocytotic vesicles, rudimentary cell junctions, discontinuous external lamina (basement membrane)</td>
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<tr>
<td></td>
<td>SMA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Desmin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>One marker, focal</td>
<td></td>
</tr>
<tr>
<td>Neural</td>
<td>Markers</td>
<td>Major criteria: interdigitating cytoplasmic processes joined by rudimentary cell junctions, dense core neurosecretory granules (100 nm), bulbous synapse-like structures with variable content of granules and vesicles (60-80 nm)</td>
</tr>
<tr>
<td></td>
<td>NSE</td>
<td>Minor criteria: intermediate filaments and arrays of microtubules in the processes</td>
</tr>
<tr>
<td></td>
<td>Neurofilaments (axons)</td>
<td>Skeinoid fibers: curvilinear, nodular tangles of collagen fibers that appear as eosinophilic globules</td>
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<tr>
<td></td>
<td>Chromogranin (granules)</td>
<td></td>
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<tr>
<td></td>
<td>Synaptophysin (vesicles)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>Markers</td>
<td>Criteria: mixtures of cell with features of leiomyocytes and GANT</td>
</tr>
<tr>
<td></td>
<td>Vimentin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>One smooth muscle marker</td>
<td></td>
</tr>
<tr>
<td></td>
<td>One neural marker</td>
<td></td>
</tr>
<tr>
<td>GIST</td>
<td>Markers</td>
<td>Criteria: no ultrastructural features of differentiation</td>
</tr>
<tr>
<td></td>
<td>CD117</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CD34</td>
<td></td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>Markers</td>
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<tr>
<td></td>
<td>Vimentin</td>
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<tr>
<td></td>
<td>CD34</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lack of other markers</td>
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sheet-like, organoid (nested), myxoid, inflammatory, and alveolar. Tumor cells may adopt different morphologies: spindle, round (epithelioid), plasmacytoid, myxoid, signet ring, granular, and multinucleated. Attempts to correlate cellular morphology with immunophenotype have not been successful. Two thirds of spindle cell tumors express desmin and muscle actin but usually in less than 10% of the tumor cells. Only 20% express desmin, and 40% express SMA in a diffuse manner. Of the round cell tumors, less than 10% express desmin and SMA. Myxoid tumors, with demonstrated smooth muscle differentiation, can be confused with mucin-producing adenocarcinoma or neoplasms with clear cell or signet-ring cell features. Furthermore, cellular morphology can be misleading, since tumors undistinguishable from schwannoma have revealed strong desmin expression. However, schwannomas are negative for CD117 and CD34 and positive for S-100.

### Histologic Grading

Grading of GISTs has proven to be as difficult as classifying them. From a prognostic point of view, GISTs have been divided into three prognostic groups: benign, borderline, and malignant (Tables 3-6). Evans reported that low-grade GISTs with 1-5 mitoses/50 high-power fields (HPF) have a median survival of 98 months, while high-grade tumors with more than 10 mitoses/10 HPF have a median survival of 25 months. For patients with a complete resection, histologic grade is the major prognostic determinant with 18% 5-year survival rate for high-grade tumors and 72% 5-year survival rate for low-grade tumors. Similar results have been reported by Dougherty et al. in which patients with low-grade lesions (<10 mitoses/50 HPF) who underwent curative resection had a better than 80% disease-free survival rate at 8 years, compared with a mean disease-free interval of only 18 months for high-grade lesions (>10 mitoses/50 HPF). In their experience, tumor grade was the most important prognostic factor in resectable disease. In GANTs, size larger than 10 cm and more than 5 mitoses/10 HPF have been shown to correlate with aggressive behavior.

### Molecular Genetics

The clinicopathologic features of GISTs have been analyzed in numerous studies, but reliable indicators of behavior have yet to be elucidated. Nevertheless, molecular studies are expected to provide information regarding prognosis that cannot be obtained by histopathologic assessment. Several DNA copy number changes correlate with the clinical behavior of GISTs and could be used as prognostic markers for tumor progression. Comparative genomic hybridization has revealed losses in 14q and 22q in both benign and malignant GISTs and various gains predominantly in malignant GISTs. Thus, DNA copy number losses at chromosome arm 14q are the most frequently occurring aberrations in GISTs, occurring in 80% of cases with equal frequency in low- and high-risk tumors. Two common deletion regions have been located at 14q11.1-q12 (71%) and 14q23-q24.3 (50%-60%), suggesting that these are two tumor suppressor loci. It has been proposed that monosomies of chromosomes 14 and 22 are early events in the malignant transformation process, and that loss of chromosomes 15 and 18, as well as structural rearrangements in chromosome 1, correlate with smooth muscle differentiation. High-level DNA amplifications assigned to 3q26-q29 (40%), 5p (30%), and 8q22-q24 (40%) have been detected only in GISTs.

Less aggressive GISTs have fewer DNA copy number changes and fewer gains than overtly malignant GISTs, and the mean number of aberrations in metastatic GISTs is even higher. High-level amplifications at 20q, gains in 5p, and losses in 9p and 13q seem to be
present only in the most aggressive GISTs. High telomerase activity is higher in GISTs than in conventional leiomyosarcomas. Aneuploidy has been reported in approximately 75% of the tumors and seems to correlate with mitotic count (< or > 5/10 HPF) and histologic grade but not with tumor size, site, or histologic appearance (Fig 3). It is useful in predicting the behavior of intermediate-grade tumors. Multivariate regression analyses have shown that proliferation index (Ki-67 or proliferating cell nuclear antigen [PCNA]) and interphase argyrophilic nucleolar organizer region staining (AgNORs) are independent predictors of clinical outcome.63

Anatomical Location

Two thirds of GISTs arise from the stomach, 25% from the small intestine (one third in the duodenum), and 10% in colorectal regions. It is generally accepted that the criteria needed for predicting biological behavior may differ significantly with location.

Esophagus

Leiomyomas are the most common esophageal mesenchymal neoplasms, although they rarely occur elsewhere in the gastrointestinal tract. In the series

Fig 3.—Microscopic appearances of GIST. (A) Spindle cell, (B) diffuse sheet-like, (C) hyalinized, (D) organoid, (E) clear cell, and (F) anaplastic.
studied by Miettinen et al, leiomyomas were clinically indolent and tended to occur in a younger population (median age = 35 years). Leiomyosarcomas, however, were large, high-grade, lethal tumors expressing smooth muscle cell markers but not CD117. GISTs, characterized by coexpression of CD117 and CD34 with occasional expression of alpha-SMA and desmin, have also been reported. In one study, all patients with GISTs larger than 10 cm and one patient whose tumor showed 5 mitoses/50 HPF died of the disease. As in other locations, esophageal GISTs have been reported to have mutations in exon 11 of *c-kit.*

**Stomach**

Mesenchymal tumors of the gastrointestinal tract have been traditionally regarded as leiomyomatous lesions. However, GISTs and other tumors have been identified with increasing frequency. The distribution of GISTs in the stomach is as follows: pars media, 40%; antrum, 25%; pylorus, 20%; submucosa, 60%; subserosa, 30%; and intramural, 10%. Gastric GISTs range from a few millimeters to 15 cm in size and often present with gastrointestinal bleeding, pain, and fatigue or malaise. Factors associated with decreased survival include 8 cm or more in size, 3 or more mitoses/HPF, positive margins or unresectability, and histopathologic grade II or higher. Surgical resection with negative margins remains the best therapy, but palliative resection is sometimes indicated to prolong survival.

**Small Bowel**

Although the small intestine constitutes 75% of the length and over 90% of the mucosal surface area of the gastrointestinal tract, only 1%-2% of gastrointestinal malignancies occur in this segment. Tumors are difficult to diagnose because the symptoms are vague and nonspecific, and metastases are usually present at the time of diagnosis. Malignant tumors occur with increasing frequency in the distal small bowel, predominantly in the ileum, and GISTs are uncommon. Benign duodenal GISTs are usually smaller than 4.5 cm and show low cellularity of spindle cell type, an organoid architectural growth pattern, and 2 or fewer mitoses/50 HPF. Malignant tumors, on the other hand, are larger than 4.5 cm, have more than 2 mitoses/50 HPF, and are hypercellular and epithelioid. In the jejunum and ileum, size larger than 5 cm is accepted as indication of malignancy. The number of mitoses required for malignancy, however, remains controversial. Some authors propose 1 mitosis/10 HPF as a cutoff for malignancy. A rare association of Crohn’s disease in the terminal ileum with high-risk GISTs has been reported.

**Colon and Rectum**

In the colon, size smaller than 2 cm and mitotic rate less than 1 mitosis/50 HPF are indicators of benignity, while size larger than 5 cm and a mitotic rate greater than 5/10 are generally accepted as predictors of malignancy. Rectal GISTs are rare.

**Clinical Considerations**

Symptoms usually depend on tumor size and location, but many patients are asymptomatic. In these cases, the tumors are often discovered incidentally during laparotomy for other conditions. Most patients present with abdominal pain. Tumors in the stomach or small bowel commonly present with bleeding. In the esophagus or rectum, the first manifestations may be obstruction, dysphagia, or altered bowel habits. At laparotomy, intra-abdominal malignant tumors are often cystic and hemorrhagic. In general, mucosal ulceration is considered a sign of malignancy (Fig 4). The only absolute criterion for malignancy, however, is tumor spread beyond the organ of origin at the time of diagnosis. Hepatic metastases and local recurrence are the predominant sites of initial failure. Those tumors locally confined at diagnosis and found incidentally during surgery generally behave in a benign fashion. However, resection of these tumors is necessary, since their behavior is unpredictable and they have to be pathologically examined.

Endosonographic studies show that tumor size of >4 cm, irregular extraluminal border, echogenic foci, and cystic spaces correlate with malignancy. When two or three of these features are present, a diagnosis of
malignancy can be rendered with 80%-100% confidence. Malignancy is also likely in cases where air is detected within a large solid mass adjacent to a bowel loop (Fig 5). For gastric lesions, there seems to be no apparent advantage in extended resections compared with lesser resections that encompass all gross disease. Radiation therapy and chemotherapy have been used to a lesser extent, mainly in a palliative setting. Neither modality has been shown to be particularly effective because these tumors seem to be resistant to chemoradiation. In recurrent tumors, surgery should be reserved largely for symptomatic control, since disease-specific survival seems to be determined by the biology and size of the primary tumor.

Knowledge that c-kit is upregulated in gastrointestinal stromal tumors suggests, however, that an alternate treatment approach may be viable. STI571 (Glivec) is a potent tyrosine kinase inhibitor that, because of its effects on BCR/ABL-expressing cells, provides a major new management option for patients with chronic granulocytic leukemia. The fact that this agent is also a potent inhibitor of c-kit suggests a potential therapeutic role of STI571 in patients with gastrointestinal stromal tumors, and early reports of this molecularly targeted therapy suggest good tolerance and appreciable antitumor activity.

Blanke et al have treated 36 patients with GISTs, all of whom were confirmed by immunohistochemistry to overexpress c-kit, with an oral daily dose of either 400 mg or 600 mg of STI571. Of the 35 patients evaluable for response and toxicity, 19 (54%) experienced a partial response and 12 (34%) had stable disease. The vast majority of initially symptomatic patients had marked clinical improvement, and the responses seem durable. Grade 3/4 toxicities were seen in 9 patients (26%), including hemorrhage in 3 patients, abdominal pain in 2, and abnormal electrolytes in 2. van Oosterom et al have treated 17 patients with GISTs at doses of STI571 ranging from 300 mg b.i.d. to 4000 mg daily. Four patients have had a PR, and 8 have SD with tumor size reduction and symptomatic improvement. Toxicity has included nausea, upper abdominal discomfort, diarrhea, liver function abnormalities, rash, and periorbital edema. These highly encouraging initial clinical results suggest that this molecularly targeted therapy will be the intervention of first choice for most patients with advanced or metastatic GISTs and will be evaluated either as primary therapy for patients who present with localized disease or as an adjuvant to tumor resection.

References
gastrointestinal tract suggests two distinct tumor suppressor loci. 


