History of GIST

• Historically GIST have been misdiagnosed as leimyomas or leimyosarcomas based on morphology.

• Immunohistochemistry in the 1980’s demonstrated that some of these tumors lacked features of smooth muscle differentiation, some had markers of neuronal differentiation and some had neither of the above markers.

• Mazur and Clark coined the term “gastrointestinal stromal tumors” to collectively refer a group of mesenchymal tumors of neurogenic or myogenic differentiation.

• The discovery of KIT led to the realization of GIST as a distinct entity from other non-epithelial GI tumors

Gastric stromal tumors
Reappraisal of histogenesis

ABSTRACT Twenty-eight gastric wall tumors classified by light microscopy as leiomyomas or leiomyosarcomas were reevaluated for histogenesis. Each case was analyzed for the presence of S-100 protein, a marker for cells derived from neuroectoderm, by the immunoperoxidase technique. Eight tumors contained cells with positive immunostaining for S-100 protein. Usually this staining was focal, but in one case staining was diffuse. In three additional cases the immunostaining outlined a nerve within the tumor. In contrast, two esophageal and 10 uterine leiomyomas, as well as normal gastric smooth muscle, gave negative reactions for S-100 protein. Twelve cases had tissue processed for electron microscopy. Only two of the tumors, one leiomyoma and one leiomyosarcoma, contained cytoplasmic myofilaments with densities expected in cells derived from smooth muscle; neither of these tumors stained for S-100 protein. In one case, the tumor with diffuse staining for S-100 protein, the cells resembled Schwann cells ultrastructurally. The remaining nine cases had neither smooth muscle nor Schwann cell features. They did contain interposed cell processes, primitive junctions, and large cytoplasmic vacuoles. The results of this study indicate that many gastric wall tumors are not derived from smooth muscle. The presence of S-100 protein suggests a nerve sheath origin in some cases. While the ultrastructure of many gastric tumors does not resemble nerve sheath cells in most peripheral nerves, the myenteric nervous system is a possible source for peri-neurial or mesenchymal nerve sheath cells with distinctive fine structure. Further study is needed to refine our knowledge of the histogenesis of gastric stromal tumors.

INTRODUCTION
The stromal tumors of the gastric wall generally are thought to originate from smooth muscle since they often have a prominent spindle-cell component and they involve the gastric musculature. Despite these reasonable assumptions, these neoplasms show light- and electron-microscopic features that are not commonly seen in leiomyomas and leiomyosarcomas arising in other sites. Specifically, by light microscopy gastric mesenchymal tumors often have epithelioid patterns, vacuolated cytoplasm, and nuclear palisading. Electron microscopy has shown that the component cells of gastric stromal tumors have cell processes and usually lack the typical microfilaments with densities, a hallmark of benign and malignant smooth muscle at other sites. Because of these morphologic differences, some authors have suggested that gastric stromal tumors may originate from other mesenchymal cells, although in the absence of additional knowledge of the exact type of progenitor cell, terminology applicable to smooth muscle has been retained.

The question of histogenesis has clinical relevance. Although it is generally possible to separate these tumors into benign and malignant categories, investigators have found that these tumors tend to have less predictable biologic behavior, based on mitotic activity, than uterine smooth muscle tumors. This clinical circumstance further suggests that these gastric tumors represent a unique and distinctive group of neoplasms that can be separated from leiomyomas and leiomyosarcomas.
In 1986 a new acute transforming feline retrovirus, the Hardy-Zuckerman 4 feline sarcoma virus (HZ4-FeSV) was isolated from a feline fibrosarcoma.

The viral genome of HZ4-FeSV contained a new oncogene that was designated v-kit. C-kit is the cellular homologue of the oncogene v-kit.

C-kit encodes a transmembrane tyrosine kinase receptor called KIT.
KIT Receptor Tyrosine Kinase

- Kit is a 145-KD glycoprotein which can be detected by immuno-histochemical staining for CD117
  - CD117 is an epitope on the extra-cellular domain of the Kit receptor
  - >95% of GIST are CD117 positive

- Steel factor (SLF), also known as stem-cell factor, is the ligand for Kit
  - Binding of SLF to Kit results in receptor homo-dimerization, activation of KIT tyrosine kinase activity, and resultant phosphorylation of a variety of substrates that serve as effectors of intracellular signal transduction.
  - GIST have characteristic gain of function mutations which result in ligand-independent activation of signal transduction

Gain-of-Function Mutations of c-kit in Human Gastrointestinal Stromal Tumors

Seichi Hirota,* Koji Isozaki,† Yasuhiro Moriya, Koji Hashimoto, Toshirou Nishida, Shingo Ishiguro, Kyoshi Kawano, Masato Hanada, Akihiko Kurata, Masashi Takeda, Ghalam Muhammad Tunio, Yui Matsuzawa, Yuzuru Kanakura, Yasuhisa Shinomura, Yukihiko Kitamura

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors in the human digestive tract, but their molecular etiology and cellular origin are unknown. Sequencing of c-kit complementary DNA, which encodes a proto-oncogene tyrosine kinase (KIT), from five GISTs revealed mutations in the region between the transmembrane and tyrosine kinase domains. All of the corresponding mutant KIT proteins were constitutively activated without the KIT ligand, stem cell factor (SCF). Stable transfection of the mutant c-kit complementary DNA induced malignant transformation of Ba/F3 murine lymphoid cells, suggesting that the mutations contribute to tumor development. GISTs may originate from the intestinal cells of Cajal (ICCs) because the development of ICCs is dependent on the SCF-KIT interaction and because, like GISTs, these cells express both KIT and CD34.

The c-kit proto-oncogene encodes a type II transmembrane protein tyrosine kinase (c-kit) that is ligand dependent. The only known substrate for this enzyme is SCF, the ligand of KIT. The c-kit gene is located on chromosome 4q12-q13. The ligand of SCF is a 100 kDa glycoprotein, which is secreted by various cell types, including fibroblasts, smooth muscle cells, and endothelial cells. SCF binds to the extracellular domain of c-kit, which is anchored to the plasma membrane by a hydrophobic amino acid sequence. The intracellular domain of c-kit contains an ATP-binding domain and tyrosine kinase activity. The activation of c-kit by SCF results in the phosphorylation of tyrosine residues in the cytoplasmic domain of the receptor, which in turn activates downstream signaling pathways, including the PI3K/AKT and MAPK/ERK pathways. These pathways are involved in cell proliferation, survival, and migration. The c-kit gene is amplified in some GISTs, leading to increased expression of the ligand-dependent c-kit protein.

Gastrointestinal stromal tumors (GISTs) are a group of mesenchymal tumors that arise from the interstitial cells of Cajal (ICCs) and other smooth muscle cells. The most common GIST is the GIST of the gastrointestinal tract, which is characterized by a gain-of-function mutation in the c-kit proto-oncogene. This mutation results in the constitutive activation of the c-kit receptor tyrosine kinase, leading to uncontrolled cell proliferation and survival. The c-kit proto-oncogene is located on chromosome 4q12-q13 and encodes a type II transmembrane protein tyrosine kinase (c-kit). The ligand of c-kit is SCF, a 100 kDa glycoprotein. The activation of c-kit by SCF results in the phosphorylation of tyrosine residues in the cytoplasmic domain of the receptor, which in turn activates downstream signaling pathways, including the PI3K/AKT and MAPK/ERK pathways. These pathways are involved in cell proliferation, survival, and migration. The c-kit gene is amplified in some GISTs, leading to increased expression of the ligand-dependent c-kit protein.

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*Corresponding author.
†Present address: Cancer Institute, Tokyo Women’s Medical University, Tokyo, Japan.
‡Present address: Department of Hematology-Oncology, National Cancer Center Hospital, Tokyo, Japan.
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P. Reichard

HELIOS Klinikum Berlin-Buch / Sarcoma Center Berlin-Brandenburg

5

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Interstitial Cells of Cajal as a Precursor to GIST

- Innervated network of KIT+ cells, amidst GI smooth muscle
- Pacemaker function coordinates peristalsis
- Absence of KIT function results in aperistalsis

Gastrointestinal Pacemaker Cell Tumor (GIPACT)

Gastrointestinal Stromal Tumors Show Phenotypic Characteristics of the Interstitial Cells of Cajal

Lars-Gunnar Kindblom, Helen E. Remotti, Frank Aldenborg, and Jeanne M. Meis-Kindblom
From the Departments of Pathology, Gothenburg Musculoskeletal Tumor Center, University of Gothenburg, Sahlgrenska University Hospital, Gothenburg, Sweden

The interstitial cells of Cajal (ICC) form a complex cell network within the gastrointestinal tract wall where they function as a pacemaker system. Expression of the kit proto-oncogene is essential for the development of this system. The aim of our study was to examine the hypothesis that gastrointestinal stromal tumors differentiate toward cells with an ICC phenotype. Ultrastructurally, 58 stromal tumors were characterized and found to share many features with ICC. Seventy-eight stromal tumors were immunophenotyped, particularly with regard to the kit receptor. All 78 tumors revealed strong, homogeneous immunoreactivity for the kit receptor as did ICC of adjacent and control gastrointestinal walls. Focal hyperplasia and hypertrophy of kit receptor positive cells were also observed in the gastrointestinal wall adjacent to the tumors. CD34 immunoreactivity observed in interstitial cells surrounding Auerbach’s ganglia suggests that a subpopulation of ICC is CD34 positive and may explain why 56 of 78 stromal tumors were CD34 positive. Thirty control tumors, including gastrointestinal leiomyomas and leiomyosarcomas, were all negative for the kit receptor. We conclude that gastrointestinal stromal tumors show striking morphological and immunophenotypic similarities with ICC and that they may originate from stem cells that differentiate toward a pacemaker cell phenotype. We propose that the noncommittal name “gastrointestinal stromal tumor” be replaced by gastrointestinal pacemaker cell tumor. (Am J Pathol 1998; 152:1259–1269)

Despite numerous studies, gastrointestinal stromal tumors remain problematic with regard to origin, differentiation, nomenclature, and prediction of prognosis. Their morphological spectrum is wide, ranging from bland to frankly malignant tumors with spindled and/or epithelioid appearances.1–3 Hence, a variety of names such as epithelioid or bizarre leiomyomas, epithelioid leiomyosarcomas or leiomyoblastomas, and gastrointestinal autonomic nerve tumors (GANT) have been used for these tumors reflecting the various views regarding their differentiation, classification, and prognosis.4–8 The noncommittal term gastrointestinal stromal tumor has recently gained wide acceptance, emphasizing their entigmatic origin and the fact that most of these lesions do not display convincing smooth muscle or neuronal differentiation.9–11

The existence of a complex system of interstitial cells of Cajal (ICC), which are intercalated between the autonomic nerves and the muscle walls of the gastrointestinal tract, has been known for over 100 years.12 Detailed morphological and electrophysiological studies in many species, including humans, have indicated that ICC have a pacemaker function.13–15 Recently, ICC were found to express the kit proto-oncogene, which encodes for a transmembrane tyrosine kinase receptor (CD117) and has the stem cell factor as its ligand. Expression of the kit gene is essential for the development of normal hematopoiesis, proliferation, and migration of primordial germ cells and melanoblasts during embryogenesis as well as for the development of the ICC and gastrointestinal pacemaker activity.16–21 A cluster of human type III receptor protein tyrosine kinase genes, including the kit gene, has been mapped to chromosome 4q11-q12.22

The present study was designed to test the hypothesis that gastrointestinal stromal tumors differentiate toward an ICC phenotype. Ultrastructural examination and immunohistochemical analysis for the kit tyrosine kinase receptor (CD117) was performed in a large series of well-characterized stromal tumors along with appropriate normal tissues and tumor controls. The results of this study support our hypothesis that gastrointestinal stromal tumors originate from a stem cell that differentiates toward an ICC phenotype.

Supported by the Swedish Cancer Society (0530:896–2338C) and Göteborgs Läkareutlaget, Sweden (23497).

Accepted for publication February 19, 1998.

Address reprint requests to Dr. Lars-Gunnar Kindblom, Sahlgrenska University Hospital, Department of Pathology, 5-413 45 Gothenburg, Sweden.
Gastrointestinal Stromal Tumors

- Around 5,000 to 6,000 new cases each year
- Tends to occur in middle aged persons with a slight male predilection
- Occur throughout the GI tract
  - Stomach 50-60%
  - Small bowel 20-30%
  - Large bowel 10%
  - Esophagus 5%
  - Elsewhere in abdomen 5%

Prognosis of GIST

• The 5-year survival for malignant GIST varies widely and has been reported to be from 28 to 60%.

• Median survival times
  - Unresectable disease: 10–23 months.
  - Metastatic or recurrent disease: 12 -19 months.

Imatinib Mesylate

- Inhibits intracellular kinase domains of ABL, KIT, and PDGFR
- Abrogates kinase signaling by inhibition of ATP binding and substrate docking

Treatment with four 100 mg capsules of STI571 once daily was started in March 2000.
**Imatinib Mesylate in Advanced/Unresectable GIST**

<table>
<thead>
<tr>
<th></th>
<th>400 Mg N = 73</th>
<th>600 Mg N = 74</th>
<th>Either Dose N = 147</th>
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<tbody>
<tr>
<td><strong>Response Rate</strong></td>
<td>49%</td>
<td>58%</td>
<td>54%</td>
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<tr>
<td><strong>Stable Disease</strong></td>
<td>32%</td>
<td>24%</td>
<td>28%</td>
</tr>
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</table>

- This trial led to the approval of imatinib mesylate for GIST in February, 2002

Time to Progression and Survival

# Studies of Imatinib Therapy in GIST

<table>
<thead>
<tr>
<th>Pilot Study Exploratory Study (N = 1)¹</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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<tbody>
<tr>
<td>Dose-Finding Study (N = 40)²</td>
<td>B2222 Open-Label Study (N = 147)³</td>
<td>EORTC 62005 Randomized Study (N = 946)⁵</td>
<td></td>
</tr>
<tr>
<td>• 1 patient</td>
<td>• Efficacy and safety</td>
<td>• Efficacy and safety</td>
<td></td>
</tr>
<tr>
<td>• 400 mg/d</td>
<td>• 400 vs 1000 mg/d</td>
<td>• 400 vs 800 mg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Metastatic GIST (EORTC)</td>
<td>• Metastatic or unresectable GIST</td>
<td></td>
</tr>
</tbody>
</table>

- EORTC phase 2 study (N = 51)⁴
  - Efficacy and safety
  - Advanced or metastatic GIST and other soft-tissue sarcomas

- US Intergroup S0033 Study (N = 746)⁶
  - Efficacy and safety
  - 400 vs 800 mg/d
  - Metastatic or unresectable KIT-positive GIST

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Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial

Jeroen Verweij, Paulus G. Comf, John Zalikher, Joep LeCerf, Peter Reichardt, Jean-François Bay, Rolf Meier, Allan van Oosterom, Pancoas C. W. Hengeveld, Martine Van Glabbeke, Rauwel van der Velden, Jan Jongsma, for the EORTC Soft Tissue and Bone Sarcoma Group, the Italian Sarcoma Group, and the Australasian Gastrointestinal Trials Group

Summary
Background Imatinib is approved worldwide for use in gastrointestinal stromal tumours (GIST). We aimed to assess dose dependency of response and progression-free survival with imatinib for metastatic GIST.

Methods 946 patients were randomly allocated imatinib 400 mg either once or twice a day. Those assigned the once-a-day regimen who had progression were offered the option of crossover. The primary endpoint was progression-free survival. Analysis was by intention to treat.

Findings At median follow-up of 769 days (IQR 644–859), 263 (56%) of 473 patients allocated imatinib once a day had progressed compared with 235 (59%) of 473 who were assigned treatment twice a day (estimated hazard ratio 0.82 [95% CI 0.68–0.98]; p=0.026). Side-effects arose in 465 (78%) patients allocated the once-daily regimen compared with 448 (72%) assigned treatment twice a day. By comparison with the group treated once a day, more dose reductions (77 [16%] vs 282 [60%]) and treatment interruptions (118 [26%] vs 302 [64%]) were recorded in patients allocated the twice daily regimen, but treatment in both arms was fairly well tolerated. 52 (5%) patients achieved a complete response, 442 (47%) a partial response, and 300 (32%) stable disease, with no difference between groups. Median time to best response was 167 days (IQR 55–172).

Interpretation If response induction is the only aim of treatment, a daily dose of 400 mg of imatinib is sufficient; however, a dose of 400 mg twice a day achieves significantly longer progression-free survival.

Introduction Gastrointestinal stromal tumours (GIST) are a subgroup of soft-tissue sarcomas with an estimated prevalence of 13–20 per 1 000 000. These tumours are thought to arise from Cajal cells in intestinal walls, which are important for intestinal motor function. GIST were previously classified as leiomyoma, leiomyosarcoma, or leiomyosarcoma. They are insensitive to conventional chemotherapy and are generally characterised by a gain-of-function mutation of the KIT receptor and, occasionally, of the platelet-derived growth factor receptor α. The clinical activity of imatinib—a small-molecule tyrosine-kinase inhibitor active against BCR-ABL, KIT, and platelet-derived growth factor—has been confirmed in GIST, both in the EORTC (European Organisation for Research and Treatment of Cancer) phase 1 study, in which the highest feasible dose of imatinib was identified as 400 mg twice a day, and in phase II studies with doses of 400–800 mg daily. Imatinib is approved worldwide for use in GIST, with a usual recommended dose of 400 mg daily. However, we still do not know whether the highest feasible daily dose yields a higher initial response rate or a better progression-free survival than the recommended dose. For this reason, we did a randomised trial to compare imatinib 400 mg once a day with 400 mg twice daily.

Verweij et al. Lancet. 2004 Sep 25-Oct 1;364(9440):1127-34
Progression-Free Survival according to mutational status

Comparison of Two Doses of Imatinib for the Treatment of Unresectable or Metastatic Gastrointestinal Stromal Tumors: A Meta-Analysis of 1,640 Patients

Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST)
Follow-up results after 9 years of the ongoing, phase II B2222 trial of imatinib mesylate in patients with metastatic or unresectable KIT+ gastrointestinal stromal tumors (GIST)
M. von Mehren et al., J Clin Oncol 29: 2011 (suppl; abstr 10016)

Results

- PFS at 9 yrs was similar for patients with CR/PR (16%) or SD (17%) as best overall SWOG response
EORTC 62005: PFS / OS

Casali PG et al., CTOS 2013
## Overall Survival Estimates for Advanced GIST patients on S0033 treated with imatinib

<table>
<thead>
<tr>
<th>Survival (years)</th>
<th>OS Estimate</th>
<th>95% CI</th>
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<tr>
<td>5</td>
<td>46%</td>
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<tr>
<td>6</td>
<td>39%</td>
<td>36% - 43%</td>
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<tr>
<td>7</td>
<td>35%</td>
<td>31% - 38%</td>
</tr>
<tr>
<td>8</td>
<td>31%</td>
<td>28% - 35%</td>
</tr>
<tr>
<td>9</td>
<td>26%</td>
<td>23% - 30%</td>
</tr>
<tr>
<td>10</td>
<td>22%</td>
<td>19% - 26%</td>
</tr>
</tbody>
</table>
Risk of recurrence after surgery alone

Pooled data from 10 population-based GIST series

~60% likely cured by surgery alone

## AFIP Risk Group Classification

<table>
<thead>
<tr>
<th>Group</th>
<th>Group definition</th>
<th>Patients with progressive disease during long-term follow-up</th>
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<tbody>
<tr>
<td></td>
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<td>Gastric</td>
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<tr>
<td>1</td>
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</tr>
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<td>3b</td>
<td>&gt;10.0 cm, &lt;5/50 HPF</td>
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<tr>
<td>4</td>
<td>&lt;2.0 cm, &gt;5/50 HPF</td>
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<tr>
<td>6a</td>
<td>5.1-10.0 cm, &gt;5/50 HPF</td>
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</tr>
<tr>
<td>6b</td>
<td>&gt;10.0 cm &gt;5/50 HPF</td>
<td>86</td>
</tr>
</tbody>
</table>

*very low numbers

*Miettinen M, Lasota J., Sem Diagn Pathol 2006;23:70-83*
## AFIP Risk Group Classification

<table>
<thead>
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<th>Group definition</th>
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<td></td>
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<td>%</td>
<td>%</td>
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<tr>
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<td>86</td>
<td>90</td>
<td>86*</td>
<td>71*</td>
<td></td>
</tr>
</tbody>
</table>

*very low numbers

Miettinen M, Lasota J., Sem Diagn Pathol 2006;23:70-83
Prognostic contour maps, 10-year RFS

Rupture?

No rupture

Rupture present

Adjuvant Imatinib Therapy for GIST: Rationale

- High rates of recurrence after resection, especially in patients with high-risk GIST

- Imatinib represents effective oral therapy with a low toxicity profile and may be effective as an adjuvant to surgery in:
  - Treatment of low-volume microscopic disease

- Randomised trials investigating use of imatinib in an adjuvant setting:
  - ACOSOG Z9001 (ASCO 2007, Lancet 2009)
  - SSGXVIII (ASCO 2011, JAMA 2012)
  - EORTC 62024
Z9001: Recurrence-Free Survival

Z9001: Overall Survival

Influence of mutational status on outcome of adjuvant imatinib

RFS for Exon 11

- Imatinib (n=173)
- Placebo (n=173)

RFS for Exon 9

- Placebo (n=22)
- Imatinib (n=13)

RFS for Wildtype

- Placebo (n=32)
- Imatinib (n=32)

RFS for PDGFRA

- Imatinib (n=29)
- Placebo (n=28)

- D842V
- Imatinib (n=15)
- Placebo (n=13)

Corless CL et al. JCO 2010; 28(15a): suppl; abstract 10006.
SSGXVIII/AIO: RFS and OS

A  Recurrence-free survival: intention-to-treat population

36 Months of imatinib

HR, 0.46 (95% CI, 0.32-0.65)
Log-rank $P < .001$

12 Months of imatinib

No. of patients
36 Months of imatinib 198 184 173 133 82 39
12 Months of imatinib 199 177 137 88 49 27

C  Overall survival: intention-to-treat population

36 Months of imatinib

HR, 0.45 (95% CI, 0.22-0.89)
Log-rank $P = .02$

12 Months of imatinib

No. of patients
36 Months of imatinib 198 192 184 152 100 56 13
12 Months of imatinib 199 188 176 140 87 46 20

Joensuu, ..., Reichardt et al., JAMA 307:1265-1272, 2012
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of patients</th>
<th>Hazard ratio (95% CI), RFS</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>36 mo better</td>
<td>12 mo better</td>
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</tr>
<tr>
<td>Age</td>
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<tr>
<td>≤65</td>
<td>256</td>
<td>0.47 (0.30-0.74)</td>
<td>.001</td>
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<td>&gt;65</td>
<td>141</td>
<td>0.49 (0.28-0.85)</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Male</td>
<td>201</td>
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<td>.002</td>
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<tr>
<td>Female</td>
<td>196</td>
<td>0.46 (0.28-0.76)</td>
<td>.002</td>
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<tr>
<td>Tumor site</td>
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<tr>
<td>Stomach</td>
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<td>Other</td>
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<td>≤10 cm</td>
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</tr>
<tr>
<td>&gt;10 cm</td>
<td>176</td>
<td>0.47 (0.29-0.76)</td>
<td>.002</td>
</tr>
<tr>
<td>Mitoses/50 HPF (local)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10 mitoses</td>
<td>209</td>
<td>0.76 (0.43-1.32)</td>
<td>.33</td>
</tr>
<tr>
<td>&gt;10 mitoses</td>
<td>154</td>
<td>0.29 (0.17-0.50)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mitoses/50 HPF (central)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10 mitoses</td>
<td>238</td>
<td>0.53 (0.30-0.94)</td>
<td>.03</td>
</tr>
<tr>
<td>&gt;10 mitoses</td>
<td>133</td>
<td>0.36 (0.22-0.59)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Tumor rupture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>318</td>
<td>0.43 (0.28-0.66)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Yes</td>
<td>79</td>
<td>0.47 (0.25-0.89)</td>
<td>.02</td>
</tr>
<tr>
<td>Tumor mutation site</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>KIT exon 9</td>
<td>26</td>
<td>0.62 (0.22-1.70)</td>
<td>.35</td>
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<tr>
<td>KIT exon 11</td>
<td>256</td>
<td>0.35 (0.22-0.56)</td>
<td>&lt;.001</td>
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<tr>
<td>Wild type</td>
<td>33</td>
<td>0.41 (0.14-1.51)</td>
<td>.18</td>
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<tr>
<td>Other</td>
<td>51</td>
<td>0.78 (0.22-2.78)</td>
<td>.71</td>
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</tbody>
</table>

Joensuu, ..., Reichardt, JAMA 307:1265-1272, 2012
EORTC 62024: Imatinib failure-free survival in high risk

Imatinib Failure free Survival (IFS)
High risk by LOCAL pathology

Overall Logrank test: p=0.087

<table>
<thead>
<tr>
<th>O</th>
<th>N</th>
<th>Number of patients at risk</th>
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<tr>
<td>61</td>
<td>262</td>
<td>248 230 208 150 62 13</td>
</tr>
<tr>
<td>48</td>
<td>266</td>
<td>259 247 230 172 76 17</td>
</tr>
</tbody>
</table>

Casali et al., J Clin Oncol 31, 2013 (suppl; abstr 10500)
Correlation of *KIT*- and *PDGFRA*-Mutations and Primary Location

GSRCB* (n=1231)
*GSRCB = GIST and Sarcoma Registry Cologne/Bonn
Risk Factors for Gastrointestinal Stromal Tumor Recurrence in Patients Treated With Adjuvant Imatinib

Heikki Joensuu, MD; Mikael Eriksson, MD; Kirsten Sundby Hall, MD; Jörg T. Hartmann, MD; Daniel Pink, MD; Jochen Schütte, MD; Giuliano Ramadori, MD; Peter Hohenberger, MD; Justus Duyster, MD; Salah-Eddin Al-Batran, MD; Marcus Schiemmer, MD; Sebastian Bauer, MD; Eva Wardeleman, MD; Maarit Sarlomo-Rikala, MD; Bengt Nilsson, MD; Harri Sihvo, PhD; Karla V. Ballman, PhD; Mika Leinonen, MSc; Ronald P. DeMatteo, MD; and Peter Reichardt, MD

![Graph showing recurrence rates over time.](image)
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B

Alive without recurrence (%)

Gastric (n = 191, censored 151)
Non-gastric (n = 165, censored 91)

P < .001

Time (years)

D

Alive without recurrence %

≤5/50 HPFs (n = 165, censored 137)
6-10/50 HPFs (n = 2, censored 39)
11-15/50 HPFs (n = 34, censored 19)
15-20/50 HPFs (n = 19, censored 10)
21-50/50 HPFs (n = 55, censored 23)
>50/50 HPFs (n = 16, censored 5)

P < .001

Time (years)

Cancer August 1, 2014
Risk Factors for Gastrointestinal Stromal Tumor Recurrence in Patients Treated With Adjuvant Imatinib

Heikki Joensuu, MD1; Mikael Eriksson, MD2; Kirsten Sundby Hall, MD2; Jörg T. Hartmann, MD4; Daniel Pink, MD5; Jochen Schütte, MD6; Giuliano Ramadori, MD7; Peter Hohenberger, MD8; Justus Duyster, MD9; Salah-Eddin Al-Batran, MD10; Marcus Schiemmer, MD11; Sebastian Bauer, MD12; Eva Warthmann, MD11; Maarit Sarlomo-Rikala, MD14; Bengt Nilsson, MD13; Harri Sihto, PhD14; Karla V. Ballman, PhD13; Mika Leinonen, MSc15; Ronald P. DeMatteo, MD15; and Peter Reichardt, MD15

A

- Lowest risk (n = 197, censored 165)
- Intermediate high risk (n = 104, censored 58)
- Highest risk (n = 39, censored 9)

Alive without recurrence (%)

P < .001

Time (years)

B

- 36 Mo, Lowest risk (n = 102, censored 89)
- 12 Mo, Lowest risk (n = 95, censored 76)
- 36 Mo, Intermediate high risk (n = 48, censored 33)
- 12 Mo, Intermediate high risk (n = 56, censored 25)
- 36 Mo, Highest risk (n = 15, censored 5)
- 12 Mo, Highest risk (n = 24, censored 4)

Alive without recurrence (%)

P < .001 for the 12-month groups
P < .001 for the 36-month groups

Time (years)

highest risk, gastric GIST with >50 mitoses or non-gastric GIST with >20 mitoses per 50 high-power fields.

Cancer  August 1, 2014
Three versus five years of adjuvant imatinib as treatment of patients with operable GIST with a high risk for recurrence: A randomised phase III study

### Trial design

**Preceding trial**
- **High-risk GIST**
  - Gastro GIST with >10 mitoses/50 HPFs; or nongastro GIST with >5 mitoses/50 HPFs

**On trial**
- **Randomise**
  - Ratio: 1:1
  - n = 300

**Arm A**
- Imatinib for 24 months
- Follow-up

**Arm B**
- Follow-up

**NUMBER OF PATIENTS**
- 300 patients to be randomised in 1:1 ratio, 150 to imatinib for further 24 months and 150 to stop imatinib.

**RANDOMISATION**
- Central randomisation. At randomisation, the patients are stratified by the imatinib dose preceding randomisation (<400 mg/day, 400 mg/day, or >400 mg/day). The centres will keep a log of patients who received the informed consent.