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Targeted therapy for cancer: the GIST model

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Synopsis

GISTs are unique tumors that arise largely due to oncogenic mutations in *KIT* or *PDGFRA* tyrosine kinases. Although surgery remains the most effective treatment, the remarkable clinical success achieved with kinase inhibition in both the adjuvant and metastatic settings has made GIST one of the most successful examples of targeted therapy for the treatment of cancer. The insight gained from this approach has allowed a deeper understanding of the molecular biology driving kinase dependent cancers, and the adaptations to kinase inhibition, linking genotype to phenotype. Mutation tailored kinase inhibition with second generation TKI's, and combination immunotherapy to harness the effects of TKIs and achieve longer durable responses, remain exciting areas of investigation.

Keywords

gastrointestinal stromal tumor; sarcoma; KIT; imatinib; tyrosine kinase

Introduction

Gastrointestinal stromal tumor (GIST) is the most common sarcoma, accounting for approximately 18% of all sarcomas and 1% of all intestinal neoplasms.[1] The annual incidence of GIST as determined by population-based studies is approximately 10 cases per million.[2–4] GISTs have historically portended a poor prognosis. Up to 50% of patients have recurrent disease 5 years after complete resection. Median survival in metastatic GIST used to be approximately 9 months as it is inherently resistant to chemotherapy and radiation.[5–7] The discovery of oncogenic tyrosine kinase mutations in GIST, and the successful application of kinase inhibitor therapies have made GIST a model of targeting aberrant signal transduction to treat cancer. Lessons learned from this approach have allowed new insight into the molecular biology and mechanisms of resistance of kinase driven cancers. It

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has spurred development of novel targeted inhibitors and uncovered exciting possibilities for combination therapy with other systemic agents.

Oncogenic kinase mutations and GIST pathogenesis

KIT

In 1998, two important discoveries were made that furthered our understanding of GIST biology. Hirota and colleagues described their landmark discovery of gain-of-function mutations in *KIT* in 5 GIST patients.[8] They hypothesized that these were oncogenic driver mutations, as Ba/F3 lymphoid cells transfected with mutant *KIT* cDNA underwent malignant transformation. Shortly thereafter, two groups reported that 95% of GISTs are immunohistochemically positive for the receptor tyrosine kinase KIT, also known as CD117.[9, 10] Since then, a causal relationship between *KIT* mutations and GIST pathogenesis has been further supported by many lines of evidence. Mutant *KIT* induces constitutive kinase activation without ligand binding.[8, 11, 12] *KIT* mutations have been discovered in very small GISTs, suggesting it occurs as a very early event.[13, 14] GIST tumor extracts almost universally demonstrate phosphorylated KIT.[15] Transgenic *Kit* knock-in mouse models develop spindle cell tumors that are morphologically similar to human GIST.[16, 17] Finally, KIT blockade in vitro and in vivo inhibits tumor growth.[12, 18–21]

KIT, a receptor tyrosine kinase, binds KIT ligand (stem cell factor), which results in receptor dimerization, phosphorylation and activation of downstream signaling pathways that promote cell proliferation and survival. It is now known that 70–80% of GISTs harbor a *KIT* mutation that induces constitutive kinase activation. Mutations most commonly occur in the juxtamembrane domain in exon 11 (Table 1, Figure 1), which normally inhibits the kinase activation loop in the absence of ligand binding. Exon 11 mutations include in-frame deletions, insertions, and substitutions, but deletions are the most common. Mutations also occur in the extracellular domains (exons 8 (rarely) and 9), and infrequently in the kinase domains (exons 13 and 17) (Table 1, Figure 1).[22] The downstream signaling pathways activated include the MAPK, PI3K-AKT, and STAT3 pathways, which lead to inhibition of apoptosis and cell proliferation.[22] Recently, ETV1, a lineage survival factor in interstitial cells of Cajal (ICC), the hypothesized cell of origin for GIST, was shown to cooperate with activated KIT to induce GIST tumorigenesis.[23]

PDGFRA

Approximately one third of GISTs that do not have a mutation in *KIT* (8% of all GISTs) harbor a mutation in a closely related tyrosine kinase, platelet-derived growth factor receptor alpha (PDGFRA).[24, 25] *PDGFRA* and *KIT* mutations are mutually exclusive in GIST. Like mutations in *KIT, PDGFRA* mutations are found in its juxtamembrane domain (Table 1, Figure 1), ATP binding domain, or activation loop, and cause ligand independent receptor activation. An oncogenic role for these mutations in GIST has followed evidence similar to that for KIT - mutant *PDGFRA* induces ligand independent receptor activation, and PDGFRA inhibition induces cellular arrest.[24–26] PDGFRA mutant GISTs do however have unique clinical profiles, including gastric location, epithelioid morphology, variable KIT expression, and a more indolent clinical course.[27]

Wild type GIST

10–15% of tumors do not have mutations in *KIT* and *PDGFRA* (WT GIST). Other mutations that may contribute to tumorigenesis have been recently uncovered (Table 1). Similar to *BRAF* mutations in melanoma, papillary thyroid cancer, and colorectal cancer, GIST *BRAF* mutations have also been identified in 7–15% of WT GISTS within the exon 15 V600E hot-spot.[28, 29] BRAF proteins and constituents of the MAPK signaling pathway can stimulate cell growth independent of KIT and are a possible cause of resistance to KIT and PDGFRA kinase inhibitors. Mutations in the succinate dehydrogenase (SDH) respiratory chain complex have also been discovered in WT GIST. *SDH* mutations were initially identified in the germline in subunits *SDHB, SDHC*, and *SDHD*, predisposing affected individuals to GIST and paraganglionomas (Carney-Stratakis syndrome). They have since been identified in 12% of WT GIST (Table 1).[30] Mutations in *SDHA* have also since been reported.[31] The precise oncogenic role of SDH mutations in GIST remains to be elucidated. Expression of insulin-like growth factor 1 receptor (IGF1R), that signals through MAPK and PI3K-AKT pathways, has also been detected and may contribute to GIST pathogenesis.[32] WT GISTs are also found in 7% of patients with neurofibromatosis type I (NF1), who harbor germline mutations in the neurofibromin 1 gene (Table 1).[33]

Targeting kinase pathways in GIST

Until 2000, outcomes in patients with metastatic GIST were extremely poor. Median survival was approximately 9 months, and responses to conventional chemotherapy was < 5%.[5–7] The discovery of oncogenic *KIT* mutations in GIST coincided with the successful clinical development and application of the tyrosine kinase inhibitor imatinib (Gleevec) for the treatment of chronic myelogenous leukemia. It was noted that the kinases KIT and ABL shared structural similarity, prompting the first clinical application of imatinib in a 50-year-old female with advanced GIST, which was met with a dramatic clinical response.[34] This led to phase I, II, and two international phase III trials to investigate the benefit of imatinib in the metastatic setting. Overall, imatinib achieved disease control in 70–85% of patients with KIT-positive GIST, with a median progression-free-survival of 20–24 months, and an estimated overall survival over 36 months (Figure 2).[6, 7, 35, 36] The advent of imatinib therapy for metastatic GIST has dramatically altered prognosis - currently, median survival is 5 years with 34% of patients surviving more than 9 years.[33] Imatinib is first line treatment in patients with metastatic GIST, and treatment is recommended to continue indefinitely as long as there is clinical benefit, as interruption is associated with high rate of relapse.[37]

Paralleling the success in GIST, a molecular approach to systemic therapy has been adopted in many other solid tumors. Genomic analyses have uncovered biologically relevant and druggable kinase mutations in other solid malignancies. Although the success achieved in these cancers has not replicated the GIST success, it has validated a molecular approach to systemic treatment and has heralded kinase based therapies as an integral component of cancer care (Table 2).

Assessing response to kinase therapy

Responses to systemic therapy in solid tumors have been traditionally assessed using the response evaluation criteria in solid tumors (RECIST), which incorporates unidirectional tumor size. However assessing responses using RECIST has been shown to be insensitive in GIST.[38] PET scans had been traditionally used to assess continuing responses to TKI treatment, as significant decreases in FDG signal is seen within 24 hours in patients responding to imatinib.[39] However, Choi and colleagues proposed using CT determined tumor size and density in assessing treatment response - responding tumors demonstrate homogeneous and hypodense features, losing solid elements and neovascularity.[40, 41] The Choi criteria correlate with PET, are superior to RECIST, and are a significant improvement in our understanding of assessing clinical responses to systemic agents in solid tumors.

Combining targeted therapy with surgery

Adjuvant imatinib

While TKI therapy induces tumor regression in the majority of patients, it rarely induces complete responses. Even long-term TKI therapy fails to eradicate GIST cells, with viable tumor cells detected even in tumors with good histologic responses.[42] In contrast, surgery for patients with primary GIST without metastases cures over 50% of patients.[43] In a double-blind, placebo-controlled, multicenter, randomized trial, the American College of Surgeons Oncology Group (ACOSOG) demonstrated that one year of adjuvant imatinib following resection of GISTs at least 3 cm in size significantly improved 1-year RFS (83% in placebo arm versus 98% in imatinib arm, Figure 3).[44] Based on these results, the Food and Drug Administration (FDA) approved imatinib for use in the adjuvant setting. Recently, it was shown that patients at high risk of recurrence treated with 3 years of adjuvant imatinib following surgical resection have 5-year RFS and overall survival (OS) rates of 65.6% and 92% respectively, compared to 47.9% and 81.7% in patients treated with 1 year of adjuvant imatinib.[45] However, there was no difference in disease-specific survival between 1 and 3 years of therapy. An additional phase III trial is currently examining the outcomes after 2 years of adjuvant imatinib following surgery. A phase II, non-randomized, multicenter trial is also evaluating the efficacy of 5 years of adjuvant imatinib following complete resection of primary GIST. The success of adjuvant imatinib in GIST ranks with trastuzumab as one the most successful applications of kinase inhibitor therapy for the adjuvant treatment of solid tumors.[46]

Neoadjuvant imatinib

When primary GIST appears borderline resectable or unresectable, neoadjuvant imatinib treatment may allow for tumor shrinkage and a subsequent R0 resection. Preliminary phase II trials have demonstrated the safety and efficacy of preoperative imatinib.[47–49] However, there are no published phase III data on neoadjuvant imatinib for unresectable GIST. This is an area of ongoing investigation.

Molecular biology and risk stratification

Similar to other sarcomas, tumor size, mitotic index, and location have been shown to determine biological aggressivenesss in GIST.[50] However, the discovery of oncogenic kinase mutations has allowed new insight into links between molecular biology and clinical behavior. It is now clear that recurrence patterns after primary resection are also governed by mutation type - deletion and insertion mutations in *KIT* exon 11, and exon 9 confer higher recurrence rates compared to other mutations.[50, 51] Within exon 11 mutations, deletions (specifically in amino acids 557 and/or 558) have worse outcome.[50, 52, 53] Currently, our understanding of risk stratification to predict the natural history of resected disease is achieved through prognostic nomograms. We developed a nomogram predicting 2-year and 5-year RFS factoring tumor size, mitotic index, and location (Figure 4).[54] Dei Tos and colleagues have reported a nomogram predicting 10-year overall survival.[55] Currently, the relationship between mutation type, adjuvant imatinib, and other factors in the nomogram remain unclear.

TKI resistance

Although most patients initially respond to TKI therapy, the majority develops resistance. Over 50% of patients develop disease progression by 2 years.[56] Primary resistance, defined as progression within the first 6 months of treatment, occurs in 10% of patients. Resistance is linked to kinase genotype and TKI sensitivity - patients with *KIT* exon 11 or 9 mutation or WT GISTs have a 5%, 16%, and 23% probability of demonstrating primary imatinib resistance.[57] PDGFRA D842V mutations are strongly resistant to imatinib *in vitro* and *in vivo*. The mechanism of primary resistance remains unclear.

Patients with secondary resistance develop disease progression after an initial benefit from imatinib, predominantly due to secondary mutations in the identical gene and allele as the primary oncogenic driver mutation.[33, 56, 58–64] More than 80% of drug-resistant GIST tumors harbor secondary mutations.[33, 65–67] Secondary mutations may disrupt imatinib binding, or stabilize the active conformation of the KIT kinase.[56, 60] The mechanism of development of second site mutations remains unclear. Long-term imatinib therapy can also lead to "polyclonal acquired resistance", whereby different tumor nodules acquire different secondary mutations, and progress independently.[56, 63, 68, 69] Additionally, up to one-third of secondary resistant GIST lack secondary mutations, where possible mechanisms of resistance include *KIT* genomic amplification and alternate tyrosine kinase activation.[42] These findings have provided invaluable insight into a common endpoint of kinase inhibitor therapy in solid tumors and have guided the development of second line TKIs. However, the genetic complexity of acquired resistance argues against second line TKI monotherapy providing durable clinical benefit.

Strategies to combat TKI resistance

Second line TKIs

Imatinib dose escalation is the initial recommendation for patients progressing on imatinib as 20–30% of patients may have 1 year or more of disease control.[36] Multiple salvage TKIs

are in development to combat imatinib resistance (Table 3). Currently, sunitinib, a TKI that inhibits KIT, PDGFRA, PDGFRB, Fms-like tyrosine kinase-3 receptor, RET, and vascular endothelial growth factor receptors (VEGFR) 1, 2, and 3, is the second line TKI of choice in patients with generalized disease progression who have failed imatinib dose escalation or who are imatinib intolerant. Demetri et al. demonstrated that patients with imatinib-resistant GIST treated with sunitinib had a median time to progression of 27.3 weeks compared to 6.4 weeks for placebo.[70] Despite the remarkable success with imatinib, results with second line TKIs in GIST have been poor, underscoring the need for new treatment strategies.[71–74] Regorafenib was recently FDA approved as a third line agent.[74]

Surgery and TKI therapy for metastatic disease

TKI therapy has been combined with surgery in the metastatic setting. We found that metastatic GIST patients with focal resistance (1 tumor growing) on imatinib who were treated with surgery had a 2-year OS of 36% compared to 100% in patients with imatinib-responsive or stable tumors. Patients with multifocal resistance (more than 1 tumor growing) had a 1-year OS of 36%.[75] Other groups have also reported a lack of clinical benefit for patients progressing on imatinib treated with surgery.[76, 77] Identifying the patient cohort and quantifying the precise benefit from surgery after imatinib in the metastatic setting remains an area needing further examination.

Combination targeted therapy and immunotherapy

In addition to inhibition of oncogenic signaling pathways, targeted agents are potent immunomodulators. They promote dendritic cell maturation and T cell priming, increase death receptor expression on tumor cells sensitizing them to immune-mediated tumor clearance, and diminish tumor-induced immunosuppression.[78] The immune system has also been shown to be important in GIST. In imatinib treated GIST patients, progression-free survival correlated with IFN-γ secretion by natural killer (NK) cells in the blood.[79] We demonstrated that the antitumor effects of imatinib, previously thought to act exclusively via oncogenic kinase inhibition in tumor cells, relies partially on indirect effects of the immune system. Using a mouse model of spontaneous GIST, we found that imatinib therapy activated CD8$^+$ T cells and induced inhibitory regulatory T cell (Treg) apoptosis, thereby increasing the intratumoral CD8$^+$ T cell/ Treg ratio, a hallmark of immunologic outcome.[80] The mechanism relied on imatinib inhibiting tumor-cell expression of the immunosuppressive enzyme indoleamine 2,3-dioxygenase (IDO), by reducing expression of the transcription factor ETV4, and disrupting its ability to bind the IDO promoter. Extending these findings in vivo, we correlated the intratumoral CD8$^+$ T cell/ Treg ratio to imatinib response and intratumoral IDO expression in freshly analyzed human GIST tumors. Our results link acquired resistance to imatinib to restoration of intratumoral immunosuppression. Hence molecular and immune resistance in GIST appear to be intertwined. To investigate whether imatinib synergizes with immune modulating agents, we combined imatinib therapy with blockade of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), a known T cell and IDO modulator. Tumor size was significantly decreased in mouse GIST compared to either treatment alone. These data demonstrate the rationale and potential of combining targeted therapy with immunotherapy to improve outcomes in not only GIST, but also other solid tumors treated with TKIs. Currently, we are conducting an

NCI sponsored phase I trial examining the effects of CTLA-4 inhibition with dasatanib in GIST and other sarcomas. Multiple other groups are investigating combining targeted agents and immune agents, including a phase II trial examining vemurafenib and CTLA-4 blockade in patients with melanoma who have V600E *BRAF* mutations.[78]

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Key Points

- GISTs are unique solid tumors as they are driven predominantly by oncogenic mutations in *KIT* or *PDGFRA* tyrosine kinases.

- Surgery is the most effective treatment for localized, primary GIST. Adjuvant tyrosine kinase inhibition (TKI) with imatinib substantially decreases recurrence rates but does not appear to affect overall survival.

- Imatinib is initial therapy for metastatic GIST however acquired mutations frequently lead to resistance after initial responses. The role of surgery and TKI in metastatic GIST remains unclear.

- Imatinib dose escalation, sunitinib, and regorafenib are the initial therapeutic options for imatinib resistant GIST, with many novel TKIs currently under investigation.

- Preclinical data suggest antitumor effects of imatinib in GIST are partially dependent on host immune responses. Combination imatinib and immunotherapy may be effective in GIST and other solid tumors.
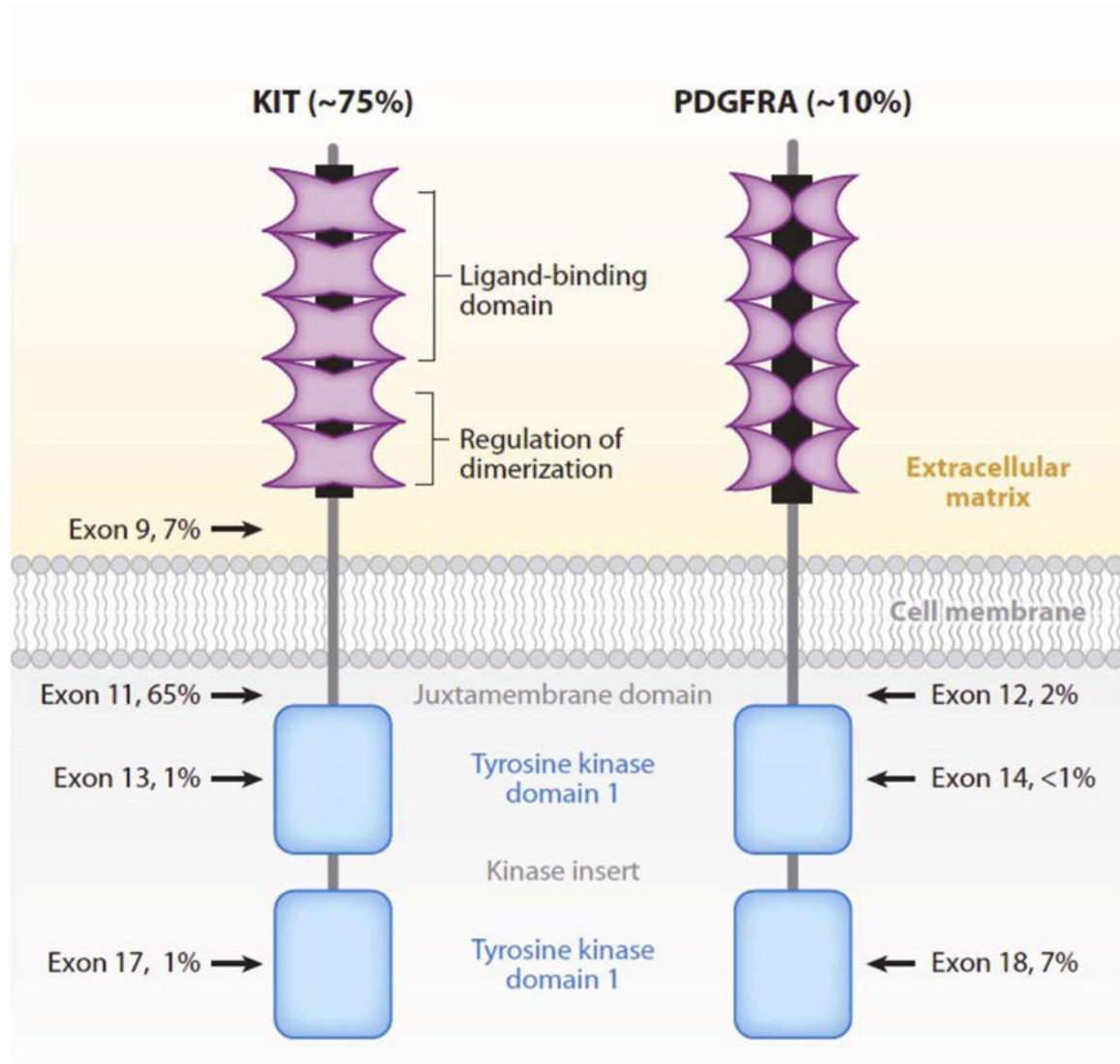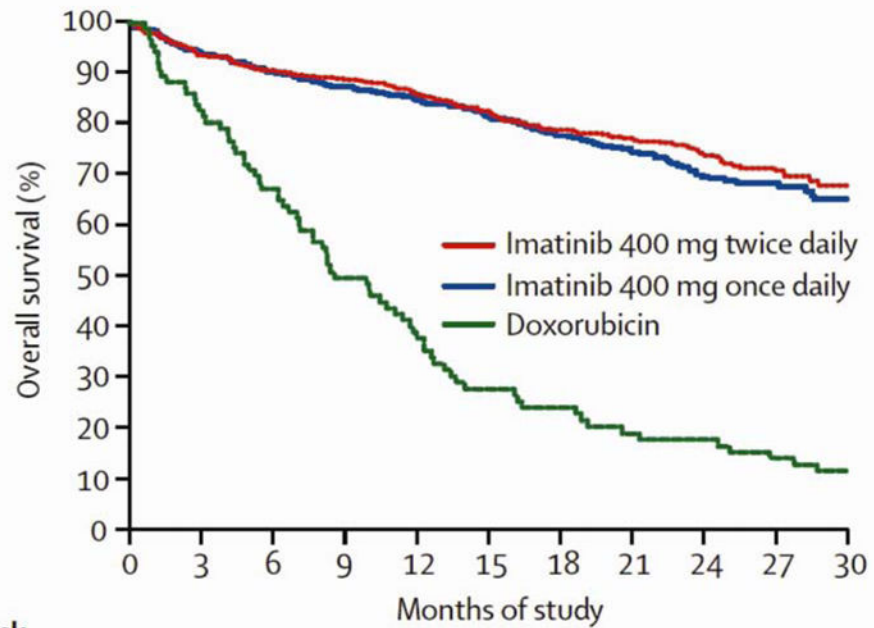
Figure 1.
Schematic structures of KIT and PDGFR. The percentages indicate the frequency of mutations detected in each exon of the gene that encodes for the protein.
From Joensuu H, DeMatteo RP. The management of gastrointestinal stromal tumors: a model for targeted and multidisciplinary therapy of malignancy. Annu Rev Med. 2012;63:247–258; with permission.

Overall survival (%)

— Imatinib 400 mg twice daily
— Imatinib 400 mg once daily
— Doxorubicin

Months of study

Number at risk

	0	6	12	18	24	30
Imatinib 400 mg once daily	473	423	387	315	192	49
Imatinib 400 mg twice daily	473	427	399	323	201	51
Doxorubicin	86	57	31	19	14	8

Figure 2.
Overall survival for study population of EORTC 62005 compared with historical controls from EORTC database.
From Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomized trial*. The Lancet. 2004; 364(9440): 1127–1134; with permission.
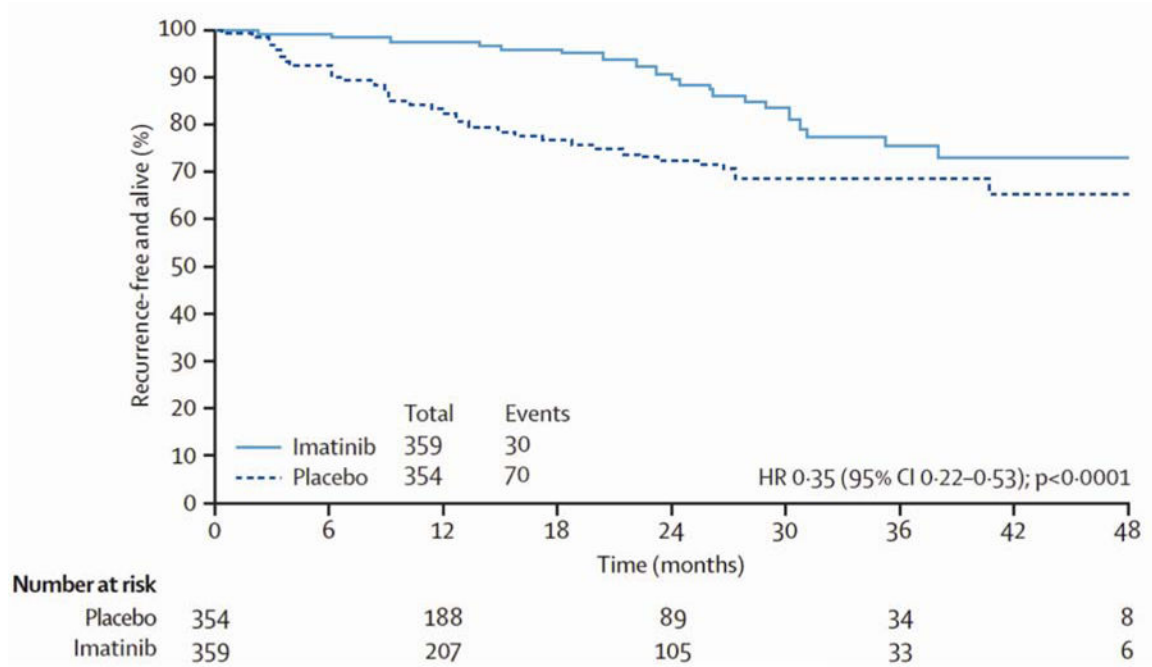
Figure 3.
Recurrence-free survival in the American College of Surgeons Group (ACOSOG) trial
Z9001 evaluating the efficacy of one year of adjuvant imatinib compared to placebo.
From DeMatteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after
resection of localized, primary gastrointestinal stromal tumour; a randomized, double-blind,
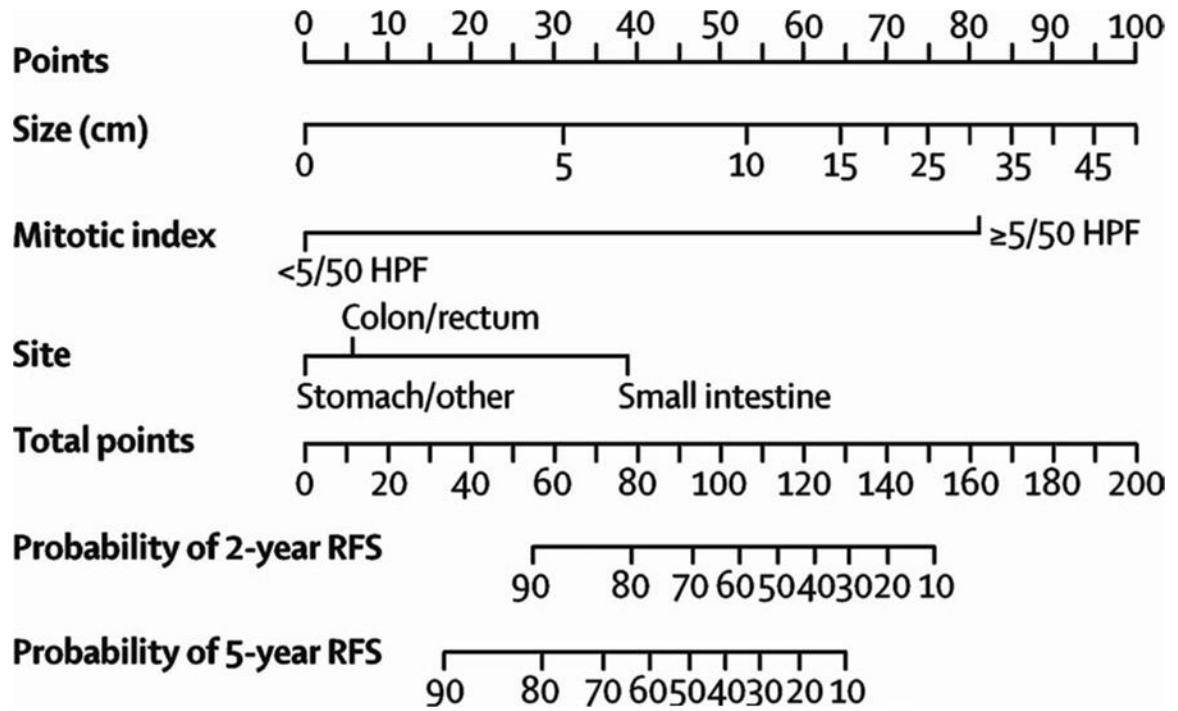placebo-controlled trial. Lancet. Mar 28 2009; 373(9669):1097–1104; with permission.

Figure 4.
Nomogram predicting 2 and 5-year recurrence-free survival in patients with resected primary GIST. Points are assigned based on tumor size, mitotic index, and site by drawing an upward vertical line to the "Points" bar. Based on the sum of the points generated, a downward vertical line is drawn from the "Total Points" line to calculate 2 and 5-year RFS. From Gold JS, Gonen M, Gutierrez A, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localized primary gastrointestinal stromal tumor: a retrospective analysis. Lancet Oncol 2009; 10:1045–1052; with permission.

Table 1

Molecular classification of GIST.

Gene	Incidence	Anatomic location	Imatinib sensitivity
Mutations in *KIT* (80%)			
Exon 9	7%	Small intestine, colon	Yes, consider 800mg/day
Exon 11	65%	All locations	Yes
Exon 13	1%	All locations	Variable
Exon 17	1%	All locations	Variable
Mutations in *PDGFRA* (5–8%)			
Exon 12	2%	All locations	Yes
Exon 14	<1%	Stomach	Yes
Exon 18	7%	Stomach, mesentary, omentum	D842V insensitive, most other sensitive
WT (12–15%)			
BRAF V600E	7–15% [*]	Stomach, small intestine	Possibly
SDHA, SDHB, SDHC, SDHD	12% [*]	Stomach, small intestine	Usually not
Familiar GIST			
KIT, rarely *PDGFRA*	Very rare	Small intestine	Usually not
Syndromic GIST			
Unknown gene (Carney Triad)	Very rare	Stomach	Usually not
SDHB, SDHC, SDHD (Carney-Stratakis)	Rare	Stomach	Usually not
NF1 (Neurofibromatosis-1)	Rare	Small intestine	Usually not

[*] indicates % of WT GISTs.

Data from Joensuu H, DeMatteo RP. The management of gastrointestinal stromal tumors: a model for targeted and multidisciplinary therapy of malignancy. *Annu Rev Med.* 2012;63:247–258.

Table 2

Tyrosine kinase mutations and targeted agents in solid tumors.

Gene	Tumor	Agent
KIT	Melanoma, seminoma, small cell lung cancer, synovial sarcoma, thymic carcinoma	Imatinib[81–89]
PDGFRA	Dermatofibrosarcoma protuberans	Imatinib[90,91]
EGFR	Non-small cell lung cancer	Gefitinib, Erlotinib[92–96]
	Squamous cell, ovarian, renal cell, and colorectal cancer, glioblastoma multiforme	Erlotinib[97], gefitinib[98], Lapatanib[99], Cetuximab[100] Panitumumab[101]
BRAF	Melanoma, papillary thyroid cancer, colon cancer	Vemurafenib[102,103]
HER-2	Breast cancer, lung cancer	Trastuzumab[104,105]
VEGFR	Non-small cell lung, breast, prostate, renal, colorectal	Bevacizumab, VEGF inhibitors[106]
RET	Multiple endocrine neoplasia 2A, 2B, Familial Medullary Thyroid Cancer, Radiation-associated papillary thyroid cancer	Cabozantinib[107], Vandetanib[108], Sorafenib[109]

Table 3

New targeted agents under investigation for GIST.

Tyrosine kinase inhibitors	Molecular Target	Development phase
Nilotinib	KIT, PDGFR, BCR-ABL[110–112]	Phase III
Dasatinib	KIT, ABL, SRC[113]	Phase III
Sorafenib	KIT, PDGFR, VEGFR, BRAF[114–116]	Phase II
Regorafenib	KIT, PDGFRA, VEGFR, BRAF, FLT-3, Raf-1[74,117]	Phase III
Masitinib	KIT, PDGFR, LYN[71,118]	Phase III
Pazopanib	KIT, PDGFRA, VEGFR	Phase II
Vatalanib	KIT, PDGFRA, VEGFR[73,119]	Phase II
Crenolanib	PDGFRA D842V[120]	Phase II