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GIST tumors: Who should get imatinib and for how long?

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Introduction

Gastrointestinal stromal tumor (GIST) is the most common sarcoma accounting for 18% of all sarcomas and 1% of all intestinal neoplasms.¹ The annual age-adjusted incidence in the United States is 7 cases per million, with a prevalence of 130 cases per million.² GISTs are hypothesized to arise from interstitial cells of Cajal, the intestinal pacemaker cells. GISTs can arise anywhere along the gastrointestinal tract but most commonly occur in the stomach, small intestine, and less frequently in the rectum, esophagus, or elsewhere in the abdominal cavity.³ GISTs are an aggressive tumor that have historically portended a poor prognosis. Approximately 50% of GISTs recur by 5 years after complete resection.^{4,5} The tumor commonly spreads to the liver and peritoneum.^{2,3} Historically, median survival in metastatic GIST was approximately 9 months given its inherent chemotherapy and radiation resistance.⁶

In 1998, a groundbreaking discovery was made that GISTs arise due to oncogenic mutations in the KIT tyrosine kinase, and subsequently it was found that mutations in platelet derived growth factor receptor α (*PDGFRA*) can also occur.^{7–9} Over the past 15 years, much progress has been made in uncovering the kinase driven biology of GIST and targeting the mutant oncoproteins. This has translated into remarkable gains in clinical outcomes in GIST and has stimulated considerable investigation into the role of kinase mutations and targeted agents in other solid tumors. GIST has become the most successful application of targeted therapy for treatment of a solid cancer, with now efficacy demonstrated in both the adjuvant and metastatic settings.

Oncogenic kinase mutations and imatinib

It is now evident that 70–80% of GISTs harbor mutations in the *KIT* proto-oncogene and induce constitutive kinase activation, activate downstream signaling pathways that inhibit apoptosis, and stimulate cell proliferation. Mutations most commonly occur in the juxtamembrane domain in exon 11 that normally inhibits the kinase activation loop in the absence of ligand binding (Table 1). Deletions are the most common variant, with insertions

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and substitutions also seen (Table 1). Extracellular (exon 8, 9) and kinase domain (exon 13, 17) mutations occur rarely.¹⁰ About 10% of GISTs are driven by a *PDGFRA* mutation, which also then drives ligand-independent receptor activation. The landscape of mutations in *PDGFRA* is similar to that of *KIT*, with mutations found predominantly in the juxtamembranous domain, ATP binding domain, or in the kinase activation loop. 10–15% of GISTs do not have a *KIT* or *PDGFRA* mutation and are termed wild-type. Among these, 7–15% have now been found to harbor a *BRAF V600E* mutation and 12% have a mutation in the succinate dehydrogenase (SDH) respiratory chain complex (Table 1).

The initial discovery of *KIT* mutations in GIST by Hirota in 1998 fortuitously coincided with the clinical application of imatinib (Gleevec) for the treatment of the BCR-ABL kinase mutation that drives chronic myelogenous leukemia. Structural similarities between the BCR-ABL and *KIT* kinases prompted administration of imatinib to a patient with advanced GIST that resulted in a dramatic response.¹¹ This initial breakthrough triggered a wave of clinical trials examining imatinib in GIST, starting with trials in metastatic disease followed by evaluation of imatinib in the adjuvant setting.

Metastatic GIST and Imatinib

Is imatinib effective in metastatic GIST?

Although a randomized controlled trial comparing imatinib to standard chemotherapy has never been performed, the efficacy of imatinib in metastatic GIST is clear.

Following initial efficacy in smaller phase I and II trials^{12,13}, the U.S-Finnish B2222 randomized phase II trial examined two different imatinib dosing regimens in a cohort of 147 metastatic GIST patients.¹⁴ 81.6% of all treated patients demonstrated disease regression or stabilization, with the median duration of response not reached at 24 weeks median follow-up. No differences in efficacy were observed between the two dosage arms but progression free survival (PFS) and overall survival (OS) were improved compared to historical controls. Estimated 1-year OS for all patients was 88%, strongly supporting the beneficial effects of systemic imatinib treatment.¹⁴ The therapy was well tolerated, with most patients experiencing mild to moderate adverse events. 21.1% of patients had grade 3 or 4 events, with serious intra-abdominal bleeding in 4.8% of patients. Notably, survival was independent of the extent of response – patients with partial responses or stable disease experienced similar survival benefits, the first clues to the inadequacy of response evaluation criteria in solid tumors (RECIST) in categorizing responses to molecular therapy. With longer follow up and an extension phase of the initial trial, the authors reported an updated overall objective response rate of 68.1%, median PFS of 24 months, and median overall survival of 57 months. Nearly 50% of patients survived more than 5 years, irrespective of imatinib starting dose.¹⁵ These results confirmed the favorable safety profile and significant benefit of imatinib compared to the historical PFS of 4–6 months,¹⁶ and OS of 9 months with conventional chemotherapy.⁶ These results have since been validated in two international, multicenter, phase III trials (Table 2, Figure 1).^{6,17} Imatinib is therefore highly effective in delaying progression and prolonging life in patients with metastatic GIST.

What is the optimal initial dosing scheme in metastatic GIST?

The European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group in conjunction with Italian and Australasian groups performed a prospective, randomized trial to address the question of whether 400 mg twice daily imatinib achieves better PFS than 400 mg once daily (EORTC 62005).⁶ In a cohort of 473 patients per treatment arm, and a median follow-up of just over two years, 56% of those taking once daily imatinib progressed compared to 50% ($p=0.026$), with no difference in OS (Table 2, Figure 1). However, of patients treated with the higher dose, 60% had dose reductions and 64% had treatment interruptions compared to only 16% and 40% with once daily treatment, respectively. The phase III Southwest Oncology Group (SWOG) S0033 trial evaluated the identical dosing regimen but did not reproduce the benefit in PFS at the higher dose (Table 2).¹⁷ Hence, given the marginal benefit with twice daily dosing based on EORTC data, the inability to reproduce these results by the SWOG trial, and the greater side-effect profile with higher dosing confirmed by two trials, 400mg imatinib per day is established as the standard first line therapy in metastatic GIST.

Is higher dose imatinib ever appropriate as first line therapy?

Follow-up analyses of EORTC 62005 revealed that patients with exon 9 mutations experienced delayed disease progression with 400 mg twice daily imatinib, whereas patients with exon 11 mutant tumors and WT tumors did not.¹⁸ A similar mutational analysis of SWOG S0033 showed improved response rates with 400 mg twice daily imatinib in exon 9 mutant tumors (67% vs. 17% complete/partial response; $p=.02$), but no statistical difference in time to progression (9.4m vs. 18m) or OS (38.6m vs. 38.4m).¹⁹ A planned meta-analysis of both above trials concluded that patients with exon 9 mutations had significantly longer PFS but not OS with higher dose therapy.²⁰ Hence, to achieve a goal delaying disease progression, 400 mg twice daily imatinib can be used as first line therapy in patients with exon 9 mutant tumors (Figure 2).

How is response to therapy optimally assessed?

RECIST criteria that incorporate unidimensional tumor size has traditionally been used to assess response to systemic treatment in solid tumors. Using RECIST, the median time to response is approximately 3 months, and median time to disease progression on imatinib is about 2 years.^{6,15} RECIST criteria are however insensitive in GIST.²¹ PET scans have been used to assess treatment response as GISTs responding to imatinib demonstrate significant decreases in uptake of fluorodeoxyglucose within 24 hours.²² Nevertheless, PET scans remain investigational in GIST. Choi and colleagues proposed computer tomography (CT) based criteria to assess response, incorporating tumor size and density. Choi criteria are superior to RECIST and correlate with PET and should be used to assess response to imatinib treatment in GIST.^{23,24}

Does the type of mutation affect prognosis in advanced GIST?

Multiple trials have confirmed the superior prognosis of patients with advanced GIST who have a *KIT* exon 11 mutation and are treated with imatinib. Debiec-Rychter et al. demonstrated that patients on the EORTC 62005 trial who had an exon 11 mutation had a

relative risk increase of 171% and 190% in PFS and OS compared to patients with exon 9 mutations.¹⁸ Similarly, those with exon 11-mutant tumors fared better than patients with WT tumors, however no difference was detected between WT and exon 9 mutants. These findings were confirmed in the long-term results of the B2222 phase II trial¹⁵ and subsequently in the SWOG S0033 phase III trial. The median time to progression (TTP) was greater in exon 11 mutants compared to either exon 9 or WT tumors, with TTPs of 24.7, 16.7 and 12.8 months respectively.¹⁹ OS was also different in exon 11 mutants compared to exon 9 or WT GIST patients - 60, 38.4, and 49 months, respectively. A difference in OS was not detected between exon 9 and WT GIST patients. It is currently unknown if imatinib is effective compared to chemotherapy in different *KIT* mutant subtypes, however all mutant subtypes treated with imatinib appear to have improved PFS, and OS compared to unstratified historical controls treated with chemotherapy. An exception to this case lies in tumors with D842V mutations in *PDGFRA*. These mutations have been shown to be insensitive *in vitro* and no clinical benefit has been demonstrated with imatinib in these patients.²⁵ Crenolanib, a *PDGFRA* inhibitor is currently in phase II trials.

How long do you continue imatinib treatment?

A clinical trial addressed the question of imatinib interruption in the metastatic setting. Blay and colleagues of the French Sarcoma group randomized 58 patients with responding or stable disease on one year of 400mg daily imatinib to interruption of therapy (n=32) or continuation (n=26).²⁶ Within 2 years of randomization, 30.7% in the continuation arm progressed compared to 81.2%. Median PFS was 18m in the continuation arm and 6.1m in the interruption arm. Interestingly, 90% of patients in the interruption arm who had no residual disease at randomization progressed at 1 year, suggesting that even with no residual tumor visible on CT, patients have occult viable disease. Imatinib interruption did not predispose to imatinib resistance as 92% of patients experienced tumor control after imatinib reintroduction in the interruption arm, and PFS was no different in patients following imatinib reintroduction compared to continuation arm. The same group published a follow up report examining if imatinib interruption following longer initial duration of therapy was sufficient to induce disease quiescence. Le Cesne reported on 50 patients randomized to continue or interrupt imatinib treatment following non-progressive disease on 3 years of imatinib.²⁷ 2 year PFS was 80% in the continuation group and 16% in the interruption group (p<0.001). 5 of 9 patients with complete response prior to randomization relapsed after imatinib interruption, confirming their prior findings that recurrence is common following imatinib interruption in patients with no radiographic evidence of residual disease. Imatinib reintroduction following recurrence continued to remain efficacious, with 2 year PFS of 80% in the continuation group and 87% in the imatinib interruption group.

Thus, in metastatic GIST patients, even after 3 years of continuous imatinib treatment and no residual disease notable on imaging, interruption of therapy is associated with a high risk of relapse and therefore imatinib is recommended to be continued until disease progression (Figure 2). Imatinib interruption is not associated with a shorter PFS after reintroduction of therapy.

Is there a role for surgery in metastatic patients treated with imatinib?

We found that metastatic GIST patients with imatinib-responsive or stable tumors gained the greatest benefit with cytoreductive surgery, with 2-year OS of 100%. In contrast, patients with 1 tumor growing on imatinib (focal resistance) had 2-year OS of 36%, and multifocal resistance (>1 tumor growing) had a 1-year OS of 36% (Figure 3). Raut et al. reported 1-year OS of 95%, 86%, and 0% for patients with stable, limited, and generalized disease progression, respectively.²⁸ Similar results have been reported in an Italian study.²⁹ Hence, patients with responsive or stable disease on imatinib have the greatest benefit from cytoreductive surgery. Patients with focal resistance treated with surgery appear to have OS that is no worse than patients on continuous imatinib and thus surgery is an option (Figure 2). Further research to quantify the precise benefit from surgery after imatinib in the metastatic setting is needed as the benefit from surgery has not been proven in a clinical trial.

What is appropriate therapy with evidence of disease progression?

Three trials have demonstrated a benefit with higher dose imatinib in patients progressing on 400 mg per day. Of patients who crossed over to a higher dose following progression on a lower dose,³⁰ 29% had objective responses with a median PFS of 81 days. Two other trials have confirmed these findings – long-term data in the phase II US-Finnish B2222 trial demonstrated that approximately 25% of patients progressing on low dose benefited from a dose increase.¹⁵ Additionally, the SWOG phase III trial of low versus high dose imatinib also reported a 33% response rate with higher dose therapy, and a PFS of 5 months following crossover.¹⁷ Consequently, a dose increase to 400 mg twice daily is an option when imatinib resistance develops (Figure 2).

What is second line therapy for patients progressing on imatinib?

For patients who are imatinib-resistant or intolerant, sunitinib has shown efficacy as a second-line therapy. Demetri and colleagues demonstrated in a blinded, placebo-controlled, randomized trial that patients treated with sunitinib had a significantly longer time to progression of 27.3 weeks, compared to 6.4 weeks in the placebo group, with minimal adverse drug effects.³¹ 7% of sunitinib treated patients had a partial response, 58% stable disease, and 19% had progression compared to 0%, 48%, and 37% in the placebo arm respectively. The authors also noted a survival benefit for patients in the sunitinib arm compared to placebo. Hence, for metastatic GIST patients who are intolerant or resistant to imatinib, initiating sunitinib is appropriate. For patients who progress on imatinib and sunitinib, the FDA has recently approved regorafenib as a third line agent in GIST (Figure 2). In a phase III randomized, blinded, placebo-controlled trial, median PFS was shown to be 4.8 months in regorafenib treated patients compared to 0.9 months in placebo.³² The investigators found no differences however in OS, underscoring the diminishing returns in combating imatinib resistance with TKI monotherapies.

What agents are under investigation for imatinib refractory GIST?

Multiple salvage TKIs are in development to combat imatinib resistance (Table 3). We recently reported that the antitumor effects of imatinib, previously thought to act exclusively

through oncogenic kinase inhibition, also relied on effects of the immune system.³³ Using a mouse model of spontaneous GIST and freshly analyzed human GIST specimens, we found that imatinib activated cytotoxic CD8⁺ T cells and induced apoptosis of suppressive regulatory T cells by inhibiting the immunosuppressive enzyme indoleamine 2,3-dioxygenase (Ido). In examining if these immunomodulatory effects of imatinib can be harnessed, we found that imatinib synergized with blockade of cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), an immunomodulatory agent that has recently been approved for use in malignant melanoma.³⁴ We are conducting a phase I trial combining CTLA-4 inhibition and TKI therapy in GIST and other sarcomas. We are also analyzing the intratumoral myeloid cell infiltration in GIST as another approach.³⁵ Combination of TKI with other molecular inhibitors is another promising therapeutic strategy in GIST and a trial combining imatinib and MEK inhibition is underway at our institution.

Imatinib as adjuvant therapy

Who is at greatest risk for recurrence following resection?

Current data demonstrate that tumor size, site, and mitotic index are the most important prognostic indicators.^{36–38} Each has been shown on multivariate analysis to independently predict recurrence-free survival (RFS) after resection of primary, localized GIST.³⁸ Tumor rupture has also been shown to increase risk of risk of peritoneal recurrence.⁴ Multiple stratification schema have been developed incorporating these risk factors to predict risk of recurrence and hence identify patients most suitable for adjuvant therapy. These include the NIH consensus criteria, Armed Forces Institute of Pathology (AFIP) criteria, and the modified NIH criteria.^{39–41} These stratification systems have all been prospectively validated, and their prognostic accuracy is roughly similar.³ Contour maps to predict risk of recurrence have also been developed, that are marginally more accurate than the above mentioned schema.³ We developed a nomogram to predict the risk of 2 and 5-year recurrence based on tumor size, mitotic index, and location (Figure 4).⁴² The nomogram performed better than existing risk assessment schemes and is available online. Dei Tos recently reported a nomogram predicting 10-year RFS using mitotic index and size as continuous variables.⁴³

The AFIP criteria remain the most commonly used stratification method (Figure 5). Patients classified as intermediate or high risk (AFIP groups 3a and above) are generally considered to be at a higher risk for recurrence and therefore suitable for consideration of adjuvant therapy. Based on nomogram evaluation, this roughly corresponds to patients with a 5-year recurrence rate of 30%. Previously, deletion and insertion mutations in *KIT* exon 11 and *KIT* exon 9 mutations were thought to be associated with higher recurrence rates after primary resection.^{38,44} Recent data from the American College of Surgeons Oncology Group (ACOSOG) has demonstrated that *KIT* mutation status is not an independent predictor of recurrence in patients treated with adjuvant imatinib, however patients with *KIT* exon 11 deletions do have a higher recurrence rate compared to other *KIT* exon 11 mutations.⁴⁵ Microscopic positive margins have not yet been shown to influence recurrence in patients treated with adjuvant imatinib.^{5,46}

Does adjuvant imatinib prolong RFS or OS compared to placebo?

The ACOSOG Z9000 trial was a single arm, multicenter, phase II trial in 106 patients at high risk for recurrence following surgery, treated with 1 year of 400mg daily of adjuvant imatinib. After a median follow-up of 7.7 years, 5-year OS was 83% compared to a historical OS of 35%.⁴⁷ In the subsequent Z9001 trial, the ACOSOG investigators answered the question if adjuvant imatinib decreased recurrence in a randomized, double-blinded, placebo controlled trial of one year of adjuvant therapy in patients with primary, resected GIST ≤ 3 cm.⁴⁸ Accrual was halted early when interim results crossed the efficacy boundary set for RFS, at a median follow-up at only 19.7 months. Imatinib significantly improved RFS compared to placebo (98% vs. 83% at 1 year; Figure 6). Based on these trial results, the FDA approved imatinib for adjuvant treatment of KIT-positive GISTs. After long follow up (74 months), there is still no difference in OS.⁴⁵

A non-randomized, single-center phase II study in 105 patients comparing 3 years of adjuvant therapy to no treatment confirmed the benefit of adjuvant imatinib in decreasing recurrence (3-year RFS 89% vs. 48%, $p < 0.001$).⁴⁹ The EORTC recently reported interim results in their larger, phase III trial comparing 2 years of adjuvant imatinib compared to placebo in patients with intermediate/high risk GIST. In 454 patients per treatment arm and a median follow-up of 4.7 years, RFS was 84% and 69% in imatinib treated patients at 3 and 5 years, versus 66% and 63% in the placebo group respectively ($P < 0.001$). 5-year OS was no different at 100% in imatinib vs. 99% in placebo treated patients.⁵⁰ Hence adjuvant imatinib does prolong RFS in patients with primary, resected GIST ≤ 3 cm but does not appear to prolong OS (Figure 7).

Do all patients benefit from adjuvant imatinib?

The Z9001 trial demonstrated an overall benefit in tumors ≤ 3 cm. Stratified results in tumors of sizes 3–6cm, 6–10cm, and ≥ 10 cm all demonstrated prolonged RFS in imatinib treated patients compared to placebo.⁴⁸ Patients with a high mitotic index or small bowel site also have improved outcome on imatinib.⁴⁵

Recent data from the Z9001 trial has shed light on the efficacy of imatinib on mutational subtypes. Imatinib was superior to placebo in prolonging RFS only in patients with deletions in *KIT* exon 11. It did not delay recurrence compared to placebo in *KIT* exon 11 point mutations or insertions, exon 9 mutations, or WT GIST.⁴⁵ Imatinib was not statistically superior to placebo in *PDGFRA*-mutant tumors however the sample size was small and a trend was observed. Similar data have been reported by the Scandinavian Sarcoma Group sponsored SSGXVIII/AIO trial examining the effect of 1 vs. 3 years of adjuvant imatinib. Three years of adjuvant treatment decreased recurrence compared to 1 year of treatment only in patients with exon 11 mutations, and not in exon 9, WT, or other mutations.⁵¹

Given the risk of recurrence and hence need for adjuvant therapy is currently determined based on risk stratification subgroups, further studies must clarify the specific benefit of imatinib over placebo within these subgroups stratified by mutational subtype. This will allow a more accurate understanding of who truly needs adjuvant therapy, and among those who do, who actually benefits from it (Figure 7).

Is a longer duration of adjuvant treatment beneficial?

The SSGXVIII/AIO trial addressed the question of prolonged imatinib treatment. They performed a randomized, phase III trial comparing 1 year to 3 years of adjuvant therapy in patients at high risk for recurrence (>5cm in size, >5 mitoses/HPF or risk of recurrence > 50% after surgery).⁵¹ RFS at 5 years was 47.9% in patients who received one year of treatment versus 65.6% in 3 years of treatment. Although the authors reported an improvement in OS with prolonged therapy (5-year OS 92% vs. 81.7%), there was in fact no difference in disease-specific survival with prolonged therapy. 3 years of adjuvant imatinib decreased recurrence independent of location, size (>10cm or ≤10cm), presence of rupture, R0/R1 resection, or mitotic index (>10 mitoses/50 HPF or ≤10 mitoses/50 HPF). However, 3 years of therapy only decreased recurrence in patients with *KIT* exon 11 mutations, and not *KIT* exon 9 mutations, WT, or other mutations. Whether prolonged therapy is only effective in exon 11 deletions, and the specific benefit in different recurrence risk subgroups stratified by mutational status also remains unknown. Until these questions are answered, 3 years of adjuvant imatinib in patients at high risk for recurrence post resection is appropriate to decrease the risk of recurrence (Figure 6).

Does adjuvant imatinib affect development of imatinib resistance?

Interim results from the EORTC phase III study examining 2 years of adjuvant imatinib compared to placebo reported that the time to initiation of a different TKI following recurrence, a surrogate for secondary resistance, was equivalent in both treatment arms (87% imatinib, 84% placebo, $p=0.23$).⁵⁰ The SSGXVIII/AIO trial also demonstrated no difference in time to progression following salvage imatinib in patients initially treated with either 1 or 3 years of adjuvant imatinib.⁵² Hence these early results suggest that adjuvant imatinib does not hasten development of imatinib resistance. Final results of the EORTC trial are awaited.

Is salvage imatinib following recurrence effective?

Initial subgroup analysis of patients with recurrent GIST in the SSGXVIII/AIO trial demonstrated no difference in clinical benefit (87.9% vs. 76.9%, $p=0.385$), or time to progression (39.6m vs. 20.8 m; $p=0.289$) after salvage imatinib in patients initially treated with either 1 or 3 years of adjuvant imatinib respectively. A single center Korean singlearm, phase II trial in 47 patients with exon 11 tumors similarly demonstrated high response rates with salvage imatinib (87% partial response, 13% stable disease) in patients who developed recurrent disease after 2 years of adjuvant treatment.⁵³ As mentioned earlier, interim results of the EORTC phase III study also suggest salvage imatinib is effective as time to a second TKI was no different in patients treated with 2 years of adjuvant imatinib or placebo.⁵⁰ Thus, early results suggest that salvage imatinib is effective and is appropriate in patients with recurrent disease. Final results of the EORTC trial are expected to definitively answer this question.

When is neoadjuvant imatinib indicated?

Two phase II trials have demonstrated the safety and efficacy of neoadjuvant imatinib to allow for tumor shrinkage and a subsequent R0 resection with primary GIST that appears

borderline or unresectable.^{54,55} However, no phase III data exist currently examining this question. Patient selection and duration of therapy are currently at the discretion of the surgeon and medical oncologist. NCCN guidelines recommend neoadjuvant imatinib in patients who have primary, unresectable tumors or resectable tumors with a risk of significant morbidity, to reduce the tumor size before surgery and minimize morbidity. An initial dose of 400 mg daily is indicated, however patients with exon 9 mutations may benefit from dose escalation. Optimal duration of therapy is unknown but generally imatinib should be continued for 6–9 months, after which additional tumor shrinkage is usually minor.⁵⁶

Conclusions

The application of imatinib for the treatment of GIST remains a remarkable illustration of the ability and promise of targeted molecular therapy. It is gradually becoming evident that the benefit of imatinib depends on the complex interplay between mutational variations that govern tumor sensitivity to the drug, and biologic variables that drive clinical outcome. Evidence is mounting that only a select fraction of patients in the adjuvant setting may benefit from imatinib. Unfortunately, most patients with metastatic disease develop resistance to imatinib, as occurs in other diseases with kinase inhibitors. Thus, although imatinib has demonstrated that kinase inhibitor therapy is an integral component of cancer care, it has also revealed the challenges in treating a dynamic cancer with a static monotherapy. As greater insight is gained into when imatinib does not help, it will uncover the obvious next path in cancer treatment, namely individualized, genotype directed therapy that is modulated according to the genetic and immunologic landscape of the tumor.

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Key Points

- Imatinib is the first line therapy for GIST patients with unresectable, recurrent, or metastatic disease, except those with *PDGFRA* D842V mutations, which do not respond to imatinib.
- When there is imatinib resistance or intolerance in advanced disease, imatinib dose escalation, sunitinib, regorafenib, or clinical trials are indicated.
- Cytoreductive surgery may be considered for imatinib-sensitive or imatinib-stable advanced disease, although clinical trials are lacking.
- Adjuvant imatinib is indicated in patients who are deemed at intermediate/high risk for recurrence following resection of primary GIST.
- 1 year of adjuvant imatinib in intermediate/high risk patients decreases the risk of recurrence, but does not prolong overall survival. It is particularly beneficial in patients with *KIT* exon 11 deletions.
- 3 years of adjuvant imatinib in high risk patients decreases the risk of recurrence, but does not prolong disease-specific survival and may only be beneficial in patients with *KIT* exon 11 mutations.

Number at risk						
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 1.

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: randomised trial*. *The Lancet*. 2004;364(9440): 1127–1134. With permission.

Figure 2.
Who should get Gleevec and for how long in advanced GIST?

Figure 3.

Progression-free survival and overall survival after resection of metastatic GIST treated with tyrosine kinase inhibitors.

From DeMatteo RP, Maki RG, Singer S, Gonen M, Brennan MF, and Antonescu CR. *Ann Surg* 2007; 245(3): 347–352.. 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 Rates of metastases or tumor-related death in GISTs of stomach and small intestine by tumors grouped by mitotic rate and tumor size						
Group	Tumor Parameters		Percentage of Patients with Progressive Disease During Long-Term Follow-up and Characterization of Risk for Metastasis			
	Size	Mitotic Rate	Gastric GISTs	Jejunal and Ileal GISTs	Duodenal GISTs	Rectal GISTs
1	≤2 cm	≤ 5 per 50 HPF	0, None	0, None	0, None	0, None
2	>2cm ≤5 cm	≤ 5 per 50 HPFs	1.9, Very low	4.3, Low	8.3, Low	8.5, Low
3a	>5cm ≤10 cm	≤ 5 per 50 HPF	3.6, Low	24, Moderate		
3b	>10 cm	≤ 5 per 50 HPF	12, Moderate	52, High	34, High ^a	57, High ^a
4	≤2 cm	>5 per 50 HPF	0	50		54, High
5	>2cm ≤5 cm	>5 per 50 HPF	16, Moderate	73, High	50, High	52, High
6a	>5cm ≤10 cm	>5 per 50 HPF	55, High	85, High		
6b	>10 cm	>5 per 50 HPF	86, High	90, High	86, High ^a	71, High ^a

Figure 5.

Rates of metastases or tumor-related death in GISTs of stomach and small intestine by tumors grouped by mitotic rate and tumor size.

Groups 3a and 3b or 6a and 6b are combined in duodenal and rectal GISTs because of small number of cases. From Miettinen M, Lasota J Gastrointestinal stromal tumors: Pathology and prognosis at different sites. Semin Diagnostic Pathol 2006; 23:70; with permission.

Figure 6.

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 double-placebo-localised, primary gastrointestinal stromal tumour: a randomised, double blind, placebo controlled trial. *Lancet*. Mar 28 2009;373(9669):1097–1104. With permission.

Figure 7.

Who should get Gleevec and for how long as adjuvant therapy?

* See figures 4 and 5 for risk assessment.

Table 1

Molecular classification of GIST.

Gene	Incidence	Anatomic location	Imatinib sensitivity
Mutations in <i>KIT</i> (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 <i>PDGFRA</i> (5–8%)			
Exon 12	2%	All locations	Yes
Exon 14	<1%	Stomach	Yes
Exon 18	7%	Stomach, mesentery, omentum	D842V insensitive, most other sensitive
WT (12–15%)			
<i>BRAF V600E</i>	7–15% *	Stomach, small intestine	Possibly
<i>SDHA, SDHB, SDHC, SDHD</i>	12% *	Stomach, small intestine	Usually not
Familial GIST			
<i>KIT</i> , rarely <i>PDGFRA</i>	Very rare	Small intestine	Usually not

Adapted from reference 11 with permission.

* indicates % of WT GISTs

Table 2

Phase III clinical trials in advanced, unresectable GIST.

Trial	Treatment (n)	Results			Conclusion
		PR	SD	PD	
EORTC 62005 ⁷	400 mg qd (473) 400 mg bid (473)	45% PR, 5% CR 48% PR, 6% CR	32% 32%	13% 9%	2-yr PFS 56%, 32% Grade III-IV toxicity 2-yr PFS 50%, 50% Grade III-IV toxicity 400 mg daily achieves adequate response in advanced GIST
US-Canadian SWOG S0033 ¹⁷	400 mg qd (345) 400 mg bid (349)	40% PR, 5% CR 42% PR, 3% CR	25% 22%	12% 10%	43% grade 3 toxicity 63% grade 3 toxicity 400mg initial dose, consider dose escalation with disease progression Median PFS 18m vs 20m, OS 55m vs. 51m (400 mg qd vs. 400 mg bid respectively; p=ns) 33% response after crossover to higher dose following progression

PR – Partial response; SD – Stable disease; PD – Progressive disease, as defined by RECIST criteria.

PFS – Progression Free Survival (survival from date of randomization to date of progression or all cause death)

OS – Overall Survival (survival from date of randomization to date of all cause death)

Table 3

Targeted agents for GIST.

Tyrosine kinase inhibitors	Molecular Target
Imatinib *	KIT, PDGFR, ABL
Sunitinib *	KIT, PDGFR, VEGF, FLT3, RET
Nilotinib	KIT, PDGFR, BCR-ABL
Dasatinib	KIT, ABL, SRC
Sorafenib	KIT, PDGFR, VEGFR, BRAF
Regorafenib *	KIT, PDGFRA, VEGFR, BRAF, FLT-3, Raf-1
Masitinib	KIT, PDGFR, LYN
Pazopanib	KIT, PDGFRA, VEGFR
Vatalanib	KIT, PDGFRA, VEGFR
Crenolanib	PDGFRA D842V

* FDA approved for GIST

Adapted from *Targeted therapy for cancer: the GIST model*. Balachandran VP, and DeMatteo RP. Surg Oncol Clin N Am 2013; 22(4): 805–821. With permission