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Towards global consensus in the treatment of gastrointestinal stromal tumor

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Abstract

The contemporary clinical landscape of gastrointestinal stromal tumor (GIST) has evolved rapidly over the past several years. Widely used treatment guidelines – from the European Society of Medical Oncology (ESMO) and the National Comprehensive Cancer Network – have recently been updated and represent the most up-to-date, comprehensive tools guiding the optimal management of GIST. In these, and in other published guidelines, close alignment among recommendations now exists for many of the clinical issues relevant to GIST management – surgery, use of the tyrosine kinase inhibitors imatinib and sunitinib and the role of pre- and post-operative imatinib, among others. This trend towards a global consensus in the treatment of GIST is the result of a relatively large amount of new data across the spectrum of its management. However, for some clinical considerations, recommendations still partially deviate. This review examines clinical recommendations and opinions on the management of GIST in the context of the latest data in the field and with an eye towards a multidisciplinary approach including surgical oncology, medical oncology, pathology and diagnostic radiology. Points of consensus are highlighted. Expert opinion is presented on management areas where no scientific evidence or firm recommendations currently exist; lingering and unresolved questions or issues are included. Within this framework, we present an evaluation of current global guidelines on the following areas in GIST management: surgery in the metastatic setting; neoadjuvant therapy; adjuvant therapy; mutational analysis; maintenance tyrosine kinase inhibitor therapy; and radiological

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imaging in GIST. A summary of consensus across these guidelines based on clinical trial data is juxtaposed with expert opinion where gaps in data still remain.

Keywords

adjuvant; European Society of Medical Oncology; gastrointestinal stromal tumor; guidelines; imatinib; KIT; National Comprehensive Cancer Network; nilotinib; PDGFR- α ; sarcoma; sunitinib; tyrosine kinase inhibitor

In a therapeutic area once poorly understood, the experience with gastrointestinal stromal tumor (GIST) over the recent past has been said to help "...transform solid tumor oncology..." [1]. Changes in management practices influenced by advances in diagnosis, assessments of response to surgical and medical treatment, definitions of drug resistance, and notably, in the understanding of the role of specific mutations of the genes involved in the pathogenesis of GIST, have led to the creation of a variety of guidelines in order to help clinicians who may be facing the treatment of GIST keep pace with these improvements in healthcare delivery.

Guidelines from the European Society of Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) in the USA, are among the more widely recognized and consulted for the management of patients with GIST. These were both updated in 2009 to reflect the continually evolving clinical landscape for patients with this tumor type [2,3]. Still, it is important to recognize that other guidelines have also been developed with the expressed goal of providing summary recommendations for GIST management in specific countries, for example, Canada, Switzerland and Japan [4-6]. These were developed to address particular clinical concerns and/or health regulatory authorities' treatment requirements. For example, according to the authors of Japanese practice guidelines, two unique conditions exist in that country: a substantial proportion of GIST is incidentally found as submucosal tumor (SMT) during routine endoscopic screening examinations; and the relatively high incidence of SMT-like gastric cancer make the differential diagnosis of GIST from that of gastric cancer resembling SMT clinically important.

The science of GIST has evolved from that of a poorly characterized mesenchymal neoplasm of the GI tract and mesentery with an ambiguous pathobiology to one of an archetype of molecularly targeted malignancies. The discovery that approximately 85% of GISTs are driven by oncogenic mutations that occur, to varying degrees, in two mutually exclusive pivotal tyrosine kinase receptors intricately involved in cell signaling pathways – KIT and PDGF receptor- α (PDGFRA) – spurred the current management paradigm for advanced GIST that relies on the use of imatinib mesylate and other tyrosine kinase inhibitors (TKIs) [7,8]. These agents inhibit the function of the GIST-associated, mutated tyrosine kinase receptor proteins. In the face of such 'activating mutations', both cell proliferation and apoptotic pathways become aberrantly altered. Nevertheless, surgery remains the cornerstone of therapy for primary localized, resectable GIST. Recently, the role of surgery has been investigated even in advanced/metastatic cases [9-11]. The use of post- and/or pre-operative imatinib – that is, adjuvant and/or neoadjuvant therapy – have each

been shown to improve surgical outcomes, and their effects on rates of recurrence and, perhaps, overall survival, continue to be evaluated [12-17].

Updated guidelines are beginning to offer consistent recommendations, especially in areas where new data from randomized trials are available, for example, on the use of adjuvant imatinib; yet there remain gaps in the continually evolving field of GIST. Emerging data now exist that could not be fully considered during the development of existing guidelines, and other data regarding, for example, the potential role of second-generation TKI therapies, such as nilotinib, are still needed.

The goals of this review are to integrate established and late-breaking data in GIST, identify unresolved questions/issues, and juxtapose expert opinion where no scientific evidence or firm recommendations currently exist. A main goal is to highlight the global consensus that has emerged in major treatment guidelines, reflecting in part the accumulation of mature trial data as well as the growing worldwide clinical experience in this field. The vast majority of clinical data and management recommendations relate to the use of first-line imatinib and it is on these that this review focuses.

It is widely recognized that the successful management of GIST clearly relies on a multidisciplinary approach comprised of medical oncologists, surgical oncologists, pathologists and diagnostic radiologists. With this in mind, topics include: surgery in metastatic GIST; neoadjuvant and adjuvant therapy with imatinib; role of mutational analysis; maintenance TKI therapy; and radiological assessments of treatment response. While not intended to offer yet another set of guidelines, it is nevertheless hoped that the information provided herein might help resolve some of the potential confusion clinicians may face as they approach a diagnosis of GIST, as well as contribute to future iterations of such recommendations.

Current guidelines for the management of GIST: a brief overview

The ESMO and NCCN guidelines are arguably the most frequently employed worldwide by a broad variety of medical professionals involved in the management of GIST [2,3]. An abridged comparison of NCCN, ESMO, Canadian, Japanese and Swiss guidelines is shown in Table 1. A commonality exists among them on several aspects of GIST management. Perhaps foremost, a multidisciplinary approach should always be used for treatment planning, including highly qualified medical personnel (medical oncologists, surgical oncologists, pathologists and radiologists) with specific expertise in the management of GIST and related sarcomas. While they currently partially deviate in some of their recommendations, updates for the older of these are expected soon to reflect new data.

General considerations: localized disease

There is a general agreement that when GIST presents as small (< 2 cm) upper GI tract nodules in the esophagus, stomach or duodenum, the recommended approach is to perform endoscopic ultrasound and subsequent follow-up (ESMO guidelines [2]). Larger nodules (>2 cm) carry a higher risk for aggressive behavior and a biopsy should be performed followed by excision if a GIST diagnosis is made. Biopsy of the primary lesion of any size is also

recommended if neoadjuvant therapy is planned and if a multivisceral resection is to be performed; biopsy may also be proposed for suspected sites of metastatic disease. For rectal GIST, endoscopic ultrasound and MRI assessment followed by biopsy and wide excision is the standard approach, regardless of tumor size [2].

Staging and risk assessment are important aspects of GIST management. Excised tumor samples should be fixed in formalin. Collection of frozen tissue samples is encouraged to facilitate further research. Morphological and immunohistochemical analysis should be part of the pathological work-up that also includes determination of tumor size, mitotic count and KIT (CD117) positivity. Mutational analysis of *KIT* and *PDGFRA* is strongly recommended in the diagnostic work-up of patients.

Contrast-enhanced abdominal and pelvic CT scan is the technique of choice for staging and follow-up. A chest x-ray can complement staging and work-up. MRI should be used in rectal GIST as it provides better preoperative staging information. PET or PET-CT/MRI is not routinely required but may be useful for early detection of tumor response during neoadjuvant treatment.

Complete surgical resection that achieves negative margins (R0 surgery) is the standard of care for primary localized, operable GIST. Laparoscopic resection should be reserved for small, favorably located gastric GIST, and should be performed in centers experienced in this technique. Following complete resection in patients with intermediate- and high-risk GIST, NCCN guidelines support the use of adjuvant imatinib therapy for at least 1 year [3]. Whereas past ESMO guidelines had considered this approach, investigational, updated, 2009 recommendations now propose adjuvant imatinib for a period of 1 year in patients at a substantial risk of relapse following primary resection. Also, patients who have a low or very low risk of recurrence are recommended not to receive adjuvant treatment [2].

Following complete surgical resection but with positive margins (R1 surgery), re-excision should be performed when the site(s) of positive margin can be precisely located, and when surgical risks of short- and long-term morbidity are acceptably low. When the site(s) of positive margin is/are uncertain and/or the risk of morbidity is high, the patient should be placed under observation. Referral to a specialty center should be considered in this situation. Of note, R1 resection was allowed in inclusion criteria in trials on adjuvant imatinib. Subgroup analysis on this cohort of patients is not available so far.

Recommendations for neoadjuvant imatinib are generally consistent across guidelines and suggest that preoperative imatinib may be useful in the following situations: negative margins are difficult to obtain; a multivisceral resection is indicated; to optimize timing of surgery; or to facilitate organ function-sparing resections. In these cases, maximal tumor response with imatinib is desirable (~6–12 months) before surgery is performed. Again, referral to a specialty center should be considered before the initiation of imatinib in this situation.

General considerations: advanced disease

In locally advanced, inoperable and metastatic GIST, imatinib 400 mg daily is the standard of care. This also refers to patients who have undergone complete resection of metastatic disease.

In patients whose GIST harbors *KIT* exon 9 mutations, imatinib 800 mg daily is the recommended dose: data for patients in this subgroup suggest an improved progression-free survival (PFS) with this higher dose of imatinib [18]. Continuous imatinib therapy is recommended (unless side effects occur that can hinder further treatment). Prolonged treatment interruption has been associated with rapid progression [19]. For patients whose disease progresses while on imatinib 400 mg daily, the recommended standard approach is dose escalation of imatinib to 800 mg daily.

Surgical excision in patients with controlled or limited progressive disease is deemed investigational, but guidelines are consistent in that excision should not be considered when diffuse progression is evident. Sunitinib is currently the standard treatment for patients who have progressed on or are intolerant to imatinib. Upon failure with sunitinib, the patient should be considered for a clinical trial of a novel agent or treatment regimen.

Emerging data & clinical opinion surrounding the management of GIST

Clinical outcome before & after the imatinib era

The clinical benefit of surgical resection for primary GIST has been demonstrated in several retrospective studies evaluating surgical outcomes. In one report of a series of 200 GISTs, surgery resulted in a median survival benefit of 66 months compared with 22 months for patients receiving complete or incomplete resection, respectively [20]. In the pre-imatinib era, recurrence following surgery in patients remained a major concern, with 5-year survival rates for primary, resected GIST ranging from 50 to 55% [21-23].

Following the introduction of imatinib, the magnitude of survival improvement it provides in the treatment of patients with locally advanced and metastatic GIST was first demonstrated by the landmark US/Finland B2222 study [24,25], the North American Sarcoma Intergroup study (S0033) [26] and the European Organisation for Research and Treatment of Cancer (EORTC)/Australasian study [27].

Median PFS using imatinib in the Phase II B2222 study was 24 months overall: 20 months in the 400 mg/day group and 26 months in the 600 mg/day group [24,25]. Median overall survival (OS) was 57 months for the total population, with no significant differences between treatment groups. In the S0033 trial, the median PFS was 18 months for patients in the standard-dose (400 mg daily) imatinib arm and 20 months for those receiving high-dose (800 mg daily) imatinib; median OS was 55 and 51 months, respectively [26]. In the EORTC/Australasian study, progression of disease occurred in 56% of patients who received 400 mg imatinib daily compared with 50% for those who received 800 mg daily (hazard ratio: 0.82; 95% CI: 0.69–0.98; $p = 0.026$) [27]. OS was 85% at 1 year and 69% at 2 years for the 400 mg group; for the 800 mg group, OS was 86% at 1 year and 74% at 2 years.

A consensus approach for the multimodal management of metastatic GIST is shown in Figure 1; several of the challenges and unanswered questions it infers are addressed here. For example, despite the impressive efficacy of imatinib in the advanced setting, it is apparent that the majority of patients will progress within 5 years of initiation of imatinib treatment. This observation has prompted the evaluation of the potential utility of additional surgery in the advanced/metastatic setting.

Surgery in metastatic GIST: can it be justified?

A rationale for resecting metastases in patients with advanced GIST is to eradicate clones that may potentially confer drug resistance. So far, limited data exist on the clinical benefit of secondary excisions in patients with advanced GIST. Chen and colleagues provided preliminary evidence that metastasectomy has clinical benefit in leiomyosarcoma patients with isolated liver metastases, with some of these patients probably having GIST [28]. More recently, in a study of patients who all underwent surgery after TKI therapy, prolonged PFS and OS were experienced in the group that had stable or limited disease progression compared with those who had generalized disease progression [10]. Several other studies that evaluated the utility of excision of resistant metastases in the setting of focal resistance have resulted in data consistent with these findings [9,11-14,29-31]. Overall, in these studies, complete excision of residual metastatic lesions was associated with improved prognosis but remained dependent on satisfactory responses to imatinib. Nevertheless, pending further evaluation, surgery in this setting is still considered investigational across guidelines. Experts do agree, however, that when the decision to perform surgery for metastatic GIST is made, continued TKI therapy should always be a part of the procedure; this recommendation is supported by the pivotal, BFR14 randomized trial [19,32].

Generally, despite these promising data, in cases of local progression in a limited number of sites, experts remain in alignment with the latest guidelines, agreeing that surgery in this setting has not yet been demonstrated to be useful. While further evaluation of this surgical approach in randomized clinical trials is recommended, it may still be considered on an individualized case basis. In cases of generalized progression, experts maintain that currently available data do not support a clinical benefit of surgery. In fact, recurrence within 3 months of surgery has been reported in such cases [11,12,14]. Experts also agree that clinical data do not currently support surgical resection of metastases in patients responding to imatinib.

Surgery following TKI therapy in advanced disease

Case reports and clinical studies have supported a role for primary imatinib therapy for locally advanced and metastatic disease. In a study of 90 patients with metastatic GIST, Bauer and colleagues showed that imatinib enabled 12 patients with mostly recurrent and advanced metastatic disease to subsequently be considered for resection of residual disease [9]. A key finding of this study was that in the 11 patients who underwent complete resection, the median OS in this patient population was 46 months (range: 4–85 months).

In the study by Raut and colleagues, 69 patients with advanced (mostly metastatic) GIST treated with a combination of surgery and either imatinib or sunitinib were evaluated [10].

Surgical outcome correlated closely with disease status following TKI therapy: 78% of patients with stable disease had no residual disease postoperatively, whereas no residual disease occurred postoperatively in 25 and 7% of patients with limited disease, and generalized disease progression, respectively. PFS at 1 year favored patients with stable disease and limited disease compared with those whose presurgical disease classification following TKI treatment was generalized progression (88, 33 and 0%, respectively); OS was 95, 86 and 0%, respectively, in these patients. Although not planned as a 'neoadjuvant study', these results may nevertheless suggest a role for preoperative TKI therapy in patients with advanced GIST. However, the precise contribution of subsequent surgery appears to depend on patients' response to TKI treatment and resulting disease status at time of surgery.

The role of neoadjuvant therapy

Phase I and II clinical trials in locally advanced and metastatic GIST showed that over 50% of patients responded to imatinib with decreased tumor size [25,33,34]. Thus, a rationale for neoadjuvant imatinib is to downstage inoperable GIST by reducing tumor size, thereby helping to minimize the potential loss of normal tissue. Major guidelines have convergent recommendations on the use of neoadjuvant imatinib, stressing cytoreduction to reduce surgical morbidity, facilitate R0 resection and to reduce associated complications.

The ESMO recommendations now support the use of neoadjuvant imatinib when R0 surgery is not feasible or if it might be attained with less mutilating surgery after the tumor has been reduced in size [2]. They also recommend neoadjuvant therapy if a planned surgery can be performed more safely, with a lower risk of bleeding or tumor rupture, following cytoreduction. Similarly, NCCN guidelines state that neoadjuvant therapy should be instituted in cases of marginally resectable tumors and for those with resectable GIST when surgical morbidity would be reduced following tumor shrinkage [3]. Other guidelines make similar suggestions regarding tumor downsizing to reduce surgical morbidity, and all stress that a sufficient length of time on imatinib be allowed to pass in order to attain maximal response to imatinib before surgery is performed; this length of time is generally up to 12 months (Table 1). Experts also recommend neoadjuvant imatinib for downstaging GIST in cases of nonmetastatic, localized, unresectable disease, if feasible. For operable tumors, neoadjuvant imatinib may also be considered a potential option to mitigate surgical morbidity or multiple organ resection; if its use is considered, it should be done so in the context of a multidisciplinary setting at expert centers. Mutational analysis should also be performed to assess the presence of imatinib-insensitive GIST or to adjust starting dosage, for example, 800 mg/day in the case of patients with *KIT* exon 9 mutation [2,3].

Outcomes from the CSTI571-BDE43 and Radiation Therapy Oncology Group (RTOG) S-0132/ACRIN 6665 trials should prove valuable in helping to determine appropriate treatment options for patients whose GIST was previously classified as unresectable, and to validate the role of neoadjuvant (and adjuvant) therapy.

CSTI571-BDE43 is a nonrandomized, multicenter study of neoadjuvant imatinib in patients with locally advanced GIST [35]. Patients receive imatinib for periods of 4–6 months and

surgical resection performed in patients who respond to imatinib or display stable disease. Follow-up will be at 4 weeks, 6 months and 1 year.

The RTOG S-0132/ACRIN 6665 is the first prospective (nonrandomized design) trial of neoadjuvant/adjuvant therapy [36]. Results were recently published and showed that both neoadjuvant and adjuvant imatinib yielded apparently improved outcomes for primary and metastatic GIST, respectively [15]. Briefly, imatinib at daily doses of 600 mg resulted in 2-year PFS in 83 and 77% of patients with primary and recurrent metastatic GIST, respectively. The estimated OS was 93 and 91% for those groups, respectively.

Adjuvant therapy in GIST

While the majority of primary GISTs are resectable and associated with high cure rates during early disease – especially in high-risk tumors – the risk of relapse remains significant, even following R0 resection. Risk of recurrence is now known to be highly dependant on mitotic count, tumor size and tumor site in the GI tract [37,38]. The benefit of postoperative imatinib has been shown by recent trials in patients with high-risk GIST. In American College of Surgeons Oncology Group (ACOSOG) Z9000, a single-arm (nonrandomized), open-label, Phase II multicenter trial of adjuvant therapy, treatment with standard-dose imatinib (400 mg daily) for 1 year following surgical resection extended PFS and was associated with improved OS, with rates of 99, 97 and 97% after 1, 2 and 3 years of follow-up, respectively [17].

Interim analyses of the large ACOSOG trial, Z9001, had found that patients treated with 1 year of standard dose imatinib experienced significantly longer PFS compared with patients in the placebo arm [39]. Final results of ACOSOG Z9001 confirmed and extended those findings: following complete surgical resection of KIT-positive, primary GIST 3 cm and above, significantly greater PFS was observed in 98% of those who received adjuvant imatinib compared with 83% of those in the placebo arm [16]. Patients with larger tumors (> 10 cm) appeared to benefit the most, although the trial was not prospectively powered to assess efficacy according to tumor size. Longer follow-up will determine whether an increased OS benefit is imparted by 1 year of adjuvant imatinib.

Based on results from ACOSOG Z9001, imatinib 400 mg/day was approved on December 19, 2008 by the US FDA for the post-surgery treatment of adult patients following complete surgical removal of KIT (CD117)-positive GIST [101]. Following an earlier positive opinion, the European Medicines Agency (EMA), on 29 April 2009, also approved the use of adjuvant imatinib in GIST for patients who are at significant risk of relapse [102]. Of note, neither the FDA nor the EMA include recommendations on treatment duration in their respective approvals.

These Phase III, controlled, randomized data, and subsequent approvals provided the impetus to update both ESMO and NCCN guidelines regarding the use of adjuvant therapy. Previously considered ‘investigational’ in earlier ESMO statements, the 2009 recommendations support 1 year of adjuvant imatinib in patients at a substantial risk of relapse following primary resection. It is also made clear that patients at a low or very low risk of recurrence should not receive adjuvant treatment [2]. The recommendation for 1 year

of treatment follows on from the 1-year data in ACOSOG Z9001. NCCN 2009 guidelines state that adjuvant therapy should be used as an “alternative to observation, for patients who have undergone complete resection for primary GIST” [3]. While similar in overall recommendation, NCCN guidelines make no comment on the optimal duration of therapy, choosing rather to recommend administering adjuvant imatinib for at least 1 year in patients with intermediate- to high-risk GIST. Canadian 2006 guidelines are expected to be updated soon and make similar recommendations for adjuvant therapy (Table 1).

Other recent data on the use of adjuvant imatinib in patients with intermediate- or high-risk GIST include an uncontrolled Phase II study in which 105 patients with intermediate- and high-risk GIST who underwent radical surgery (R0) and were then treated with 400 mg/day adjuvant imatinib for 1 year experienced higher PFS at 1, 1.5 and 2 years, respectively [40].

In another uncontrolled study evaluating 2-year adjuvant imatinib in 47 patients who had undergone complete resection of primary GIST with a high risk of recurrence according to Fletcher criteria [41], and with *c-KIT* exon 11 mutation. The 1- and 2-year PFS rates were 97.9 and 93.3%, respectively [42].

Two large, randomized prospective trials of adjuvant imatinib are the EORTC 62024 and Scandanavian Sarcoma Group XVIII/Arbeitsgemeinschaft Internistische Onkologie (AIO; German Cooperative Group on Medical Oncology) studies; results from these are anticipated to help provide guidance on the relevance and the optimal duration of adjuvant therapy [43,44]. Clearly, the role of adjuvant imatinib therapy in the management of GIST is a developing paradigm, and data elucidating its impact on overall survival – the ultimate end point of adjuvant treatment – may not be available for the next 5 years while trial results are collected and analyzed. Experts do agree now, however, that the duration of adjuvant imatinib therapy that will provide the optimal clinical benefit may surpass 1 year.

Experts also agree and strongly recommend that the decision to use adjuvant imatinib should always be based on a careful evaluation of the risk of relapse for individual patients, taking into account not only tumor size, but also mitotic rate and site of primary tumor, as well as patient preference. Experts further agree that additional and better clinical data are necessary to determine which risk groups will benefit the most from adjuvant imatinib.

Mutational analysis in GIST: when & how?

The 2009 ESMO guidelines assert that “mutational analysis ... is strongly recommended in the diagnostic work-up of all GIST”. Updated ESMO recommendations also suggest that when considering adjuvant imatinib, “...mutational analysis may guide the selection of those patients who are more likely to benefit from the treatment.” According to the 2009 NCCN guidelines, “...molecular analysis can be considered in the diagnosis of GIST”. Although guidelines place a somewhat variable emphasis on the importance and timing of mutational analysis, a greater role of testing in the future is likely.

In a study conducted by Debiec-Rychter and colleagues, expression of the exon 9-mutated KIT protein was associated with improved PFS with high-dose imatinib (800 mg/day), whereas increasing the dose of imatinib in patients harboring exon 11 mutations did not

provide additional clinical benefit [18]. This study indicated that patients harboring *KIT* exon 9 mutations should be administered with high-dose imatinib, a recommendation that has since been incorporated in all the latest GIST guidelines.

Although testing for *KIT* exon 9 mutation is supported by experts, the exact role of mutational analysis of *c-KIT* exons 11, 13 and 17 and *PDGFRA* exons 12 and 18 in treatment decision-making remains undetermined. What is more is that there is also disagreement on whether mutational testing should be performed for all patients at the time of diagnosis; agreement does exist, however, that testing should not be performed on GISTs that are 3 cm or less in size. Experts also stress that mutational testing should only be performed in validated, high-volume laboratories.

In the metastatic setting, experts do not support the routine use of mutational analysis on patients pretreated with TKIs, but would consider it for those who are treatment naïve. In advanced GIST, experts support the use of 800 mg/day imatinib as the standard dose in patients harboring the exon 9 mutation. Although *in vitro* data have demonstrated that the *PDGFRA* substitution mutation D842V confers resistance to imatinib, it remains to be determined what the role of this and other *PDGFRA* mutations (the frequencies of which are overall much lower than those of other *KIT* mutations) should play in treatment decision-making. In tumors that histologically resemble GIST, but in which immunohistochemistry does not detect expression of KIT, mutational testing may reveal the presence of a *KIT* or *PDGFRA* mutation. If identified, treatment with imatinib is appropriate.

Maintaining therapy in responding patients

Maintenance of TKI therapy should equally be considered during periods when disease is controlled as well as after treatment failure, a recommendation, which is incorporated in the latest guidelines. More specifically, the ESMO guidelines suggest that “treatment should be continued indefinitely, since treatment interruption is generally followed by relatively rapid tumor progression in virtually all cases, even when lesions have been previously surgically excised.” The NCCN guidelines state that “...continuous use of imatinib is recommended for metastatic GIST until progression.” Results of the Phase III BFR14 study conducted by the French Sarcoma Group have provided strong support to this concept [19,32].

Treatment interruption (INT) versus maintenance instituted after 1 year of treatment in patients with metastatic or unresectable malignant GIST (n = 182) was prospectively evaluated in the BFR14. There were 58 evaluable patients, and progression was observed in eight out of 26 patients in the maintenance arm and 26 out of 32 patients in the INT arm (p = 0.0001). In total, 24 out of 26 patients with documented progression in the INT arm responded to reintroduction of imatinib, although no differences in OS or in imatinib resistance were observed between the two treatment arms. Imatinib interruption resulted in rapid (~6 months) progression in most patients, leading the authors to conclude that unless drug-associated toxicity prevents it, imatinib should be maintained even when disease is controlled [19]. Further data for BFR14 confirmed that for patients who were maintained on therapy, clinical benefit was garnered for up to 3 years (Figure 2) [32].

Maintaining therapy in progressing patients

Experts also recommend TKI maintenance therapy in patients shown to be truly progressing. Cessation of TKI therapy in progressing patients is associated with a ‘PET flare’, corresponding to the progression of imatinib- or sunitinib-sensitive clones after approximately 1 month off drug.

It has been hypothesized that the ‘slow down’ of progression by continued TKI therapy may retard the evolution of the disease, providing a prolonged benefit to OS as suggested by the observation of the discrepancy between PFS (20–24 months) in the EORTC trial and OS (58 months) in the B2222 trial [24,26,27]. In line with this reasoning, the 2009 ESMO guidelines infer that there may be some benefit to rechallenging these patients with imatinib; this should be further evaluated in prospective controlled randomized clinical trials. They also affirm that maintaining TKI therapy even in progressive disease may slow down progression by containing the growth of still-sensitive clones [2]. The 2009 NCCN guidelines state that “...imatinib should be continued at the same dose or at increased dose as tolerated in patients’ with limited progressive disease” [3].

Overall, regarding TKI maintenance therapy, expert opinion remains in alignment with current guidelines. In the advanced setting, imatinib treatment should not be stopped before progression unless intolerance is experienced. In the case of focal progression, maintenance therapy after local treatment is advised. Maintaining TKI therapy in case of general progression and absence of alternative systemic treatment options to slow down further progression is also recommended. There is also a benefit to some patients of imatinib rechallenge after alternate TKI treatment failure. In both of the preceding instances, recommendations are supported by expert opinion and not definitive clinical evidence.

Radiology in GIST management

Radiological findings play an integral role in surgical and therapeutic decision-making in the management of GIST. Contrast-enhanced abdominal and pelvic CT scans are cornerstones of disease staging and follow-up, providing superior assessments in most cases. In select instances MRI is an alternative to a CT scan, providing superior preoperative staging information in rectal GIST. While experts consider fluorodeoxyglucose-PET especially useful for the early detection of tumor response to imatinib, they also indicate that it is not mandatory for every patient treated with TKIs. The majority of experts also agree that ‘volumetric response’ as defined by Response Evaluation Criteria In Solid Tumors (RECIST) is not the optimum surrogate marker of benefit due to imatinib therapy: there are patients whose tumors do not show volumetric response, but in fact have prolonged stable disease. Data show that such patients gain the same benefit from imatinib with equivalent rates of OS compared with patients whose tumors exhibit volumetric response. This opinion is supported by data from the B2222 trial [25], as well as by studies conducted by Benjamin and colleagues and Le Cesne and colleagues [45,46].

Choi and colleagues investigated alternative measures of response; these studies resulted in new criteria for ‘good response’, based on CT, and are essentially defined as follows: over 10% mean decrease in tumor size or over 15% mean decrease in tumor density [47]. It has

been suggested that the prognostic value of response determined by the 'Choi criteria' for GIST that is treated with imatinib is more useful than that based on RECIST.

The study conducted by Benjamin and colleagues (n = 98) specifically sought to determine whether Choi criteria are superior predictors of PFS compared with RECIST [45]. Investigators concluded that patients who met Choi criteria at the 2 months stage displayed significantly better PFS than patients not meeting the criteria (p = 0.0002). In addition, in the group where response was assessed by RECIST, no significant correlation with PFS was observed (p = 0.1). In comparison, GIST response rates to imatinib by Choi criteria and RECIST in this study were 83 and 46%, respectively. In the EORTC Intergroup 62005 study, patients who exhibited 'stable disease' at 6 months had similar clinical outcome to 'responders' (complete response and partial response) at 6 months [46]. This pattern of response was also seen in the B2222 study by Blanke and colleagues [24].

It is on these data that experts have based the opinion that 'stable disease' is as good as 'response' (both complete and partial response) according to RECIST. Experts have noted that, in some patients, an increase in lesion size may actually represent a genuine biological response in cases of false tumor progression. Furthermore, because patients with stable disease by RECIST are not classified as responders, but have the same outcomes as responders, panel members agreed with the statement by Benjamin that "we should desist using RECIST at least in GIST" and should "insist on objective progressive disease in non-cystic GIST" [44].

Expert commentary

In the contemporary landscape of GIST management, data continue to accumulate and more clinical trial results are anticipated over the coming years that may further influence principles of GIST management. A key outcome of new data surrounding some of the major issues outlined here is the actual or impending revision of major global guidelines. Conversely, where mature data are still lacking, consensus remains elusive. With an overarching goal being the creation of globally applicable recommendations, we propose a summary of consensus statements for the management of GIST (Box 1). This summary juxtaposes accepted consensus recommendations (based on clinical trial data) with current expert opinion (expected to be, although not yet, validated by clinical trial data). Simultaneously, we propose several key unresolved issues and 'gaps' that should be investigated further. These include:

- Defining the use and circumstances when neoadjuvant therapy should be utilized;
- Deciphering the clinical benefit of adjuvant imatinib therapy on overall survival and determining the duration of therapy necessary to receive the optimal clinical outcome;
- Determining which risk groups would clearly benefit from adjuvant imatinib therapy;
- Establishing which *KIT* and *PDGFRA* mutations should be integrated into diagnosis for prognostic and treatment decision-making;

- Evaluating the relevance of maintenance therapy;
- Devising a novel response paradigm for imatinib and other TKI therapies;
- Delineating the role of surgery in the advanced setting, particularly in focal and multifocal progression;
- Defining the true significance and establishing the prognostic value of stable disease following imatinib therapy.

Five-year view

The last decade of research has dramatically changed the management of GIST. The next 5 years are likely to result in a better understanding of the appropriate length of imatinib therapy in the metastatic disease setting, and provide additional insight into the tumor characteristics of GIST at the highest risk of recurrence. The use of genotyping in GIST is becoming more frequent and with multiple TKIs now being tested, it is incumbent upon the field to individualize the choice of treatment using genotyping results in order to achieve the best outcome for individual patients. The duration of adjuvant imatinib therapy and the appropriate candidate patients for this approach will evolve in this context. For those with advanced disease, alternate strategies in cases of imatinib resistance is a clinical challenge, one which is the focus of much ongoing clinical and preclinical investigation, from the evaluation of novel agents to an improved understanding of surgery and other focal therapies to delay the emergence of resistant disease.

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References

Papers of special note have been highlighted as:

- of interest
- of considerable interest

1. Corless CL, Heinrich MC. Molecular pathobiology of gastrointestinal stromal sarcomas. *Annu Rev Pathol.* 2008; 3:557–586. [PubMed: 18039140]
2. Casali PG, Jost L, Reichardt P, Schlemmer M, Blay JY. Gastrointestinal stromal tumours: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol.* 2009; 20(Suppl. 4): 64–67. [PubMed: 19454466]
3. National Comprehensive Cancer Network. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (Version 1.2009I). National Comprehensive Cancer Network; PA, USA: 2009.
4. Blackstein ME, Blay JY, Corless C, et al. Gastrointestinal stromal tumours: Consensus statement on diagnosis and treatment. *Can J Gastroenterol.* 2006; 20(3):157–163. [PubMed: 16550259]
5. Montemurro M, Dirnhofer S, Bornerc M, et al. Diagnosis and treatment of GIST in Switzerland. *Schweiz Med Forum.* 2008; 8:544–549.

6. Nishida T, Hirota S, Yanagisawa A, et al. Clinical practice guidelines for gastrointestinal stromal tumor (GIST) in Japan: English version. *Int J Clin Oncol*. 2008; 13(5):416–430. [PubMed: 18946752]
- 7•. Corless CL, Schroeder A, Griffith D, et al. PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and *in vitro* sensitivity to imatinib. *J Clin Oncol*. 2005; 23(23):5357–5364. Study reporting on PDGF receptor α -mutated gastrointestinal stromal tumor (GIST). [PubMed: 15928335]
8. Taylor ML, Metcalfe DD. KIT signal transduction. *Hematol Oncol Clin North Am*. 2000; 14(3): 517–535. [PubMed: 10909038]
9. Bauer S, Hartmann JT, de Wit M, et al. Resection of residual disease in patients with metastatic gastrointestinal stromal tumors responding to treatment with imatinib. *Int J Cancer*. 2005; 117(2): 316–325. [PubMed: 15900603]
10. Raut CP, Posner M, Desai J, et al. Surgical management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitors. *J Clin Oncol*. 2006; 24(15):2325–2331. [PubMed: 16710031]
11. Sym SJ, Ryu MH, Lee JL, et al. Surgical intervention following imatinib treatment in patients with advanced gastrointestinal stromal tumors (GISTs). *J Surg Oncol*. 2008; 98(1):27–33. [PubMed: 18452195]
12. DeMatteo RP, Maki RG, Singer S, Gonen M, Brennan MF, Antonescu CR. Results of tyrosine kinase inhibitor therapy followed by surgical resection for metastatic gastrointestinal stromal tumor. *Ann Surg*. 2007; 245(3):347–352. [PubMed: 17435539]
13. Gronchi A, Fiore M, Miselli F, et al. Surgery of residual disease following molecular-targeted therapy with imatinib mesylate in advanced/metastatic gist. *Ann Surg*. 2007; 245(3):341–346. [PubMed: 17435538]
14. Rutkowski P, Nowecki Z, Nyckowski P, et al. Surgical treatment of patients with initially inoperable and/or metastatic gastrointestinal stromal tumors (GIST) during therapy with imatinib mesylate. *J Surg Oncol*. 2006; 93(4):304–311. [PubMed: 16496358]
15. Eisenberg BL, Harris J, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant imatinib mesylate (IM) for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumor (GIST): early results of RTOG 0132/ACRIN 6665. *J Surg Oncol*. 2009; 99(1):42–47. [PubMed: 18942073]
- 16••. DeMatteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2009; 373(9669):1097–1104. Presents final results of the large, randomized trial of adjuvant imatinib versus placebo for 12 months; demonstrated benefit of imatinib in increasing disease-free survival in primary resected disease. [PubMed: 19303137]
17. DeMatteo, RP.; Owzar, K.; Antonescu, CR., et al. Efficacy of adjuvant imatinib mesylate following complete resection of localized, primary gastrointestinal stromal tumor (GIST) at high risk of recurrence: the U.S. Intergroup Phase II trial ACOSOG Z9000. Program and Abstracts of the Gastrointestinal Cancers Symposium; Orlando, FL, USA. 25–27 January 2008; Abstract 8
- 18••. Debiec-Rychter M, Sciot R, Le Cesne A, et al. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. *Eur J Cancer*. 2006; 42(8):1093–1103. Report of the benefit of high-dose imatinib in advanced GIST carrying an exon 9 mutation. [PubMed: 16624552]
- 19•. Blay JY, Le Cesne A, Ray-Coquard I, et al. Prospective multicentric randomized Phase III study of imatinib in patients with advanced gastrointestinal stromal tumors comparing interruption versus continuation of treatment beyond 1 year: the French Sarcoma Group. *J Clin Oncol*. 2007; 25(9):1107–1113. Demonstration of the need to use imatinib continuously in advanced disease. [PubMed: 17369574]
20. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. *Ann Surg*. 2000; 231(1):51–58. [PubMed: 10636102]
21. Hassan I, You YN, Shyyan R, et al. Surgically managed gastrointestinal stromal tumors: a comparative and prognostic analysis. *Ann Surg Oncol*. 2008; 15(1):52–59. [PubMed: 18000711]

22. Langer C, Gunawan B, Schuler P, Huber W, Fuzesi L, Becker H. Prognostic factors influencing surgical management and outcome of gastrointestinal stromal tumours. *Br J Surg.* 2003; 90(3): 332–339. [PubMed: 12594669]
23. Singer S, Rubin BP, Lux ML, et al. Prognostic value of KIT mutation type, mitotic activity, and histologic subtype in gastrointestinal stromal tumors. *J Clin Oncol.* 2002; 20(18):3898–3905. [PubMed: 12228211]
24. Blanke CD, Demetri GD, von Mehren M, et al. Long-term results from a randomized Phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. *J Clin Oncol.* 2008; 26(4):620–625. Long-term follow-up of the Phase II trial of imatinib in GIST. [PubMed: 18235121]
25. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med.* 2002; 347(7):472–480. [PubMed: 12181401]
26. Blanke CD, Rankin C, Demetri GD, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the KIT receptor tyrosine kinase: S0033. *J Clin Oncol.* 2008; 26(4): 626–632. Phase III data on low- versus high-dose imatinib in advanced disease. [PubMed: 18235122]
27. Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumors with high-dose imatinib: randomised trial. *Lancet.* 2004; 364(9440):1127–1134. Phase III data on low- versus high-dose imatinib in advanced disease; demonstrated superiority of the high-dose arm for progression-free survival. [PubMed: 15451219]
28. Chen H, Pruitt A, Nicol TL, Gorgulu S, Choti MA. Complete hepatic resection of metastases from leiomyosarcoma prolongs survival. *J Gastrointest Surg.* 1998; 2(2):151–155. [PubMed: 9834411]
29. Bonvalot S, Eldweny H, Pechoux CL, et al. Impact of surgery on advanced gastrointestinal stromal tumors (GIST) in the imatinib era. *Ann Surg Oncol.* 2006; 13(12):1596–1603. [PubMed: 16957966]
30. Hasegawa J, Kanda T, Hirota S, et al. Surgical interventions for focal progression of advanced gastrointestinal stromal tumors during imatinib therapy. *Int J Clin Oncol.* 2007; 12(3):212–217. [PubMed: 17566845]
31. Hohenberger P, Wardelmann E. Surgical considerations for gastrointestinal stroma tumor. *Chirurg.* 2006; 77(1):33–40. [PubMed: 16372188]
32. Adenis A, Cassier P, Bui BN, et al. Does interruption of imatinib (IM) in responding patients after three years of treatment influence outcome of patients with advanced GIST included in the BFR14 trial? *J Clin Oncol.* 2008; 26(Suppl) Abstract 10522.
33. Eisenberg BL, Judson I. Surgery and imatinib in the management of GIST: emerging approaches to adjuvant and neoadjuvant therapy. *Ann Surg Oncol.* 2004; 11(5):465–475. [PubMed: 15123459]
34. van Oosterom AT, Judson I, Verweij J, et al. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a Phase I study. *Lancet.* 2001; 358(9291):1421–1423. Dose escalation study demonstrating safety and efficacy of imatinib in GIST. [PubMed: 11705489]
35. Technische Universität München. Csti571-bde43. Open-label trial of neoadjuvant imatinib mesylate (Gleevec) in patients with locally advanced malignant gastrointestinal stromal tumors (GIST) expressing *c-KIT* or platelet-derived growth factor receptor- α (NCT identifier: NCT00112632) (2009)
36. Radiation Therapy Oncology Group, National Cancer Institute (NCI), American College of Radiology Imaging Network, Eastern Cooperative Oncology Group. RTOG S-0132. A Phase II trial of neoadjuvant/adjuvant STI-571 (Gleevec NSC #716051) for primary and recurrent operable malignant GIST expressing the KIT receptor tyrosine kinase (CD117). NCT identifier: NCT00028002. 2009
37. DeMatteo RP, Gold JS, Saran L, et al. Tumor mitotic rate, size, and location independently predict recurrence after resection of primary gastrointestinal stromal tumor (GIST). *Cancer.* 2008; 112(3): 608–615. [PubMed: 18076015]

- 38•. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol.* 2006; 23(2):70–83. Reports on differences in risk of recurrence based on features of the primary tumor. [PubMed: 17193820]
39. DeMatteo, R.; Owzar, K.; Maki, R., et al. Adjuvant imatinib mesylate increases recurrence free survival (RFS) in patients with completely resected localized primary gastrointestinal stromal tumor (GIST): North American Intergroup Phase III trial ACOSOG Z9001. Program and Abstract of the American Society of Clinical Oncology Annual Meeting; Chicago, IL, USA. 1–5 June 2007; Abstract 10079
40. Shen L, Li J, Li J, Gong J, Wu A. Adjuvant post-surgery therapy with imatinib in intermediate or high-risk gastrointestinal stromal tumour (GIST) patients: interim analysis from a single centre comparison study. *Ann Oncol.* 2008; 19(Suppl. 8):Viii 267. Abstract 870pd.
41. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Hum Pathol.* 2002; 33:459–465. [PubMed: 12094370]
42. Kang, Y.; Kang, BW.; Ryu, M., et al. A Phase II study of imatinib mesylate as adjuvant treatment for curatively resected high-risk localized gastrointestinal stromal tumors with *c-KIT* exon 11 mutation. Presented at: Gastrointestinal Cancers Symposium: Science and Multidisciplinary Management of GI Malignancies; San Francisco, CA, USA. 15–17 January 2009; Abstract 95
43. European Organization for Research and Treatment of Cancer, Italian Sarcoma Group, Federation Nationale des Centres de Lutte Contre le Cancer, Sarcomas GEdIe. EORTC 62024. Intermediate and high risk localized, completely resected, gastrointestinal stromal tumors (GIST) expressing KIT receptor: a controlled randomized trial on adjuvant imatinib mesylate (Glivec) versus no further therapy after complete surgery. NCT identifier: NCT00103168. 2009
44. Scandinavian Sarcoma Group. SSGXVIII/AIO. Short (12 months) versus long (36 months) duration of adjuvant treatment with the tyrosine kinase inhibitor imatinib mesylate of operable GIST with a high risk of recurrence. NCT identifier: NCT00116935. 2009
45. Benjamin RS, Choi H, Macapinlac HA, et al. We should desist using RECIST, at least in GIST. *J Clin Oncol.* 2007; 25(13):1760–1764. [PubMed: 17470866]
46. Le Cesne A, van Glabbe M, Verweij J, et al. Is a stable disease according to RECIST criteria a real stable disease in GIST patients treated with imatinib mesylate (IM) included in the intergroup EORTC/ISG/AGITG trial? *J Clin Oncol.* 2006; 24(18s) Abstract 9510.
- 47•. Choi H, Charnsangavej C, Faria SC, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. *J Clin Oncol.* 2007; 25(13):1753–1759. Importance of changes in density in GIST tumors in identifying benefit to tyrosine kinase inhibitor therapy. [PubMed: 17470865]

Websites

101. [30 September 2009] US FDA approves Gleevec to prevent recurrence of rare gastrointestinal cancer. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116997.htm
102. [30 September 2009] Glivec: procedural steps taken and scientific information after the authorisation. www.emea.europa.eu/humandocs/PDFs/EPAR/glivec/241801en8b.pdf

Box 1**Expert summary of consensus and opinion on the management of gastrointestinal stromal tumor****Surgery in metastatic GIST**

- For multifocal progression, surgery is not recommended*
- For focal progression, surgery is not known to be effective owing to a lack of randomized clinical trials; panel members recommend clinical trial
- Surgery for focal progression may be proposed in a multidisciplinary setting, case by case*
- Surgical resection of metastasis when a patient is responding to imatinib has not been shown to be useful yet and so should enter a clinical trial*

Neoadjuvant therapy

- Recommended to downstage GIST in the setting of nonmetastatic, localized, unresectable tumors; if feasible tumor should be resected*
- Should be proposed as an option in the setting of operable tumor, to mitigate surgical morbidity, or to avoid multiple organ resection*
- Should be discussed in a multidisciplinary setting in expert centers

Adjuvant therapy

- Adjuvant imatinib is effective at delaying relapse in patients with lesions 3 cm or more; true benefit on overall survival remains to be seen*
- Optimal duration of therapy unknown; preliminary data indicate 1 year*
- Risk groups for which adjuvant therapy should be administered should be established

Mutational analysis

- Mutational analysis is important in the diagnostic work-up of all GIST*
- Mutational analysis should be performed in metastatic GIST in patients not pretreated with TKIs*
- No published consensus for localized disease and metastatic GIST pretreated with TKIs
- In advanced GIST, 800 mg/day is the standard dose for patients with an exon 9 mutation*
- PDGF receptor D842V may be important but further clinical studies are needed to deduce role in treatment decision-making with imatinib or another TKI
- Mutational analysis should be performed in audited high-volume laboratories*

Maintaining therapy

- In advanced GIST, imatinib treatment should not be stopped before progression unless intolerance*
- Maintenance of imatinib after treatment of focal progression advisable*
- Maintaining TKI therapy in absence of alternative treatment options to slow progression is a recommended strategy
- Potential benefit of rechallenge with imatinib after failure of previous TKI*

Radiology in GIST

- PET not mandatory for every patient treated with TKIs*
- RECIST is not the optimum means of determining which patients benefit from imatinib therapy*
- Response criteria including density measurements and size changes are superior to RECIST in predicting long-term outcomes*
- PD using RECIST valid if noncystic

*Statements supported by clinical trial data.

GIST: Gastrointestinal stromal tumor; RECIST: Response Evaluation Criteria in Solid Tumors; TKI: Tyrosine kinase inhibitor.

Key issues

- Management paradigms for gastrointestinal stromal tumor (GIST) – both primary and advanced – are rapidly evolving.
- Across current guidelines, alignment exists for many clinical issues but some differences remain.
- Neoadjuvant imatinib is a feasible strategy and is now recommended in several common clinical scenarios in GIST.
- Adjuvant imatinib for a least 1 year is now recommended for select patients; data suggest longer duration may be needed for subsets of these.
- Mutational analysis is useful in primary GIST; a greater role in other settings is likely.
- Imatinib 800 mg/day is a standard for advanced GIST patients with *c-KIT* exon 9 mutations.
- Tyrosine kinase inhibitor (imatinib) maintenance is important both when disease is controlled and after treatment failure.
- Limited data exist on the clinical benefit of secondary resections in advanced GIST.
- ‘Volumetric response’ by RECIST is not the optimum marker of benefit of imatinib.
- Unresolved issues in GIST management must be addressed by clinical trials.

Figure 1. Multimodality therapy for metastatic gastrointestinal stromal tumor

Figure 2. Maintaining therapy in responding patients (BFR14 study)

Progression-free survival (PFS) in randomly assigned patients with advanced GIST comparing continuous (CONT) with interrupted (STOP) imatinib therapy after (A) 1 year or (B) 3 years of treatment in patients with advanced GIST. GIST: Gastrointestinal stromal tumor; PFS: Progression-free survival. Data from [19,32].

Table 1

Snapshot comparison of clinical guidelines/recommendations for adjuvant and neoadjuvant imatinib.

Organization	Year	Neoadjuvant therapy	Adjuvant therapy	Ref.
ESMO	2009	<p>Recommended when R0 surgery is not feasible, or when R0 can be achieved by less mutilating surgery</p> <p>Recommended when planned surgery can be conducted more safely after reducing tumor size</p> <p>PET scan ± CT/MRI scan recommended for early assessment of treatment response after a few weeks</p> <p>Imatinib continued until maximal tumor response (generally 6–12 months); dose not specified</p> <p>State that mutational analysis may help exclude nonsensitive mutations from therapy with imatinib</p>	<p>Results from Z9001 are mentioned</p> <p>Adjuvant imatinib proposed as an option for those patients with a substantial risk of relapse</p> <p>Mutational analysis may guide the selection of those patients who are more likely to benefit from adjuvant treatment</p>	[2]
NCCN	2009	<p>Recommended for patients with marginally resectable GIST</p> <p>Recommended for patients with resectable GIST who have a significant risk of surgical morbidity; close monitoring essential</p> <p>Considered if surgical morbidity would be improved by reducing the size of the tumor</p> <p>Recommended starting dose is 400 mg/day, but a dose of 800 mg/day should be considered for those with <i>KIT</i> exon 9 mutations</p> <p>PET scan recommended for early assessment of response after 2–4 weeks</p> <p>Imatinib continued until maximal tumor response, which may take 3–6 months</p> <p>Imatinib should be resumed after surgery as soon as patient can tolerate oral medications</p>	<p>Results from Z9001 and Z9000 are mentioned</p> <p>Adjuvant imatinib included as an alternative to observation for patients who have undergone complete resection</p> <p>Optimum duration of adjuvant therapy is unknown, but should be 12 months in patients with intermediate or high risk of recurrence; higher risk patients may require longer duration of treatment</p> <p>Adjuvant imatinib should be continued if any persistent gross disease is seen following resection</p>	[3]
Canadian Advisory Committee on GIST	2006*	<p>Recommended for borderline unresectable GIST, and should be considered for 'functionally unresectable' GIST when a decrease in tumor size would lower risk of surgical morbidity and preserve organ function</p> <p>PET scan recommended at 1–2 weeks for early assessment of response</p> <p>Imatinib continued until maximum tumor response (~4–12 months); dose not specified</p>	<p>Z9001 and EORTC 62024 mentioned as ongoing trials</p> <p>Adjuvant imatinib is not recommended as standard therapy in 2006 guidelines</p> <p>Based on results from Z9001 and recent approvals, an impending recommendation for adjuvant imatinib in intermediate- and high-risk patients is expected</p>	[4]
Japan Society of Clinical Oncology	2008	<p>Suggested for marginally resectable GIST</p> <p>Suggested for preserving organ function in GIST located in the esophagus, duodenum, or rectum</p> <p>PET scan recommended in first month of imatinib therapy for early assessment of response</p>	<p>Positive safety and RFS results from Z9001 mentioned</p> <p>Patients considering adjuvant therapy should be advised according to its risks</p> <p>No recommendation regarding adjuvant imatinib pending survival data from ongoing studies</p>	[6]

Organization	Year	Neoadjuvant therapy	Adjuvant therapy	Ref.
		<p>Imatinib therapy may be needed for 3–12 months to maximize response and avoid resistance</p> <p>Surgery should be performed in patients with partial response or stable disease; surgery may be postponed in patients with complete response while continuing imatinib</p> <p>Imatinib should be continued following surgery</p>		
Swiss clinical practice recommendations	2008	<p>Recommended for allowing easier surgical procedure and avoiding mutilating surgery</p> <p>PET scan recommended every 2 months during neoadjuvant therapy</p> <p>Imatinib may be continued for 6–12 months in responding patients; dose not specified</p>	<p>Preliminary results from Z9001 mentioned</p> <p>Adjuvant imatinib recommended in intermediate- and high-risk patients (as defined by NIH consensus classification)</p> <p>Imatinib should be continued for 1 year; duration of adjuvant therapy to be re-evaluated pending results from ongoing trials</p>	[5]

* Canadian guidelines are currently being updated.

EORTC: European Organisation for Research and Treatment of Cancer; ESMO: European Society of Medical Oncology; GIST: Gastrointestinal stromal tumor; NCCN: National Comprehensive Cancer Network; RFS: Recurrence-free survival.