ELSEVIER

EJC Supplements Vol. 4 Suppl. 1 (2006) 10–18

EJC Supplements

www.ejconline.com

Molecular basis for treatment of gastrointestinal stromal tumours[1]

Michael C. Heinrich*

Department of Medicine, Oregon Health and Science University Cancer Institute and Portland Veterans Affairs Medical Center, Portland, Oregon, USA

Abstract

Gastrointestinal stromal tumour (GIST) is a rare tumour of the gastrointestinal tract that arises from activating mutations in KIT or platelet-derived growth factor receptor α (PDGFRα). Imatinib, a molecularly targeted therapy that inhibits the kinase activity of KIT, PDGFRs, ABL, and BCR-ABL, has been shown to be highly efficacious in patients with advanced GIST. Most patients with advanced GIST treated with imatinib achieve either a partial response or experience stable disease, and median survival is longer than 3 years in either case. There is a strong correlation between the type of *KIT* or *PDGFRA* mutation and the clinical response to imatinib in patients with advanced GIST. In a phase II trial, significantly higher partial response rates were achieved in patients with GISTs harbouring *KIT* exon 11 mutations than in patients with GISTs harbouring *KIT* exon 9 mutations or in patients with GISTs exhibiting no detectable *KIT* or *PDGFRA* mutations. Resistance to imatinib treatment is a clinical challenge in the management of patients with advanced GIST. Many imatinib-resistant GISTs have an associated secondary kinase mutation of *KIT* or *PDGFRA*. Continuing research efforts are directed at optimising the use of imatinib in patients with advanced GIST as well as the development of novel treatment approaches to prevent and/or treat imatinib-resistant clones of GIST.

Keywords: Gastrointestinal stromal tumour; molecular mechanisms; KIT; PDGFRα; imatinib; clinical response; resistance; activating mutations; management strategies

1. Introduction

Gastrointestinal stromal tumour (GIST) is the most common mesenchymal tumour of the gastrointestinal (GI) tract. GISTs bear striking morphologic and immunophenotypic similarities to interstitial cells of Cajal (ICC), a network of innervated GI tract cells that regulate peristalsis [1,2]. These similarities, including expression of the haematopoietic progenitor cell antigen CD34, have led to the speculation that GISTs are derived from or share a multipotential mesenchymal stem cell progenitor with ICC [1,3–7]. Notably, ICC and GIST express the transmembrane receptor for stem cell factor or Steel factor, KIT [4]. Identification of KIT activating mutations as a key factor in the pathogenesis of GIST has substantially altered the diagnosis and treatment of GIST.

2. Cellular and molecular aetiology of GIST

KIT, a 145-kD glycoprotein, is normally expressed by haematopoietic progenitor cells, mast cells, melanocytes, germ cells, and ICC [4]. KIT expression has a critical role in the development of ICC, as mice that are nullizygous for genes encoding either functional KIT or KIT ligand are deficient in ICC [8–13]. In 1998, two groups reported that KIT is highly expressed in GIST, supporting the hypothesis that these tumours arise from or share a common progenitor with ICC [1,14].

Dr Hirota's group further showed that the vast majority of GISTs have *KIT* mutations resulting in constitutive kinase activity. Together, these observations suggested that *KIT* mutations are oncogenic and play an important role in the growth and survival of GISTs. Follow-up studies from many laboratories around the world strongly support this hypothesis. For example, KIT isolated from GIST extracts is highly phosphorylated, an indicator of KIT kinase activity [15]. *KIT* gene mutations are detectable in 80–85% of all GISTs [16–18], and such mutations are as common in small (<2 cm), incidentally discovered lesions as they are in larger, more advanced lesions [18,19]. In addition, a number of kindreds with germline *KIT* gene mutations have been identified in which affected individuals have an extremely high risk for developing one or more GISTs [20–25]. More recently, two groups have generated mouse models of GIST by targeted insertion of *KIT* genes containing exon 11 or 13 mutations that are homologous to *KIT* mutations seen in sporadic human GISTs [26,27]. Transgenic mice expressing

* Michael C. Heinrich, MD. R&D-19 3710SW US Veterans Hospital Rd, Portland, OR 97239, USA. Tel.: +1 503 220 3405; fax: +1 503 402 2817.
E-mail address: heinrich@ohsu.edu (M.C. Heinrich).

[1] Supported in part by a Merit Review Grant from the Department of Veterans Affairs.

1359-6349/ $ – see front matter

these constitutively activated forms of KIT develop diffuse hyperplasia of ICC and focal GIST formation. Thus, oncogenic activation of KIT is not only common in GISTs but occurs early in their tumorigenesis – making KIT an excellent therapeutic target.

KIT mutations, however, are not found in all GISTs. A small subset of GISTs have constitutively activating mutations in the gene encoding platelet-derived growth factor receptor α (PDGFRα), a receptor tyrosine kinase homologous to KIT, whereas other GISTs harbour wild-type genes encoding KIT and PDGFRα [2,27–29]. This suggests that GIST oncogenesis is multifactorial and can be triggered by constitutive activity of KIT, PDGFRα, or other unknown molecular targets [14,28–31].

3. Current therapy for GIST

Complete surgical resection is currently the first-line therapy for patients with resectable GIST [32,33]. However, many patients develop recurrent or metastatic disease after resection of the primary tumour.

Standard chemotherapy is ineffective for treatment of GIST, yielding disappointing results both as adjunctive therapy after primary resection and as therapy for recurrent or metastatic disease [34–36]. Radiotherapy is also of limited value in the management of GIST, due to the relative radioresistance of the tumours and the potential dose-limiting toxic effects of radiotherapy on surrounding vital organs [35,37]. The prospects for patients with locally advanced or metastatic GIST have been significantly improved with the availability of imatinib in both the USA and Europe.

4. Targeted therapy with imatinib

Imatinib is a relatively selective, small-molecule inhibitor of KIT, PDGFRα, PDGFRβ, c-FMS, BCR-ABL, and ARG tyrosine kinase activity [33,38–41]. Imatinib is currently indicated as first-line therapy for metastatic, unresectable, or recurrent GIST, as well as for chronic myeloid leukaemia in all phases [42,43]. The use of imatinib for GIST was based on the discovery that most of these tumours arise from KIT activating mutations, and the hypothesis that inhibition of KIT would exert an anti-proliferative and/or apoptotic effect on GIST cells [44,45]. This hypothesis was supported by studies in human KIT-dependent cell lines demonstrating that imatinib, at clinically relevant concentrations, blocked KIT kinase activity as well as induced anti-proliferative and pro-apoptotic responses in these cells. These early preclinical studies led to extensive clinical trials that have since established the efficacy and safety of imatinib in patients with advanced GIST.

5. Immunohistochemical classification of GIST

Approximately 95% of GISTs stain positively with an immunohistochemical assay for the CD117 antigen, an extracellular epitope of KIT [18,46], whereas another 5% express undetectable levels of KIT [47]. This nearly ubiquitous immunopositivity for KIT is a valuable diagnostic criterion enabling GIST to be differentiated from other tumours included in the differential diagnosis that typically do not exhibit detectable KIT [6,7,46,48]. Other malignancies stain positively for KIT, however, they are rarely included in the differential diagnosis of GIST [13,49]. Expression of other markers by GIST is more variable, including BCL-2 (80%), CD34 (70%), muscle-specific actin (50%), smooth muscle actin (35%), S-100 (10%), and desmin (5%) [6,17,18,48]. KIT (CD117), CD34, and desmin are a useful combination of markers for confirming the diagnosis in a morphologically typical GIST, with desmin stain serving primarily to rule out leiomyosarcoma.

6. Molecular classification of GIST

KIT and PDGFRα, as members of the class III receptor tyrosine kinase family, share a high degree of homology in their cytoplasmic domains [50]. Mutation of a number of discrete domains of these proteins can result in constitutive kinase activation (Fig. 1). The reported frequency of *KIT*-activating mutations in GIST ranges from 80% to 85% [18]. Analysis of data from 322 GIST cases showed that *KIT* mutations occurred most frequently (66.1%) in exon 11 [18], whereas mutations in exons 9, 13, and 17 occurred at much lower frequencies. Additionally, 7.1% of the GISTs in this series had mutations in *PDGFRA* exon 12 or 18. The remainder of the GISTs in this series expressed wild-type *KIT* and *PDGFRA*. In a recent update these investigators recently reported on 1105 GISTs, of which 80 tumours (7.2%) harboured a *PDGFRA* mutation: 66 in exon 18, 11 in exon 12, and 3 in exon 14 [51]. Other studies have indicated that most GISTs that do not express detectable levels of KIT and lack *KIT* mutations express *PDGFRA* mutations [28,47,52–54].

Several reports have suggested that GIST mutations are associated with tumour location and, possibly, prognosis. Occurrence of *KIT* exon 11 mutations does not seem

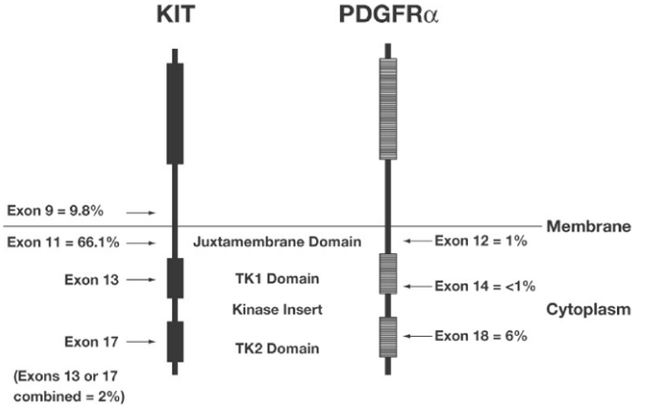

Fig. 1. Structural diagram of KIT and PDGFRα indicating regions and approximate frequency of activating mutations encoded by the respective genes [16,51].

to be related to tumour site, with similar frequencies of such mutations reported for the stomach, small intestine, oesophagus, and anorectum [6,55,56]. In contrast, *KIT* exon 9 mutations seem to preferentially occur in the small intestine [56,57], although this has not been a consistent finding [58].

The vast majority of GISTs with *PDGFRA* mutations originate in the stomach and, less frequently, in the omentum and mesentery [47,51,54,59,60]. In a recent study of 25 KIT-negative GISTs, mutational analysis showed that 18 tumours harboured *PDGFRA* mutations. Of these tumours, 15 (83%) had mutations in exon 18; 9 of these tumours originated in the stomach, 3 in the abdomen, and 1 each in the omentum, mesentery, and small bowel [47]. Two of the tumours, 1 in the abdomen and 1 in the omentum, expressed *PDGFRA* mutations in exon 12. The remaining tumour, with a *PDGFRA* mutation in exon 14, also originated in the abdomen. Sakurai *et al.* [53] examined 30 GISTs that were immunohistochemically weak or negative for KIT, and found *PDGFRA* mutations in 20 tumours. Twenty (67%) of these tumours had mutations in *PDGFRA* (18 in exon 18, 2 in exon 12); 18 originated in the stomach, and 2 in the omentum. Recently, Lasota *et al.* [59] analysed 447 GISTs lacking *KIT* exon 11 mutations and found mutations of *PDGFRA* exon 12 (11 cases) or exon 18 (128 cases) in 31% of these cases. Notably, 98% of the *PDGFRA*-mutant GISTs arose from the stomach.

Approximately 10% to 15% of GISTs that arise in adults lack identifiable mutations of *KIT* or *PDGFRA*. While the molecular pathogenesis of these tumours is unknown, the majority of these tumours strongly express KIT protein and have evidence of KIT activation [15]. In contrast, the vast majority of GISTs that arise in children or adolescents do not have *KIT* or *PDGFRA* mutations. GISTs arising in young adults (age <30 years) comprise a heterogeneous group of tumours with some cases having "adult" characteristics (*KIT* or *PDGFRA* mutations, "adult" gene expression profiles) and others having "paediatric" characteristics (female predominance, lack of *KIT/PDGFRA* mutations, "paediatric" gene expression profile) [61].

In addition, GISTs can arise in association with familial syndromes such as neurofibromatosis or the Carney triad – these cases rarely have *KIT* or *PDGFRA* mutations [18, 61–65].

Evidence suggests that the type of tumour mutation may be a prognostic risk factor for GIST [66–68]. In a study that evaluated the prognostic relevance of *KIT* mutations in 48 GIST patients, those with exon 11 missense mutations were found to have a higher 5-year recurrence-free survival rate than patients with other mutation types (89% vs 40%, $P=0.03$) [67]. In addition, there are studies suggesting that mutations in *KIT* exon 9 (56, 57) or exon 13 [57] are associated with an unfavourable prognosis. Conversely, another study in GIST patients found no difference in prognosis between patients with exon 9 and exon 11 mutations [69]. In view of the conflicting data in this area, further research on the prognostic value of mutation type is warranted. However, as described below, compelling evidence suggests that mutation type is predictive for the quality and duration of response to imatinib. Based on the above considerations, Corless *et al.* [18] have proposed a molecular classification of GISTs (Table 1).

Table 1
Molecular classification of GISTs [18]

GIST Type	Comments
Sporadic GIST	
KIT mutation	
– Exon 11	Best response to imatinib
– Exon 9	More commonly associated with primary imatinib resistance than exon 11 mutant GISTs
– Exon 13	Sensitive to imatinib in vitro; clinical responses observed
– Exon 17	Sensitive to imatinib in vitro; clinical responses observed
PDGFRA mutation	
– Exon 12	Sensitive to imatinib in vitro; clinical responses observed
– Exon 18	D842V has poor response to imatinib; most other mutations are sensitive
Wild type	Less responsive to imatinib
Familial GIST	
KIT	
– Exon 11 (V559A, delV559, W557R)	Skin pigmentation, urticaria pigmentosa, mastocytosis
– Exon 13 (K642E)	No skin pigmentation or mastocytosis
– Exon 17 (D820Y)	No skin pigmentation or mastocytosis; abnormalities in oesophageal peristalsis
Pediatric GIST	
Sporadic	*KIT* mutations much less frequent than in adults
Carney's triad	Gastric GIST with pulmonary chondroma and/or paraganglioma; female : male = 7 : 1; no *KIT* mutations identified
NF-1 Related GIST	*KIT* mutations are very rare No reported *PDGFRA* mutations

7. Treatment considerations for GIST

7.1. Imatinib efficacy

The first clinical report suggesting efficacy of imatinib in treatment of GIST was that describing its use in a 50-year-old woman [70]. The patient had extensive metastatic GIST despite multiple surgeries and chemotherapy. Treatment with imatinib 400 mg once daily (QD) decreased tumour size by 50% after 1 month; after 8 months of treatment, 6 of 28 hepatic lesions were no longer detectable by magnetic resonance imaging (MRI), others were smaller,

Table 2
Imatinib trial results in advanced GIST

Trial	Phase	Dose	Objective response (PR+CR, %)	Tumour control (PR+CR+SD, %)
EORTC [71]	I	400–800 mg	63	90
EORTC [72]	II	400 mg BID	71	89
EORTC [73]	III	400 mg QD	50	82
EORTC [73]	III	400 mg BID	54	86
US–Finnish [74]	II	400 mg QD	66	83
US–Finnish [74]	II	600 mg QD	66	83
US–Canadian [75]	III	400 mg QD	48	75
US–Canadian [75]	III	400 mg BID	48	74

and no new lesions had appeared. The patient continued to improve, as demonstrated by MRI, histologic evaluations, and [^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET). Improvement was sustained and imatinib was well tolerated.

The impressive results in this patient, together with the success achieved with imatinib in the treatment of patients with chronic myeloid leukaemia, rapidly led to the initiation of a phase I dose-finding study by the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group [71, 76]. The study included 40 patients with advanced soft tissue sarcomas, 35 of whom had GIST. Patients received imatinib at doses of 400 mg QD or 300 mg, 400 mg, or 500 mg twice daily (BID). After 8 weeks, 19 (54%) patients with GIST had a confirmed partial response and 13 (37%) had stable disease [71,76]. At the 10-month follow-up, 18 GIST patients (51%) continued with partial responses, and 11 (31%) with stable disease [76]. This study helped establish the efficacy of imatinib as a treatment for GIST, and indicated that 400 mg BID was the maximum tolerated dose in patients with advanced GIST.

The US–Finland phase II trial evaluated the effects of imatinib doses of 400 mg or 600 mg QD in 147 patients with unresectable or metastatic KIT-expressing GIST [74]. At a median follow-up of 288 days (~9 months), 54% of patients had partial response and 28% had stable disease. Early resistance to imatinib was observed in 14% of patients. There were no statistically significant differences in response rates between the 400 mg and 600 mg doses of imatinib. At the 21-month follow-up, <1% of patients achieved complete response, 67% had partial response, 16% had stable disease, and 12% experienced progressive disease. No significant differences in survival rates were found between patients with stable disease (92%) and those with partial response (95%). At the time of the report (October/November 2004), median survival exceeded 3 years [77,78]. Recent follow-up data from this trial indicate that overall median survival is 4.8 years and median survival has yet to be reached in the subpopulation of patients with *KIT* exon 11 mutations [79]. This trial demonstrated that stable disease is a relevant clinical endpoint in GIST treatment, at least in the context of imatinib therapy.

A phase II study conducted by the EORTC Soft Tissue and Bone Sarcoma Group enrolled 27 patients with advanced and/or metastatic GIST [72]. Patients received imatinib 400 mg BID, the maximum tolerated dose identified in their phase I study. In all, 4% of patients achieved complete response, 67% had partial response, 18% had stable disease, and 11% of patients experienced disease progression (Table 2). Responses and stable disease were maintained, with 73% of the patients free from progression at 1 year.

7.2. Correlation of imatinib efficacy with molecular characterisation of GIST

KIT or *PDGFRA* mutations in GIST differ in type and affect different receptor domains. Several studies have examined the relationship between various activating *KIT* or *PDGFRA* mutations and the clinical response to imatinib in patients with advanced GIST. The findings of these studies indicate that tumour mutational status influences the clinical response of GISTs to imatinib.

In the US–Finland phase II study, the correlation between mutation type and clinical response to imatinib was studied in 127 metastatic GIST patients treated with 400 mg or 600 mg QD. In this study, the mutational frequency of *KIT* or *PDGFRA* mutations was 88.2% (n = 112) and 4.7% (n = 6), respectively [16,77]. Partial response rates were significantly higher in patients with GISTs harbouring *KIT* exon 11 mutations (83.5%) than in patients with tumours harbouring *KIT* exon 9 mutations (47.8%, $P = 0.0006$) or no *KIT* or *PDGFRA* mutations (0.0%, $P < 0.0001$). No significant differences in response rates were noted between patients with *KIT* exon 11 point mutations and those with *KIT* exon 11 deletion mutations. Imatinib-treated GIST patients with *KIT* exon 11 mutations also had longer event-free survival and overall survival than those with either *KIT* exon 9 mutations or no mutations in *KIT* or *PDGFRA* ($P \leqslant 0.004$) (Fig. 2).

The investigators also performed in vitro biochemical profiling of different types of GIST-associated mutations. All of the profiled *KIT* mutations (in exons 9, 11, 13, and 17) were sensitive to imatinib. In addition, *PDGFRA* exon 12 and certain exon 18 mutations were also shown to be imatinib sensitive. However, the most common GIST-associated *PDGFRA* exon 18 mutation, D842V, was found to be resistant to clinically achievable levels of imatinib. The clinical results seen in treating patients with *PDGFRA*-mutant tumours in this trial were congruent with the in vitro predictions of drug sensitivity. Notably, none of 3 patients with *PDGFRA* mutations encoding the PDGFRα D842V substitution had an objective response to imatinib, whereas 2 of the 3 patients with *PDGFRA* mutations encoding imatinib-sensitive PDGFRα had a partial response during imatinib therapy.

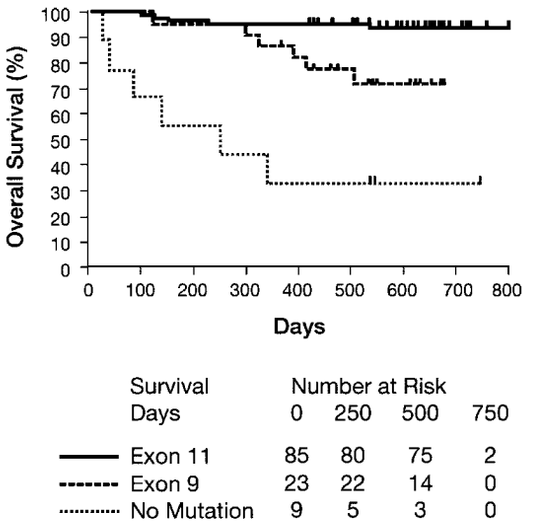

Fig. 2. Genotype correlates with overall survival in patients with GIST. $P = 0.0034$ for *KIT* exon 11 vs exon 9 [16]; $P < 0.0001$ for *KIT* exon 11 vs GIST tumours with no *KIT* or *PDGFRA* mutation.

A second study [80] examined GISTs from 37 patients enrolled in the EORTC phase I and phase II trials to explore the predictive value of *KIT* and *PDGFRA* mutations [71,72, 76]. Patients with GISTs expressing *KIT* exon 11 mutations were more likely to achieve partial responses to imatinib therapy (83%) than were patients with GISTs harbouring mutations in *KIT* exon 9 (25%), *KIT* exon 13 (0%), *PDGFRA* exon 18 (0%), or no mutations (33%). Patients with *KIT* mutations had longer median survival times and were less likely to experience disease progression during imatinib therapy than patients with *PDGFRA* mutations or no mutations in either *PDGFRA* or *KIT*.

The relationship between *KIT* or *PDGFRA* mutations and clinical response to imatinib was further examined in a randomised phase III study that compared imatinib doses of 400 mg and 800 mg QD in 746 patients with KIT-positive GISTs [75]. Pretreatment tumour samples from 324 patients were screened for mutations in *KIT* or *PDGFRA* [81]. *KIT* mutations were found in 86.4% of patients, and *PDGFRA* mutations were found in 1% of patients. Patients with *KIT* exon 11 mutations demonstrated objective responses more frequently (67%) than patients with *KIT* exon 9 mutations (40%) or no kinase mutations (39%, $P = 0.0022$). No significant differences in response rates were observed between GISTs with different types of exon 11 mutations (point mutation vs deletion/insertion) among the patients with *KIT* exon 11 mutations. Multivariate analysis showed that a *KIT* exon 11 mutation was the best predictor of objective response. *KIT* exon 11 mutations also conferred longer median time to treatment failure (576 days) than *KIT* exon 9 mutations (308 days) or no detectable kinase mutations (251 days) ($P = 0.0012$). There was a very strong trend for a higher objective response rate for *KIT* exon 9 mutant GISTs (odds ratio = 8.0) treated with high-dose versus standard-dose imatinib. However, this difference in the interim analysis did not reach the level of statistical significance. In contrast, there was no evidence that the imatinib dose influenced the likelihood of an objective response for GISTs with *KIT* exon 11 mutations or GISTs without *KIT* or *PDGFRA* mutations.

8. CD117 staining

Although positive staining for KIT (CD117) is considered to be the best immunophenotypic marker for GIST, the level of KIT expression does not correlate with imatinib response [82]. A single-patient case report suggested that even GISTs with very low levels of KIT expression may respond to treatment with imatinib [82]. The patient had a metastatic gastric tumour that contained a *KIT* exon 11 mutation and stained positively for CD34. However, the biopsies of the primary tumour and the liver metastasis stained only weakly or not at all for CD117. Despite the near-negative staining for CD117 of the tumours, the patient responded well to imatinib therapy, suggesting that a low level of KIT expression in GIST does not preclude clinical response of the tumour to imatinib.

Samples from the US–Canadian phase III trial were centrally reviewed for confirmation of diagnosis and KIT expression, the latter being a criterion for eligibility for enrollment in the study [81,83]. A diagnosis of a KIT-expressing GIST was confirmed in 94% of cases (377/401), with a diagnosis of KIT-negative GIST or leiomyosarcoma in 3.5% and 2.5% of cases, respectively. Molecular analysis of a subset of these cases revealed *KIT* or *PDGFRA* mutations in 87.5% of KIT-positive GIST (86% *KIT* mutations, 1.5% *PDGFRA* mutations), 87.5% of KIT-negative GIST (37.5% *KIT*, 50% *PDGFRA*), and 0% of leiomyosarcoma cases. Outcome assessment showed that response rates and progression-free survival in patients with KIT-negative GIST did not differ significantly from that in patients with KIT-positive GIST (43% vs 49%, estimated 2-year progression-free survival). However, the estimated 2-year overall survival rate was significantly greater in patients with KIT-positive GIST than in those with KIT-negative GIST (77% vs 57%, $P < 0.01$). These results indicate that imatinib therapy can provide a clinical benefit for patients with KIT-negative GIST, and that the high incidence of kinase mutations in KIT-negative GIST supports trials of imatinib in all GIST patients, irrespective of CD117 expression. These results also highlight the utility of clinical mutation testing in the diagnosis of KIT-negative GIST, as kinase mutations are found in the vast majority of KIT-negative GISTs, but are not found in histologic mimics of GIST [47,52,84,85].

9. Resistance to imatinib

9.1. Scope of the problem

Although imatinib is effective in most patients with advanced GIST, early or late resistance of tumours to imatinib is an increasing clinical problem. Early resistance has been reported in only 10–26% of patients (Table 2). However,

the vast majority of responding patients will eventually develop secondary tumour progression. In phase II/III clinical studies, the median time to tumour progression was 20 to 24 months [71,73–76]. At the current time, it remains unclear whether a small fraction (<15%) of patients with metastatic GIST actually are cured with imatinib treatment.

Because of the potential for tumour recurrence, surveillance during imatinib treatment is crucial. It should be noted that development of imatinib resistance and subsequent disease progression can follow several patterns, including the standard patterns of tumour enlargement and metastasis, as well as the recently described "nodule within a mass". First described in 2004 [86], the nodule-within-a-mass pattern was observed in 21 of 39 patients who developed recurrent GIST after an initial response to imatinib therapy [87]. In 17 patients, the appearance of the nodules on a computerised tomography (CT) scan was the first sign of disease progression. This novel pattern was believed to reflect the emergence of imatinib-resistant clones, an interpretation supported by the presence of new activating kinase mutations in the tumour genotype [86]. This pattern is considered important for the diagnosis of progressive disease because conventional tumour assessments – which depend on size or volume as measures of progression (e.g., Response Evaluation Criteria in Solid Tumors [RECIST]) – would not consider nodular recurrence as a criterion for disease progression. Other changes in the internal structure of tumour tissue indicative of both response and reprogression without change in tumour size have also been noted [88]. Thus, radiological imaging surveillance requires an awareness on the part of the interpreter of these unique imaging characteristics of GISTs treated with imatinib [89].

9.2. Molecular mechanisms in resistance

Imatinib resistance can appear early (appearing after <180 days of therapy without initial objective response) or late (appearing after >180 days of therapy and initial objective response). Early resistance is most commonly associated with patients whose GIST harbours *KIT* exon 9 mutations, *PDGFRA* D842V mutations, or no *KIT/PDGFRA* mutations [16,80]. In the case of GISTs with *KIT* exon 9 mutations or no kinase mutations, it is hypothesised that imatinib resistance is due to intrinsic molecular abnormalities that are present in the tumours before initiation of therapy. Specifically, these tumours are thought to have a lesser dependence on KIT signalling for cellular proliferation and avoidance of apoptosis and can more easily adapt to conditions of KIT inhibition. In the case of GISTs with mutations involving codon D842 (most commonly D842V), it is hypothesised that although these GISTs depend upon PDGFRα activation, mutations involving codon 842 result in an imatinib-resistant form of the PDGFRα kinase [16,29, 51,80]. In support of this hypothesis, the development of a secondary D842V mutation has been reported in association with a case of acquired imatinib-resistance [91].

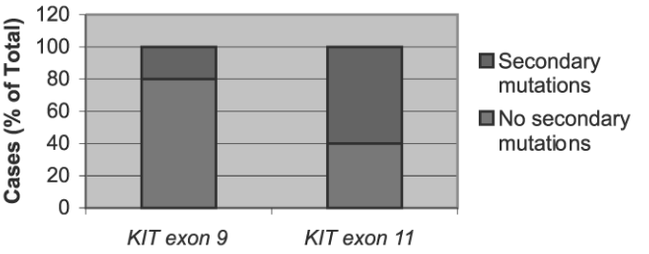

Fig. 3. Frequency of acquired *KIT* mutations in secondary (late) imatinib-resistant GISTs is lower in GISTs with primary *KIT* exon 9 mutations than in GISTs with primary *KIT* exon 11 mutations. Mutational data are compiled from Antonescu *et al.* (2005) [90] and Debiec-Rychter *et al.* (2005) [91].

Late imatinib resistance is most commonly associated with acquisition of secondary *KIT* kinase mutations in a GIST with a primary (pre-imatinib) *KIT* exon 11 mutation. Secondary mutations can also be found in association with *KIT* exon 9 mutant GISTs, but the frequency of secondary mutations is markedly lower than that seen with *KIT* exon 11 mutant GISTs (Fig. 3). These secondary mutations are clustered in two discrete regions of the KIT kinase domain: [1] the ATP/imatinib binding pocket of the protein (exons 13 and 14); and [2] the KIT activation loop (exon 17) (Table 3). These secondary mutations are believed to abrogate imatinib binding, either by directly altering the drug-binding pocket or stabilising the kinase in the active conformation (imatinib can only bind to the inactive conformation of the kinase) [40]. The development of secondary kinase mutations is associated with reactivation of KIT kinase activity in GIST cells, despite continued treatment with imatinib.

Amplification of the KIT locus has been reported as an infrequent event in GISTs with secondary imatinib resistance and no secondary kinase mutations. Theoretically, such amplification when accompanied by KIT overexpression might result in progression with standard dose imatinib [90,91].

KIT-independent molecular mechanisms of imatinib resistance in GIST include activating mutations or direct activation of receptor tyrosine kinases that utilise shared signalling pathways with KIT (eg, PI3K/AKT), increased imatinib metabolism, or the development of multi-drug re-

Table 3
Secondary *KIT* mutations conferring imatinib resistance in GIST

Domain	Codon	Reported mutations	Reference(s)
ATP/imatinib binding	654	V654A	[90–92]
	670	T670I, T670E	[93]
Activation loop	816	D816E, D816G	[91,94]
	820	D820Y, D820E	[90,91]
	822	N822K	[90,91,94]
	823	Y823D	[95]

sistance. In some cases, these KIT-independent mechanisms can be associated with deletion of the *KIT* locus and/or loss of *KIT* expression. Development of imatinib resistance through the mutation of a different kinase gene was first reported in a mutational analysis of 26 imatinib-resistant GISTs, where 1 newly acquired *PDGFRA* mutation was detected.

The discovery that many cases of imatinib resistance are due to reconstitution of KIT-dependent signalling pathways has led to the hypothesis that switching to structurally unrelated KIT/PDGFRα kinase inhibitors might be an effective form of salvage therapy. As discussed by Dr Reichardt in his paper entitled *Optimising therapy for GIST patients*, a number of new KIT/PDGFRα kinase inhibitors have been tested for activity against imatinib-resistant GIST. Notably, a phase III trial of sunitinib (formerly SU11248) versus placebo demonstrated significant improvements in progression-free and overall survival among the patients treated with sunitinib.

10. Conclusion

Molecularly targeted therapy has considerably improved the outlook for patients with advanced GIST. Complete responses are rare, but most patients achieve either partial response or stable disease with imatinib therapy. Median time to imatinib treatment failure is approximately 18 to 24 months, and median survival for patients with partial response, complete response, or stable disease is more than 3 years [16,77,78]. The mutational status of a given GIST is predictive of response, with patients whose GISTs harbour *KIT* exon 11 mutations being more likely to achieve a partial response to imatinib, compared with patients whose GISTs harbour *KIT* exon 9 mutations, *PDGFRA* exon mutations, or no detectable kinase gene mutation [71]. Emerging data suggest that many cases of focal progression during imatinib therapy are the end product of clonal evolution. Most acquired resistance is attributable to KIT-dependent mechanisms. Because new, resistant clones may exist concurrently with responding tumour tissue, continued imatinib therapy despite secondary progression is recommended. Continuing research efforts are directed at optimising the use of imatinib in patients with advanced GIST as well as the development of novel treatment approaches to prevent and/or treat imatinib-resistant clones of GIST.

Financial disclosure statement

Honoraria and research grants from Novartis.

References

1. Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. *Am J Pathol* 1998, **152**(5), 1259–69.
2. Chen LL, Sabripour M, Andtbacka RH, *et al.* Imatinib resistance in gastrointestinal stromal tumors. *Curr Oncol Rep* 2005, **7**(4), 293–9.
3. Miettinen M, Virolainen M, Maarit Sarlomo R. Gastrointestinal stromal tumors – value of CD34 antigen in their identification and separation from true leiomyomas and schwannomas. *Am J Surg Pathol* 1995, **19**(2), 207–16.
4. Bucher P, Villiger P, Egger JF, Buhler LH, Morel P. Management of gastrointestinal stromal tumors: from diagnosis to treatment. Swiss Med Wkly 2004, **134**(11-12), 145–53.
5. Eisenberg BL. Imatinib mesylate: a molecularly targeted therapy for gastrointestinal stromal tumors. *Oncology (Williston Park)* 2003, **17**(11), 1615–20; discussion 1620, 1623, 1626 passim.
6. Miettinen M, Lasota J. Gastrointestinal stromal tumors – definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. *Virchows Arch* 2001, **438**(1), 1–12.
7. Miettinen M, Monihan JM, Sarlomo-Rikala M, *et al.* Gastrointestinal stromal tumors/smooth muscle tumors (GISTs) primary in the omentum and mesentery: clinicopathologic and immunohistochemical study of 26 cases. *Am J Surg Pathol* 1999, **23**(9), 1109–18.
8. Nakama A, Hirota S, Okazaki T, *et al.* Disturbed pyloric motility in Ws/Ws mutant rats due to deficiency of c-kit-expressing interstitial cells of Cajal. *Pathol Int* 1998, **48**(11), 843–9.
9. Huizinga JD, Thuneberg L, Kluppel M, Malysz J, Mikkelsen HB, Bernstein A. W/kit gene required for interstitial cells of Cajal and for intestinal pacemaker activity. *Nature* 1995, **373**(6512), 347–9.
10. Isozaki K, Hirota S, Nakama A, *et al.* Disturbed intestinal movement, bile reflux to the stomach, and deficiency of c-kit-expressing cells in Ws/Ws mutant rats. *Gastroenterology* 1995, **109**(2), 456–64.
11. Kluppel M, Huizinga JD, Malysz J, Bernstein A. Developmental origin and Kit-dependent development of the interstitial cells of cajal in the mammalian small intestine. *Dev Dyn* 1998, **211**(1), 60–71.
12. Torihashi S, Horisawa M, Watanabe Y. c-Kit immunoreactive interstitial cells in the human gastrointestinal tract. *J Auton Nerv Syst* 1999, **75**(1), 38–50.
13. Heinrich MC, Rubin BP, Longley BJ, Fletcher JA. Biology and genetic aspects of gastrointestinal stromal tumors: KIT activation and cytogenetic alterations. *Hum Pathol* 2002, **33**(5), 484–95.
14. Hirota S, Isozaki K, Moriyama Y, *et al.* Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science* 1998, **279**(5350), 577–80.
15. Rubin BP, Singer S, Tsao C, *et al.* KIT activation is a ubiquitous feature of gastrointestinal stromal tumors. *Cancer Res* 2001, **61**(22), 8118–21.
16. Heinrich MC, Corless CL, Demetri GD, *et al.* Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *J Clin Oncol* 2003, **21**(23), 4342–9.
17. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. *Am J Surg Pathol* 2005, **29**(1), 52–68.
18. Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. *J Clin Oncol* 2004, **22**(18), 3813–25.
19. Corless CL, McGreevey L, Haley A, Town A, Heinrich MC. KIT mutations are common in incidental gastrointestinal stromal tumors one centimeter or less in size. *Am J Pathol* 2002, **160**(5), 1567–72.
20. Nishida T, Hirota S, Taniguchi M, *et al.* Familial gastrointestinal stromal tumours with germline mutation of the KIT gene. *Nat Genet* 1998, **19**(4), 323–4.
21. Beghini A, Tibiletti MG, Roversi G, *et al.* Germline mutation in the juxtamembrane domain of the kit gene in a family with gastrointestinal stromal tumors and urticaria pigmentosa. *Cancer* 2001, **92**(3), 657–62.
22. Maeyama H, Hidaka E, Ota H, *et al.* Familial gastrointestinal stromal

tumor with hyperpigmentation: association with a germline mutation of the c-kit gene. *Gastroenterology* 2001, **120**(1), 210–5.
23. Hirota S, Isozaki K, Nishida T, Kitamura Y. Effects of loss-of-function and gain-of-function mutations of c-kit on the gastrointestinal tract. J Gastroenterol 2000, **35**(Suppl 12), 75–9.
24. Isozaki K, Terris B, Belghiti J, Schiffmann S, Hirota S, Vanderwinden JM. Germline-activating mutation in the kinase domain of KIT gene in familial gastrointestinal stromal tumors. *Am J Pathol* 2000, **157**(5), 1581–5.
25. Hirota S, Nishida T, Isozaki K, *et al.* Familial gastrointestinal stromal tumors associated with dysphagia and novel type germline mutation of KIT gene. *Gastroenterology* 2002, **122**(5), 1493–9.
26. Rubin BP, Antonescu CR, Scott-Browne JP, *et al.* A knock-in mouse model of gastrointestinal stromal tumor harboring *Kit* K641E. *Cancer Res* 2005, **65**(15), 6631–9.
27. Sommer G, Agosti V, Ehlers I, *et al.* Gastrointestinal stromal tumors in a mouse model by targeted mutation of the Kit receptor tyrosine kinase. *Proc Natl Acad Sci USA* 2003, **100**(11), 6706–11.
28. Heinrich MC, Corless CL, Duensing A, *et al.* PDGFRA activating mutations in gastrointestinal stromal tumors. *Science* 2003, **299**(5607), 708–10.
29. Hirota S, Ohashi A, Nishida T, *et al.* Gain-of-function mutations of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors. *Gastroenterology* 2003, **125**(3), 660–7.
30. Lux ML, Rubin BP, Biase TL, *et al.* KIT extracellular and kinase domain mutations in gastrointestinal stromal tumors. *Am J Pathol* 2000, **156**(3), 791–5.
31. Tarn C, Merkel E, Canutescu AA, *et al.* Analysis of KIT mutations in sporadic and familial gastrointestinal stromal tumors: therapeutic implications through protein modeling. *Clin Cancer Res* 2005, **11**(10), 3668–77.
32. 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), 465–75.
33. Heinrich MC, Corless CL. Gastric GI stromal tumors (GISTs): the role of surgery in the era of targeted therapy. *J Surg Oncol* 2005, **90**(3), 195–207; discussion 207.
34. Ng EH, Pollock RE, Munsell MF, Atkinson EN, Romsdahl MM. Prognostic factors influencing survival in gastrointestinal leiomyosarcomas. Implications for surgical management and staging. *Ann Surg* 1992, **215**(1), 68–77.
35. 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), 51–8.
36. DeMatteo RP, Heinrich MC, El-Rifai WM, Demetri G. Clinical management of gastrointestinal stromal tumors: before and after STI-571. *Hum Pathol* 2002, **33**(5), 466–77.
37. D'Amato G, Steinert DM, McAuliffe JC, Trent JC. Update on the biology and therapy of gastrointestinal stromal tumors. *Cancer Control* 2005, **12**(1), 44–56.
38. Buchdunger E, Cioffi CL, Law N, *et al.* Abl protein-tyrosine kinase inhibitor STI571 inhibits in vitro signal transduction mediated by c-kit and platelet-derived growth factor receptors. *J Pharmacol Exp Ther* 2000, **295**(1), 139–45.
39. Okuda K, Weisberg E, Gilliland DG, Griffin JD. ARG tyrosine kinase activity is inhibited by STI571. *Blood* 2001, **97**(8), 2440–8.
40. Mol CD, Dougan DR, Schneider TR, *et al.* Structural basis for the autoinhibition and STI-571 inhibition of c-Kit tyrosine kinase. *J Biol Chem* 2004, **279**(30), 31655–63.
41. Dewar AL, Cambareri AC, Zannettino AC, *et al.* Macrophage colony stimulating factor receptor, c-fms, is a novel target of imatinib. *Blood* 2005, **105**(8), 3127–32.
42. Dagher R, Cohen M, Williams G, *et al.* Approval summary: imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. *Clin Cancer Res* 2002, **8**(10), 3034–8.
43. Demetri G, Benjamin R, Blanke CD, *et al.* NCCN Task Force Report: optimal management of patients with gastrointestinal stromal tumor (GIST) – expansion and update of NCCN Clinical Practice Guidelines. *JNCCN* 2004, **2**(Suppl 1), S1–26.
44. Heinrich MC, Griffith DJ, Druker BJ, Wait CL, Ott KA, Zigler AJ. Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor. *Blood* 2000, **96**(3), 925–32.
45. Tuveson DA, Willis NA, Jacks T, *et al.* STI571 inactivation of the gastrointestinal stromal tumor c-KIT oncoprotein: biological and clinical implications. *Oncogene* 2001, **20**(36), 5054–8.
46. Joensuu H, Fletcher C, Dimitrijevic S, Silberman S, Roberts P, Demetri G. Management of malignant gastrointestinal stromal tumours. *Lancet Oncol* 2002, **3**(11), 655–64.
47. Medeiros F, Corless CL, Duensing A, *et al.* KIT-negative gastrointestinal stromal tumors: proof of concept and therapeutic implications. *Am J Surg Pathol* 2004, **28**(7), 889–94.
48. Fletcher CD, Berman JJ, Corless C, *et al.* Diagnosis of gastrointestinal stromal tumors: a consensus approach. *Hum Pathol* 2002, **33**(5), 459–65.
49. Miettinen M, Furlong M, Sarlomo-Rikala M, Burke A, Sobin LH, Lasota J. Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the rectum and anus: a clinicopathologic, immunohistochemical, and molecular genetic study of 144 cases. *Am J Surg Pathol* 2001, **25**(9), 1121–33.
50. Hubbard SR. Juxtamembrane autoinhibition in receptor tyrosine kinases. *Nat Rev Mol Cell Biol* 2004, **5**(6), 464–71.
51. 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), 5357–64.
52. Debiec-Rychter M, Wasag B, Stul M, *et al.* Gastrointestinal stromal tumours (GISTs) negative for KIT (CD117 antigen) immunoreactivity. *J Pathol* 2004, **202**(4), 430–8.
53. Sakurai S, Hasegawa T, Sakuma Y, *et al.* Myxoid epithelioid gastrointestinal stromal tumor (GIST) with mast cell infiltrations: a subtype of GIST with mutations of platelet-derived growth factor receptor alpha gene. *Hum Pathol* 2004, **35**(10), 1223–30.
54. Wardelmann E, Hrychyk A, Merkelbach-Bruse S, *et al.* Association of platelet-derived growth factor receptor alpha mutations with gastric primary site and epithelioid or mixed cell morphology in gastrointestinal stromal tumors. *J Mol Diag* 2004, **6**(3), 197–204.
55. Miettinen M, Sobin LH, Sarlomo-Rikala M. Immunohistochemical spectrum of GISTs at different sites and their differential diagnosis with a reference to CD117 (KIT). *Mod Pathol* 2000, **13**(10), 1134–42.
56. Antonescu CR, Sommer G, Sarran L, *et al.* Association of KIT exon 9 mutations with nongastric primary site and aggressive behavior: KIT mutation analysis and clinical correlates of 120 gastrointestinal stromal tumors. *Clin Cancer Res* 2003, **9**(9), 3329–37.
57. Lasota J, Wozniak A, Sarlomo-Rikala M, *et al.* Mutations in exons 9 and 13 of KIT gene are rare events in gastrointestinal stromal tumors. A study of 200 cases. *Am J Pathol* 2000, **157**(4), 1091–5.
58. Sakurai S, Oguni S, Hironaka M, Fukayama M, Morinaga S, Saito K. Mutations in c-kit gene exons 9 and 13 in gastrointestinal stromal tumors among Japanese. *Jpn J Cancer Res* 2001, **92**(5), 494–8.
59. Lasota J, Dansonka-Mieszkowska A, Sobin LH, Miettinen M. A great majority of GISTs with PDGFRA mutations represent gastric tumors of low or no malignant potential. *Lab Invest* 2004, **84**(7), 874–83.
60. Wasag B, Debiec-Rychter M, Pauwels P, *et al.* Differential expression of KIT/PDGFRA mutant isoforms in epithelioid and mixed variants of gastrointestinal stromal tumors depends predominantly on the tumor site. *Mod Pathol* 2004, **17**(8), 889–94.
61. Prakash S, Sarran L, Socci N, *et al.* Gastrointestinal stromal tumors in children and young adults: a clinicopathologic, molecular, and genomic study of 15 cases and review of the literature. *J Pediatr Hematol Oncol* 2005, **27**(4), 179–87.
62. Yantiss RK, Rosenberg AE, Sarran L, Besmer P, Antonescu CR. Multiple gastrointestinal stromal tumors in type I neurofibromatosis: a pathologic and molecular study. *Mod Pathol* 2005, **18**(4), 475–84.

63. Diment J, Tamborini E, Casali P, Gronchi A, Carney JA, Colecchia M. Carney triad: case report and molecular analysis of gastric tumor. *Hum Pathol* 2005, **36**(1), 112–6.
64. Takazawa Y, Sakurai S, Sakuma Y, *et al.* Gastrointestinal stromal tumors of neurofibromatosis type I (von Recklinghausen's disease). *Am J Surg Pathol* 2005, **29**(6), 755–63.
65. Kinoshita K, Hirota S, Isozaki K, *et al.* Absence of c-kit gene mutations in gastrointestinal stromal tumours from neurofibromatosis type 1 patients. *J Pathol* 2004, **202**(1), 80–5.
66. Taniguchi M, Nishida T, Hirota S, *et al.* Effect of c-kit mutation on prognosis of gastrointestinal stromal tumors. *Cancer Res* 1999, **59**(17), 4297–300.
67. 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), 3898–905.
68. Kim TW, Lee H, Kang YK, *et al.* Prognostic significance of c-kit mutation in localized gastrointestinal stromal tumors. *Clin Cancer Res* 2004, **10**(9), 3076–81.
69. Hirota S, Nishida T, Isozaki K, *et al.* Gain-of-function mutation at the extracellular domain of KIT in gastrointestinal stromal tumours. *J Pathol* 2001, **193**(4), 505–10.
70. Joensuu H, Roberts PJ, Sarlomo-Rikala M, *et al.* Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med* 2001, **344**(14), 1052–56.
71. 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), 1421–3.
72. Verweij J, van Oosterom A, Blay JY, *et al.* Imatinib mesylate (STI-571 Glivec®, Gleevec) is an active agent for gastrointestinal stromal tumours, but does not yield responses in other soft-tissue sarcomas that are unselected for a molecular target. Results from an EORTC Soft Tissue and Bone Sarcoma Group phase II study. *Eur J Cancer* 2003, **39**(14), 2006–11.
73. Verweij J, Casali PG, Zalcberg J, *et al.* Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet* 2004, **364**(9440), 1127–34.
74. 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), 472–80.
75. Rankin C, Von Mehren M, Blanke C, *et al.* Dose effect of imatinib (IM) in patients (pts) with metastatic GIST – Phase III Sarcoma Group Study S0033. *Proc Am Soc Clin Oncol* 2004, **23**, 815. [Abstract.]
76. van Oosterom AT, Judson IR, Verweij J, *et al.* Update of phase I study of imatinib (STI571) in advanced soft tissue sarcomas and gastrointestinal stromal tumors: a report of the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer* 2002, **38**(Suppl 5), S83-87.
77. Blanke C, Joensuu H, Demetri G, *et al.* Long-term follow up of advanced gastrointestinal stromal tumor (GIST) patients treated with imatinib mesylate. In: *ASCO 2004 Gastrointestinal Cancers Symposium*, January 22–24, 2004, San Francisco, CA, USA, Abstract 2.
78. Demetri G, von Mehren M, Joensuu H, *et al.* Lack of progression is the most clinically significant measure of a patients clinical benefit: Correlating the effects of imatinib mesylate therapy in gastrointestinal stromal tumor (GIST) with survival benefits. In: *ESMO 2004*, October 29 – November 2, 2004, Vienna, Austria, p. iii202, Abstract 764P.
79. Blanke C, Joensuu H, Demetri G, *et al.* Outcome of advanced gastrointestinal stromal tumor (GIST) patients treated with imatinib mesylate: four-year follow-up of a phase II randomized trial. In: *Proc Am Soc Clin Oncol GI 2006*; 2006.
80. Debiec-Rychter M, Dumez H, Judson I, *et al.* Use of c-KIT/PDGFRA mutational analysis to predict the clinical response to imatinib in patients with advanced gastrointestinal stromal tumours entered on phase I and II studies of the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer* 2004, **40**(5), 689–95.
81. Heinrich M, Shoemaker J, Corless C, *et al.* Correlation of target kinase genotype with clinical activity of imatinib mesylate in patients with metastatic GI stromal tumors expressing KIT. In: *Proc Am Soc Clin Oncol* 2005; 2005, p. 3s.
82. Bauer S, Corless CL, Heinrich MC, *et al.* Response to imatinib mesylate of a gastrointestinal stromal tumor with very low expression of KIT. *Cancer Chemother Pharmacol* 2003, **51**(3), 261–5.
83. Blackstein M, Rankin C, Fletcher C, *et al.* Clinical benefit of imatinib in patients with metastatic gastrointestinal stromal tumors negative for the expression of CD117 in the S0033 trial. In: *ASCO 2005*; 2005, p. 818s.
84. Sihto H, Sarlomo-Rikala M, Tynninen O, *et al.* KIT and platelet-derived growth factor receptor alpha tyrosine kinase gene mutations and KIT amplifications in human solid tumors. *J Clin Oncol* 2005, **23**(1), 49–57.
85. Burger H, den Bakker MA, Kros JM, *et al.* Activating mutations in c-KIT and PDGFRα are exclusively found in gastrointestinal stromal tumors and not in other tumors overexpressing these imatinib mesylate target genes. *Cancer Biol Ther* 2005, **4**(11), 1270–4.
86. Desai J, Shankar S, Heinrich MC, *et al.* Clonal evolution of resistance to imatinib in patients with gastrointestinal stromal tumor (GIST): Molecular and radiologic evaluation of new lesions. In: *ASCO 2004*; 2004, p. 197.
87. Shankar S, Vansonnenberg E, Desai J, Dipiro PJ, Van Den Abbeele A, Demetri GD. Gastrointestinal stromal tumor: new nodule-within-a-mass pattern of recurrence after partial response to imatinib mesylate. *Radiology* 2005, **235**(3), 892–8.
88. Vanel D, Albiter M, Shapeero L, *et al.* Role of computed tomography in the follow-up of hepatic and peritoneal metastases of GIST under imatinib mesylate treatment: a prospective study of 54 patients. *Eur J Radiol* 2005, **54**(1), 118–23.
89. Choi H, Charnsangavej C, Faria Sde C, *et al.* CT evaluation of the response of gastrointestinal stromal tumors after imatinib mesylate treatment: a quantitative analysis correlated with FDG PET findings. *Am J Roentgenol* 2004, **183**(6), 1619–28.
90. Antonescu CR, Besmer P, Guo T, *et al.* Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. *Clin Cancer Res* 2005, **11**(11), 4182–90.
91. Debiec-Rychter M, Cools J, Dumez H, *et al.* Mechanisms of resistance to imatinib mesylate in gastrointestinal stromal tumors and activity of the PKC412 inhibitor against imatinib-resistant mutants. *Gastroenterology* 2005, **128**(2), 270–9.
92. Chen LL, Trent JC, Wu EF, *et al.* A missense mutation in KIT kinase domain 1 correlates with imatinib resistance in gastrointestinal stromal tumors. *Cancer Res* 2004, **64**(17), 5913–9.
93. Tamborini E, Bonadiman L, Greco A, *et al.* A new mutation in the KIT ATP pocket causes acquired resistance to imatinib in a gastrointestinal stromal tumor patient. *Gastroenterology* 2004, **127**(1), 294–9.
94. Wardelmann E, Thomas N, Merkelbach-Bruse S, *et al.* Acquired resistance to imatinib in gastrointestinal stromal tumours caused by multiple KIT mutations. *Lancet Oncol* 2005, **6**(4), 249–51.
95. Wakai T, Kanda T, Hirota S, Ohashi A, Shirai Y, Hatakeyama K. Late resistance to imatinib therapy in a metastatic gastrointestinal stromal tumour is associated with a second KIT mutation. *Br J Cancer* 2004, **90**(11), 2059–61.