New paradigms in gastrointestinal stromal tumour management

J.-Y. Blay
Cytokine and Cancer Unit, Léon Bérard Cancer Centre, Lyon, France

Background: Targeted agents have improved the prognosis for patients with advanced gastrointestinal stromal tumours (GISTs). Many patients exhibit intolerance or resistance to first-line therapy with imatinib mesylate. Sunitinib malate is approved multinationally for the treatment of advanced imatinib-refractory GIST.

Design: This article reviews responses to imatinib and sunitinib reported in clinical trials in advanced GIST and discusses the effect of mutational status on treatment responses; therapeutic developments in GIST treatment are also reviewed.

Results: Imatinib 400 mg/day has shown efficacy for first-line treatment of advanced GIST, particularly in patients with KIT exon 11 mutations. Sunitinib 50 mg/day (Schedule 4/2) has demonstrated effectiveness and tolerability in imatinib-refractory GIST, including patients who would be excluded from clinical trials. Sunitinib is associated with longer median overall survival in patients with primary KIT exon 9 mutations and wild-type GIST compared with KIT exon 11 mutations in a retrospective study. Ongoing studies, including imatinib in the adjuvant setting and the use of targeted agents in sequence or in combination, will further refine the therapeutic pathway for advanced GIST.

Conclusions: The availability of targeted therapies and greater knowledge of the effect of mutational status on patient responses will assist in optimising outcomes in advanced GIST.

Key words: gastrointestinal stromal tumour, imatinib mesylate, mutational status, sunitinib malate, treatment resistance

Introduction

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours affecting the gastrointestinal tract [1, 2]. Approximately 85% of GISTs are driven by oncogenic mutations in the genes for either of two receptor tyrosine kinases: KIT (75–80%) or platelet-derived growth factor receptor alpha (PDGFR-α; 5–10%) [3]. For the remaining subgroup of patients (with wild-type GISTs), trial data have suggested that mutations in the neurofibromatosis type 1 (NF1) gene, in NF1-associated GIST, B-Raf mutations and amplification of the insulin-like growth factor 1 receptor (IGF1R) may contribute to neoplastic transformation [3–5].

Imatinib mesylate (Glivec®, Novartis), a selective inhibitor of KIT and PDGFR, is recommended for first-line treatment of KIT-positive unresectable and/or metastatic GIST [6]. The introduction of imatinib has resulted in substantially improved prognoses for patients with advanced GIST [7]. However, 40–50% of patients experience disease progression within 2–3 years of commencing imatinib treatment, 4% of patients exhibit intolerance to imatinib and 12–14% show primary resistance to imatinib [7, 9–11].

Sunitinib malate (SUTENT®, Pfizer Inc.) is an oral, multitargeted receptor tyrosine kinase inhibitor (TKI) of KIT, PDGFR-α and -β, vascular endothelial growth factor receptors (VEGFR-1, -2 and -3), FMS-like tyrosine kinase-3 receptor (FLT3), colony-stimulating factor 1 receptor (CSF-1R) and glial cell line-derived neurotrophic factor receptor (REarranged during Transfection; RET) [12–16]. Sunitinib is approved multinationally for the treatment of advanced GIST after the failure of imatinib due to disease progression or intolerance [17].

This article discusses the many studies that have been conducted or are ongoing to optimise the treatment of GIST with imatinib and sunitinib.

Response to targeted therapy in patients with GIST

Imatinib

A number of clinical studies have demonstrated the effectiveness of imatinib in the treatment of unresectable or metastatic GIST (Table 1) [18–22]. These include studies examining the efficacy and tolerability of different doses of imatinib (400 mg/day, 600 mg/day or 800 mg/day) and different dosing regimens.

Preliminary results from the phase II B2222 study, in which 147 patients with GIST received treatment with imatinib at
either 400 mg/day or 600 mg/day, showed a partial response (PR) in 53.7% (95% CI 45.3–62.0) of patients overall [imatinib 400 mg/day 49.3% (95% CI 37.4–61.3); imatinib 600 mg/day 58.1% (95% CI 46.1–69.5)] [9]. Treatment with imatinib was generally well tolerated and most adverse events (AEs) were mild to moderate in intensity. Grade 3–4 AEs reported in this study included gastrointestinal or intra-abdominal haemorrhages, diarrhoea, nausea and neutropenia [9]. Long-term results from the trial showed an objective response rate (ORR) of 66.7% (95% CI 59.8–75.5) and a complete response (CR) in 1.4% of patients [imatinib 400 mg/day ORR 68.5% (95% CI 56.5–78.9); imatinib 600 mg/day ORR 67.6% (95% CI 55.6–78.0)] [18]. Median overall time to progression (TTP) was 24 months (imatinib 400 mg/day, 20 months; imatinib 600 mg/day, 26 months), while median overall survival (OS) was 57 months (95% CI 44–not available) and was consistent across the two arms [18]. Importantly, KIT exon 11 mutations were associated with a better prognostic outcome in response to imatinib than other KIT mutations or no mutations [18]; this will be discussed in more detail later in this article.

A further phase II study has also demonstrated imatinib activity at 400 mg/day in patients with advanced GIST [19]. In this study, CR and PR occurred in 4% and 67% of patients, respectively, and 73% of patients remained free from disease progression at 1 year [19]. Most AEs were mild to moderate in intensity, with the most frequently reported grade 3–4 AEs including rash (14%), anaemia (12%) and fatigue (12%) [19].

In two large phase III trials performed in parallel in patients with metastatic GIST [EORTC/intergroup 62005 (N = 946) and US/CDIN SO033 (N = 746)], comparison of imatinib 400 mg/day with 800 mg/day dosing indicated that the two dose levels resulted in similar response rates across all patients [20, 21]. However, treatment with imatinib 800 mg/day resulted in significantly longer median PFS in the EORTC 62005 trial [21], which reported disease progression at 2 years in 56% of patients receiving imatinib 400 mg/day compared with 50% of patients receiving imatinib 800 mg/day [estimated hazard ratio (HR) 0.82 (95% CI 0.69–0.98); P = 0.026]. The incidence and profile of all-grade AEs observed in the 400 mg/day and 800 mg/day treatment groups were similar, with anaemia (7% and 17%, respectively), granulocytopenia (7% each) and fatigue (6% and 11%, respectively) representing the most commonly occurring grade 3–4 AEs.

Analysis of imatinib efficacy following crossover of patients (n = 133) from the 400 mg/day treatment arm to the higher dose in this study indicated a median PFS of 81 days following crossover [26]. Anaemia and fatigue were significantly more severe after crossover (P = 0.015 and P = 0.00001, respectively), while neutropenia was less severe (P = 0.002). Of note, comparison of imatinib 400 mg/day with 800 mg/day dosing in advanced GIST according to mutational status showed greater benefit from treatment with the higher dose in patients with KIT exon 9 mutations [27]. These findings support the prognostic significance of tumour genotype for PFS and OS, which will be reviewed later in this article.

Unlike the EORTC 62005 trial, data from the SO033 study showed no significant differences with respect to median PFS and OS between patients receiving the two imatinib dose levels [20], possibly due to a smaller patient population. Patients in the imatinib 400 mg/day treatment arm achieved a median OS of 55 months (95% CI 47–62) compared with 51 months (95% CI 46–60) in the higher-dose arm. Two-year survival estimates were 76% (95% CI 72–81) and 72% (95% CI 67–77) for the 400 mg/day and 800 mg/day arms, respectively [HR 0.98

---

### Table 1. Summary of phase II and III efficacy data for imatinib and sunitinib in the treatment of gastrointestinal stromal tumours

<table>
<thead>
<tr>
<th>Study, phase [reference]</th>
<th>Patients, n</th>
<th>Dose, mg/day</th>
<th>PR (CR), %</th>
<th>SD, %</th>
<th>TTP/PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Imatinib (first-line treatment)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US B2222, phase II (core and extension) [18]</td>
<td>73</td>
<td>400</td>
<td>69 (0)</td>
<td>14</td>
<td>Median TTP: 20 months</td>
</tr>
<tr>
<td>EORTC, phase II [19]</td>
<td>74</td>
<td>600</td>
<td>65 (3)</td>
<td>18</td>
<td>Median TTP: 26 months</td>
</tr>
<tr>
<td>EORTC 62005, phase III [21]</td>
<td>27</td>
<td>800</td>
<td>67 (4)</td>
<td>19</td>
<td>1-year PFS: 73%</td>
</tr>
<tr>
<td>EORTC 62005, phase III [21]</td>
<td>473</td>
<td>400</td>
<td>45 (5)</td>
<td>32</td>
<td>2-year PFS: 44%</td>
</tr>
<tr>
<td>Intergroup SO033, phase III [20]</td>
<td>473</td>
<td>800</td>
<td>48 (6)</td>
<td>32</td>
<td>2-year PFS: 52%</td>
</tr>
<tr>
<td>BFR14, phase III [22]</td>
<td>345</td>
<td>400</td>
<td>40 (5)</td>
<td>25</td>
<td>2-year PFS: 41%</td>
</tr>
<tr>
<td>BFR14, phase III [22]</td>
<td>349</td>
<td>800</td>
<td>42 (3)</td>
<td>22</td>
<td>2-year PFS: 46%</td>
</tr>
<tr>
<td><strong>Sunitinib (imatinib-resistant or -intolerant GIST)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase III [23]</td>
<td>207</td>
<td>50.0 (Schedule 4/2)</td>
<td>7 (0)</td>
<td>58</td>
<td>Median PFS: 24 weeks</td>
</tr>
<tr>
<td>Treatment use [24]</td>
<td>117‡</td>
<td>50.0 (Schedule 4/2)</td>
<td>NR</td>
<td>NR</td>
<td>Median TTP: 41 weeks</td>
</tr>
<tr>
<td>Phase II [25]</td>
<td>60</td>
<td>37.5 (CDD)</td>
<td>12 (0)</td>
<td>42‡</td>
<td>Median TTP: 34 weeks</td>
</tr>
</tbody>
</table>

---

*Calculated in competing-risk analysis after 2 years [21].

‡Patients were randomised following 1 year of imatinib 400 mg/day to receive either maintenance of imatinib until progression/intolerance or treatment interruption until progression and then reintroduction [22].

PFS reported in October 2005 in patients randomised to treatment between May 2003 and March 2004 following 1 year of treatment; patients received between 19 and 29 months of randomised therapy [22].

Comprising intention-to-treat population at time of analysis (December 2007) in this ongoing study [24].

Stable disease reported at ≥24 weeks [25].

CR, complete response; SD, stable disease; TTP, time to tumour progression; PFS, progression-free survival; GIST, gastrointestinal stromal tumour; NR, not reported; CDD, continuous daily dosing.
Interestingly, a meta-analysis of these two trials, based on OS of 19 months (95% CI 13–23) [20].

Tumours (53 versus 31 months, respectively; P = 0.02) [20]. Interestingly, a meta-analysis of these two trials, based on a dataset of >1500 patients, confirmed the superiority of imatinib 800 mg/day in terms of PFS, but not in terms of OS [28]. Of note, the beneficial effect of the 800 mg/day dose level on PFS was confined to the subgroup of patients with GISTs showing KIT exon 9 mutations.

More recently, the phase III BFR14 study compared PFS in advanced GIST patients randomised to receive ongoing imatinib until progression/intolerance with treatment interruption until progression following 1 year of tumour control with imatinib [22]. The study showed that imatinib treatment interruption is associated with a high risk of disease recurrence. Median TTP was 6 months in patients receiving interrupted treatment and most patients relapsed within 1 year of treatment interruption, with 81% of patients in this arm experiencing disease progression, compared with 31% in the maintenance arm [22]. However, when treatment was re-started, disease control was re-established in 92% of patients with progression. The investigators concluded that imatinib discontinuation could not be recommended in routine practice, particularly in light of the high recurrence rates observed in patients without detectable residual disease [22].

Importantly, and consistently with the B2222 trial [18], a surprising discrepancy in survival data has been observed in these trials. Median OS in metastatic GIST patients was between 9 and 20 months before the imatinib era [29] and is now approaching 55–57 months [18, 20]. With a median PFS of 20–26 months in all imatinib-refractory studies reported here, we observe that the duration of survival is much longer after imatinib ‘failure’ than it was before the introduction of imatinib. The biological mechanisms underlying these observations are not known, although it can be speculated that this may be related to the antitumour activity of imatinib in the majority of tumour cells, even at the time of overt clinical resistance, since most secondary resistance begins as partial resistance (e.g. a nodule within a mass). Surgical removal of lesions, dose escalation of imatinib and second-line treatments are also likely to contribute to this as yet unexplained observation.

sunitinib

Before the introduction of sunitinib, there was no efficient systemic treatment for patients with metastatic GIST failing imatinib 800 mg/day.

In a phase III study of 312 patients with imatinib-resistant or -intolerant GIST, sunitinib 50 mg/day (administered in 6-week cycles of 4 weeks on treatment followed by 2 weeks off treatment; Schedule 4/2) demonstrated superior efficacy compared with placebo in an interim analysis [23]. Median TTP, the primary endpoint of the study, was 27.3 weeks for sunitinib-treated patients and 6.4 weeks for placebo-treated patients [HR 0.33 (95% CI 0.23–0.47); P < 0.0001]. Patients receiving sunitinib achieved median PFS of 24.1 weeks (95% CI 11.1–28.3) compared with 6.0 weeks (95% CI 4.4–9.9) for those receiving placebo [HR 0.33 (95% CI 0.24–0.47); P < 0.0001] (Table 1). In addition, sunitinib treatment resulted in improved OS compared with placebo [HR 0.49 (95% CI 0.19–0.83); P = 0.007], although median OS could not be calculated at the time of analysis (Figure 1). Treatment-related AEs were generally mild to moderate in intensity; grade 3–4 AEs observed in sunitinib-treated patients included fatigue (5%), hand–foot syndrome (4%), and diarrhoea and hypertension (3%) each [23].

Following the demonstration of significant clinical benefit in the interim analysis, the study was unblinded and patients were allowed to cross over from placebo to sunitinib treatment. Updated survival data have been published from this study using traditional statistical tests and a novel statistical method to account for crossover [30]. Using the Kaplan–Meier method, median OS was 73.9 weeks (95% CI 61.3–85.7) with sunitinib compared with 64.9 weeks (95% CI 45.7–96.0) with placebo (P = 0.161). Using the rank-preserving structural failure time (RPSFT) method to account for crossover, median OS was 73.9 weeks (95% CI 61.3–85.7) with sunitinib compared with 35.7 weeks (95% CI 25.7–49.8) with placebo (P < 0.001) [30]. Sunitinib-treated patients demonstrated a safety profile similar to that observed before study unblinding, with most treatment-related AEs of grade 1–2 intensity. In the open-label phase of this study, the most common grade 3–4 AEs included fatigue (10%), hypertension (8%) and hand–foot syndrome (5%) [30].

A worldwide treatment-use study is ongoing to confirm the results of this pivotal trial in a larger cohort of patients. This multicentre study was commenced to provide access to

---

![Graph](image_url)
sunitinib to patients with advanced GIST who are ineligible for clinical trials, or for whom no trials are available in countries in which regulatory approval has not yet been granted [24]. In an analysis of 1117 patients in the intention-to-treat population, efficacy and safety results were consistent with those observed in the phase III trial. Median TTP with sunitinib 50 mg/day (Schedule 4/2) was 41 weeks (95% CI 36–47) (Table 1), with median OS of 75 weeks (95% CI 68–84). Treatment-associated AEs were generally mild to moderate in intensity, with the most commonly reported grade 3–4 AEs comprising fatigue (8.3%), hand–foot syndrome (8.2%), neutropenia (8%), hypertension (5.2%) and diarrhoea and thrombocytopenia (each 5%) [24]. Subgroup analysis indicated that age, Eastern Cooperative Oncology Group performance status (ECOG PS) and prior imatinib dose may be important prognostic factors affecting clinical outcome (Figure 2) [24]. Further investigations are required to confirm the effects of these prognostic factors on OS in patients with advanced imatinib-refractory GIST [24].

One of the potential limitations of sunitinib 50 mg/day administration by Schedule 4/2 is the possibility of tumour flare-up during the 2-week off-treatment period. Therefore, continuous daily dosing (CDD) of sunitinib at a dose of 37.5 mg has been investigated as an alternative dosing regimen. In a phase II study in patients with advanced imatinib-intolerant or -resistant GIST [25], treatment with sunitinib 37.5 mg by CDD resulted in median PFS of 34 weeks (95% CI 25–59) (Table 1), with an estimated median OS of 107 weeks (95% CI 72–not yet calculable). Most treatment-related AEs were grade 1–2 in severity, similar to those observed with sunitinib administered by Schedule 4/2, and no grade 4 AEs were recorded. The CDD regimen was associated with relatively constant drug exposure with no signs of drug accumulation [25].

**effect of mutational status on response to targeted therapy**

A number of studies have demonstrated that mutational status can predict the probability of achieving a response to imatinib or sunitinib in patients with advanced GIST [27, 31–36].

Studies have consistently shown that patients with GISTs harbouring KIT exon 11 mutations achieve the best responses to imatinib therapy, with ORR ranging from 70% to 85%, and longer median OS and PFS relative to other GIST mutations [25, 35–37]. In contrast, the presence of KIT exon 9-activating mutations is an adverse prognostic factor for response to imatinib, increasing the relative risk of progression by 171% and the relative risk of death by 190% compared with exon 11 mutations (both \( P < 0.0001 \)) in an analysis of 377 GISTs from patients in a phase III trial [27]. In patients without detectable KIT or PDGFRA mutations (wild-type GIST), the relative risk of progression with imatinib therapy was increased by 108% (\( P < 0.0001 \)) and the relative risk of death by 76% (\( P = 0.028 \)) compared with KIT exon 11 mutations [27].
As mentioned above, in patients with KIT exon 9 mutations, treatment with higher-dose imatinib (800 mg/day) resulted in a significantly superior median PFS (P = 0.0013) relative to treatment with imatinib 400 mg/day, with a 61% reduction in the relative risk of progression [27]. Results to date indicate that patients with KIT exon 9 mutations may gain particular benefit from high-dose imatinib compared with patients with other mutations.

The relationship between primary and secondary mutational status and treatment response has been evaluated in imatinib-refractory GIST patients using biopsied samples from sunitinib-treated patients in a phase II trial [33]. Median OS was found to be significantly longer in patients with primary KIT exon 9 mutations (P = 0.012) and patients with wild-type KIT/PDGFRα (P = 0.0132) compared with patients with KIT exon 11 mutations. Secondary KIT mutations in exon 13, 14, 17 or 18 were found in 62% of patients with a primary KIT exon 11 mutation, but in only 16% of patients with a primary KIT exon 9 mutation (P = 0.003). Median PFS and OS and clinical benefit rates were greater in patients with secondary KIT exon 13 or 14 mutations, compared with those with secondary KIT exon 17 or 18 mutations (P = 0.0157, P = 0.160 and P = 0.011, respectively). These findings highlight the importance of mutational testing for patients with GIST before the initiation of TKI therapy, as stated in the updated ESMO clinical recommendations [38]. However, at the time of TKI resistance, the characterisation of possible additional kinase mutations remains investigational.

**future developments**

**adjuvant therapy**

The role of targeted therapy in the adjuvant setting for the treatment of GIST has been evaluated in several trials.

Data from one such trial, the phase II Intergroup ACOSOG Z9000 study, demonstrated that adjuvant imatinib treatment resulted in OS of 99% at 1 year and 97% in years 2 and 3 in patients with high-risk primary GISTs [39]. Recurrence-free survival (RFS) in these patients was 94%, 73% and 61% at years 1, 2, and 3, respectively, following treatment with adjuvant imatinib. In addition, patients with KIT exon 9 mutations appeared to have the highest recurrence rates [39].

Preliminary data from the phase III Intergroup ACOSOG Z9001 study showed that adjuvant imatinib increased 1-year RFS compared with placebo [97% versus 83%, HR 0.325 (95% CI 0.198–0.534), unadjusted log-rank P < 0.0000014] [40].

Further data from these ongoing trials are needed to fully characterise the role of receptor TKIs for the adjuvant treatment of GIST, including information on differential effects across patients with different mutational profiles. Thus, the role of adjuvant imatinib for the treatment of advanced GIST remains a subject of debate. Current ESMO recommendations suggest that adjuvant therapy should only be performed within clinical trials at present [38]. This guidance may evolve in the future depending on additional follow-up from the pivotal Z9001 trial [40]. In addition, the optimal duration of adjuvant imatinib therapy is still under investigation, with a treatment duration of 1 year in the Z9001 trial [40], 2 years in the ongoing 62024 EORTC intergroup trial [41] and 1 versus 3 years in the ongoing SSGXVIII/AIO trial [41].

**sequential therapy**

Studies are also ongoing to further define the optimal sequence and dosing regimen for targeted therapies in the treatment of GIST.

A phase IIIb study is currently investigating the comparative efficacy and safety of sunitinib 37.5 mg versus imatinib 800 mg/day in patients with GIST who experienced disease progression with imatinib 400 mg [42]. A lead-in substudy to the phase IIIb trial evaluated the pharmacokinetics and treatment-related AEs associated with initiating sunitinib 37.5 mg within 24 h of the final dose of imatinib 400 mg [42]. Sunitinib was well tolerated, with no treatment-related grade ≥ 3 AEs observed during the first 2 weeks of sunitinib therapy following transition from imatinib [42].

**combination therapy**

Another innovative approach currently under investigation in a number of studies involves combination therapy with established and novel targeted agents to improve outcomes in advanced GIST patients.

An open-label, phase I, dose-escalating study has evaluated the long-term efficacy and safety of nilotinib (AMN107, a novel agent that targets KIT, PDGFRs and BCR/ABL) alone or in combination with imatinib in patients who exhibited disease progression on imatinib 800 mg/day [43]. Combination therapy was associated with a median PFS of ~6 months, including patients whose disease had progressed during prior imatinib or sunitinib therapy. The most common AEs associated with combination treatment were rash and pruritis [43].

A phase I/Ii study assessed the efficacy of the oral protein kinase C (PKC) inhibitor, PKC412, in combination with imatinib in patients with imatinib-refractory GIST [44]. Data showed that PKC412 decreased exposure to imatinib due to pharmacokinetic interactions, such that higher imatinib doses were required. Following dose adjustment, preliminary data suggested efficacy with this regimen, with hyperthyroidism representing the most commonly reported treatment-associated toxicity [44]. More recently, a single case report described the use of PKC412 in combination with sirolimus in an advanced GIST patient with imatinib resistance due to a PDGFRα D842V mutation [45]. This is the most common PDGFRα mutation and is known to be resistant to both imatinib and sunitinib [37], although preclinical data have reported its sensitivity to PKC412 [46]. Combination therapy with PKC412 and sirolimus resulted in disease stabilisation in this challenging case [45].

In addition, a phase I dose-escalation study is currently investigating combination therapy with sunitinib and imatinib in GIST patients who exhibited disease progression with imatinib monotherapy [41], while the efficacy, safety and tolerability of imatinib in combination with everolimus is being assessed in a single-arm multicentre phase II study in patients with GIST whose disease recurred or progressed on imatinib 400 mg/day [41]. Imatinib in combination with bevacizumab is
also under investigation, compared with imatinib alone, in a randomised phase III trial in patients with metastatic or unresectable GIST [41]. Data from these ongoing studies are awaited with interest.

**novel agents**

A number of agents are being investigated for their effectiveness in the treatment of GIST, including the TKIs sorafenib, which targets VEGFRs, PDGFRβ, KIT, Raf-1, FLT3 and RET, and masitinib mesylate (AB1010), a novel agent that targets KIT, PDGFRs and fibroblast growth factor receptor 3 [10, 47–48].

In a preliminary analysis from a phase II study in 25 patients with GIST that was resistant to both imatinib and sunitinib, sorafenib (400 mg twice daily) was associated with median PFS of 5.3 months, median OS of 13.0 months and 1-year survival of 62% (95% CI 37–78) [47]. The most frequently reported AEs were hand–foot syndrome (28%), hypertension (24%) and rash (20%), and dose reductions were required in 67% of patients. Data suggested that sorafenib was well tolerated although treatment-related toxicities necessitated frequent dose reductions.

Preliminary efficacy and safety data for 21 of 26 patients with advanced imatinib-naïve GIST in a phase II study of masitinib showed PR in 52% of patients and stable disease in 38% of patients, suggesting activity in this setting [48].

These and other agents are currently undergoing clinical trials in the first-, second- and third-line settings and in combination therapy regimens in the management of advanced GIST.

**conclusions**

Targeted agents have revolutionised the treatment of advanced GIST. Due to the clinical resistance or intolerance developed by many patients, additional therapeutic options beyond first-line imatinib are required. Sunitinib has demonstrated efficacy in the second-line treatment of patients with imatinib-intolerant or -resistant GIST in a phase III study, extending OS compared with placebo treatment in this patient group. Sunitinib has also shown efficacy in the treatment of patients with advanced imatinib-refractory GIST who were considered ineligible for inclusion in clinical trials. Studies are ongoing to elucidate the effects of imatinib and sunitinib in GIST patients according to mutational status and in alternative dosing and combination therapy regimens. Several established and novel multitargeted agents are also under investigation, which may expand the range of treatment choices available in the future for patients with advanced GIST.

With greater knowledge of the prognostic factors that affect patient response, particularly tumour genotype, tailored treatment of individual patients with GIST is becoming increasingly important and should be used routinely to optimise treatment outcomes. Better characterisation of the molecular mechanisms involved in the development of primary and secondary TKI resistance is also needed to assist with the selection of appropriate alternative therapies for patients with advanced GIST who exhibit refractory genotypes.

**disclosures**

Editorial assistance for this paper was provided by ACUMED (Tytherington, UK), with funding from Pfizer, Inc. Jean-Yves Blay has received research grants and honoraria from Pfizer and Novartis.

**references**


18. Blanke CD, Demetri GD, von MM 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.


42. Casali PG, Fumagalli E, Aloia et al. Safety and tolerability of sunitinib (SU) initiated 24 h after the last dose of imatinib (IM) in advanced GIST. J Clin Oncol 2008; 26 (May 20 Suppl): Abstr 10557; Poster presentation.


44. Reichardt P, Pink D, Lintner T et al. A phase I/II trial of the oral PKC inhibitor PKC412 (PKC) in combination with imatinib mesylate (IM) in patients (pts) with gastrointestinal stromal tumor (GIST) refractory to IM. J Clin Oncol 2005; 23 (June 1 Suppl): Abstr 3016.


