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Phase III study of nilotinib versus best supportive care with or without a TKI in patients with gastrointestinal stromal tumors resistant to or intolerant of imatinib and sunitinib

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Background: This phase III open-label trial investigated the efficacy of nilotinib in patients with advanced gastrointestinal stromal tumors following prior imatinib and sunitinib failure.

Patients and methods: Patients were randomized 2 : 1 to nilotinib 400 mg b.i.d. or best supportive care (BSC; BSC without tyrosine kinase inhibitor, BSC + imatinib, or BSC + sunitinib). Primary efficacy end point was progression-free survival (PFS) based on blinded central radiology review (CRR). Patients progressing on BSC could cross over to nilotinib.

Results: Two hundred and forty-eight patients enrolled. Median PFS was similar between arms (nilotinib 109 days, BSC 111 days; $P = 0.56$). Local investigator-based intent-to-treat (ITT) analysis showed a significantly longer median PFS with nilotinib (119 versus 70 days; $P = 0.0007$). A trend in longer median overall survival (OS) was noted with nilotinib (332 versus 280 days; $P = 0.29$). Post hoc subset analyses in patients with progression and only one prior regimen each of imatinib and sunitinib revealed a significant difference in median OS of >4 months in favor of nilotinib (405 versus 280 days; $P = 0.02$). Nilotinib was well tolerated.

Conclusion: In the ITT analysis, no significant difference in PFS was observed between treatment arms based on CRR. In the post hoc subset analyses, nilotinib provided significantly longer median OS.

Key words: gastrointestinal stromal tumors, GIST, imatinib, nilotinib, sunitinib, tyrosine kinase inhibitor

introduction

Historically, the prognosis for patients with unresectable or metastatic gastrointestinal stromal tumors (GIST) has been poor [1]. The introduction of the tyrosine kinase inhibitor (TKI) imatinib mesylate (Gleevec®/Glivec®, Novartis Pharma AG, Basel, Switzerland) revolutionized the management of GIST, providing a median overall survival (OS) of 57 months versus the 19 expected in the preimatinib era [1–6].

Despite these improvements, most patients eventually progress on imatinib, and a small percentage of patients are intolerant of the drug [6–9]. Sunitinib malate (Sutent®, Pfizer Pharmaceuticals, New York), a multiple receptor TKI, is the only approved second-line treatment option for GIST patients intolerant of or progressing on imatinib [10].

To date, there are no approved therapies available for patients with GIST following failure of both imatinib and sunitinib. Nilotinib (Tasigna®, AMN107; Novartis Pharma AG), a phenylaminopyrimidine, is a selective TKI that may address this important unmet medical need. Like imatinib, nilotinib potently inhibits receptor tyrosine kinases KIT and PDGFR as well as BCR-ABL. Nilotinib has greater *in vitro* potency against BCR-ABL than imatinib but exhibits similar inhibitory activity against KIT and PDGFR kinases [11]. In cell lines expressing mutant KIT, nilotinib reduces cell viability to an extent similar to imatinib; it also has potent antiproliferative activity against imatinib-sensitive forms of KIT and some activity against certain imatinib-resistant forms of KIT [12].

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Whereas imatinib requires an active transport mechanism via organic cation transporter-1 for cell entry, nilotinib transport is mostly passive, which has been shown to result in a 7- to 10-fold higher intracellular concentration in imatinib-sensitive and -resistant cell lines, with comparable inhibitory activity to imatinib [13–16]. This differential cellular uptake is thought to make nilotinib less susceptible to cellular transport-driven imatinib resistance [14]. In fact, experimental evidence indicates that P-glycoprotein, associated with multidrug resistance, functions to reduce intracellular concentrations of imatinib in transformed cell lines, conferring drug resistance [15, 17–19].

Results from clinical studies have shown that nilotinib has some demonstrable activity in patients with advanced GIST who are intolerant or resistant to approved TKIs. In a phase I study of imatinib-resistant/intolerant GIST patients, nilotinib (400 mg b.i.d.) was well tolerated and demonstrated clinical activity [20]. Furthermore, retrospective analysis of data from patients in a compassionate use program with unresectable or metastatic GIST following failure of all other treatment options reported that nilotinib treatment resulted in clinical responses and stable disease (SD) in 10% and 37% of assessable patients, respectively [21].

The Evaluating Nilotinib Efficacy and Safety in Clinical Trials (ENEST) g3 study was conducted to assess the potential clinical benefit of nilotinib in heavily pretreated patients with advanced GIST and evaluated efficacy and safety of nilotinib versus best supportive care (BSC) with investigator choice to include imatinib or sunitinib as part of the BSC regimen in patients with advanced GIST following failure of both approved TKIs.

methods

study design

This phase III, randomized, open-label multicenter study was conducted at 50 clinical sites in 13 countries. Between 5 March 2007 and 22 April 2008, 248 patients were randomized 2 : 1 to nilotinib 400 mg b.i.d. ($n = 165$) or the control arm ($n = 83$). Patients in the control arm were treated at investigator discretion with BSC alone, BSC plus imatinib (BSC + I), or BSC plus sunitinib (BSC + S). If a TKI was used in BSC, the dose was also left to the investigator's discretion; however, higher doses than used previously were not allowed, and patients in the BSC arm were not permitted to switch treatments. Patients in the BSC + S group received sunitinib per the approved regimen of 50 mg/day (4 weeks on/2 week off) or continuous dosing at 37.5 mg/day. Dose reduction in the study was only permitted in cases of adverse events (AEs); once reduced, the patient remained at that reduced dose.

Patients continued treatment until disease progression, unacceptable toxicity, death, discontinuation for another reason, or until the planned number of events was reached (to achieve the designed statistical power). Patients who discontinued the study drug for any reason other than progression were permitted to have tumor assessments continued during follow-up.

Following progression assessed by anatomic imaging including computed tomography (CT) or magnetic resonance imaging (MRI), patients in the control arm were permitted to cross over to nilotinib. These patients were considered off the core study but were permitted to enter the extension study. At the completion of the core study, patients in both arms who had not progressed were also eligible for entry into the extension study. All patients were followed up for OS up to 5 years, including those who discontinued from the study.

patient selection

Eligible patients were aged ≥18 years, with a World Health Organization (WHO) performance status (PS) of ≤2, and histologically confirmed unresectable and/or metastatic GIST with either (i) prior progression (radiologically confirmed by RECIST) on imatinib (≥400 mg/day) and sunitinib therapy (initiated at 50 mg/day even if progression on a reduced dose) or (ii) were intolerant to imatinib and/or sunitinib. No limit to the number of prior therapies was specified in the study. Treatment with approved and/or investigational cytotoxic agents was not permitted within 4 weeks (6 weeks for nitrosourea or mitomycin C) before the first visit. Prior treatment with TKIs other than imatinib and sunitinib was not permitted. Institutional review board approval was obtained at each participating center, and all patients provided written informed consent. The overall study design is depicted in Figure 1.

efficacy and safety evaluations

The primary efficacy end point was progression-free survival (PFS) assessed by central radiology review (CRR). Secondary end points included OS, best overall response rate, time to tumor response, time to tumor progression, duration of response, and time to treatment failure. Tumor evaluation (CT or MRI) was conducted by the local investigator at baseline, day 28, day 56, and every 56 days thereafter until progression. Each scan was also evaluated subsequently by blinded CRR per RECIST (v1.0) [22].

AEs were graded according to the National Cancer Institute–Common Terminology Criteria for Adverse Events v3.0. Safety monitoring included standard laboratory and cardiac (echocardiogram, electrocardiogram) assessments. Pharmacokinetic analysis was performed using a sparse sampling technique for patients randomized to nilotinib. Serum samples were analyzed using a validated method by liquid chromatography–tandem mass spectrometry to determine nilotinib concentrations.

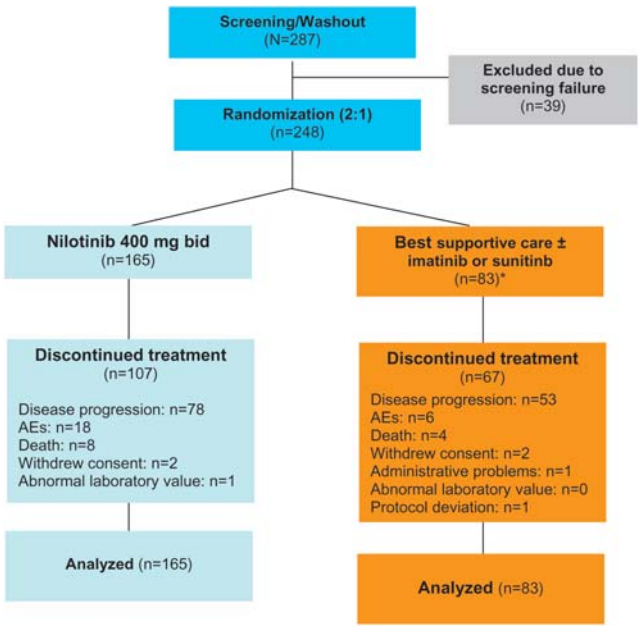


Figure 1. Consort diagram. AEs, adverse events; BSC, best supportive care. Asterisk in the control arm, patients were assigned to the BSC, BSC plus imatinib, and BSC plus sunitinib groups by the investigator.

statistical analyses

At an overall, two-sided type I error of 5%, 144 events were needed to achieve a statistical power of 90% for the primary analysis of PFS using the log-rank test. Study design hypothesized that median PFS for the nilotinib and control arms would be 14 and 8 weeks, respectively.

All efficacy data were analyzed for the intent-to-treat (ITT) population (all randomized patients) at two-sided 0.05 significance level using the log-rank test for time-to-event variables and Fisher's exact test for response rates. The hazard ratio (HR) with 95% confidence interval (CI) was estimated from a Cox regression model. The blinded central reader's assessments were used in all analyses except certain sensitivity analyses.

The same analysis methods were used in the post hoc analysis of a subgroup of patients (true third line) who had exactly one prior regimen each of imatinib and sunitinib and had well-documented progression or intolerance to second-line sunitinib [treatment must have stopped within 14 weeks (~3 months for next assessment) after progression].

All safety data were analyzed for the safety population using descriptive statistics and/or frequency tables.

results

patient characteristics and disposition

Patient demographics were similar between treatment arms (Table 1), except for WHO PS grade 0, which were higher in the nilotinib arm than the control arm (54.5% versus 39.8%, respectively). At the time of data cut-off (27 June 2008), 74 patients (29.8%) were still on study treatment [58 (35.2%) nilotinib, 16 (19.3%) control]; the remaining 174 (70.2%) had discontinued treatment [107 (64.8%) nilotinib, 67 (80.7%) control]. The most frequently reported reason for treatment discontinuation in both arms was disease progression [78 (47.3%) nilotinib, 53 (63.9%) control]. AEs were the next most common reason [18 (10.9%) nilotinib, 6 (7.2%) control]. Sixty-four patients (77%) crossed over from control to the nilotinib arm due to disease progression.

The most common primary sites of cancer among randomized patients were the small intestine ($n = 98$, 39.5%) and stomach ($n = 83$, 33.5%). Most patients were resistant to imatinib ($n = 233$, 94.0%) or sunitinib ($n = 214$, 86.3%); a minority of patients were intolerant to either medication [15 (6.0%) imatinib, 34 (13.7%) sunitinib; Table 2].

efficacy

All 248 patients were included in the ITT analysis. Based on the blinded CRR, PFS was not significantly different between the treatment arms [median 109 days nilotinib versus 111 days control, HR = 0.90, 95% CI (0.65–1.26); $P = 0.56$] (Figure 2A). Conversely, according to unblinded local investigator assessment, PFS was significantly longer in the nilotinib arm

Table 1. Patients' baseline demographics (ITT population)

Demographic variable	Nilotinib, $n = 165$	Control, $n = 83$	Total, $N = 248$
Age (years)			
n (age range)	165 (18.0–83.0)	83 (37.0–82.0)	248 (18.0–83.0)
Mean age	57.4	58.6	57.8
Sex, *n* (%)			
Male	101 (61.2)	47 (56.6)	148 (59.7)
Female	64 (38.8)	36 (43.4)	100 (40.3)
WHO performance status, *n* (%)			
Grade 0	90 (54.5)	33 (39.8)	123 (49.6)
Grade 1	62 (37.6)	41 (49.4)	103 (41.5)
Grade 2	13 (7.9)	8 (9.6)	21 (8.5)
Missing	0 (0)	1 (1.2)	1 (0.4)
Primary site of cancer, *n* (%)			
Liver	2 (1.2)	1 (1.2)	3 (1.2)
Esophagus	1 (0.6)	0 (0)	1 (0.4)
Stomach	56 (33.9)	27 (32.5)	83 (33.5)
Small intestine	67 (40.6)	31 (37.3)	98 (39.5)
Large intestine	9 (5.5)	5 (6.0)	14 (5.6)
Abdomen	11 (6.7)	11 (13.3)	22 (8.9)
Unknown	6 (3.6)	2 (2.4)	8 (3.2)
Other	13 (7.9)	6 (7.2)	19 (7.7)
Site of metastasis, *n* (%)			
Lung	1 (0.6)	1 (1.2)	2 (0.8)
Liver	93 (56.4)	54 (65.1)	147 (59.3)
Abdomen	30 (18.2)	12 (14.5)	42 (16.9)
Bone	1 (0.6)	0 (0)	1 (0.4)
Other	40 (24.2)	16 (19.3)	56 (22.6)

ITT, intent-to-treat; WHO, World Health Organization.

Table 2. Disease characteristics and history by treatment (ITT population)

	Nilotinib, $n = 165$	Control, $n = 83$	Total, $N = 248$
Prior experience with imatinib, *n* (%)			
Imatinib resistant	156 (94.5)	77 (92.8)	233 (94.0)
Imatinib intolerant	9 (5.5)	6 (7.2)	15 (6.0)
Time on imatinib (months)			
<6	15 (9.1)	5 (6.0)	20 (8.1)
6 to <12	14 (8.5)	9 (10.8)	23 (9.3)
12 to <24	37 (22.4)	24 (28.9)	61 (24.6)
24 to <36	37 (22.4)	19 (22.9)	56 (22.6)
36 to <48	35 (21.2)	12 (14.5)	47 (19.0)
48 to <60	16 (9.7)	9 (10.8)	25 (10.1)
≥60	11 (6.7)	5 (6.0)	16 (6.5)
Prior experience with sunitinib, *n* (%)			
Sunitinib resistant	146 (88.5)	68 (81.9)	214 (86.3)
Sunitinib intolerant	19 (11.5)	15 (18.1)	34 (13.7)
Time on sunitinib (months)			
<6	55 (33.3)	26 (31.3)	81 (32.7)
6 to <12	45 (27.3)	20 (24.1)	65 (26.2)
12 to <18	34 (20.6)	17 (20.5)	51 (20.6)
18 to <24	17 (10.3)	12 (14.5)	29 (11.7)
≥24	14 (8.5)	8 (9.6)	22 (8.9)
Time since diagnosis of primary site to study randomization (months)			
n	165	83	248
Mean (range)	63.6 (10.4–373.9)	62.3 (12.4–384.2)	63.1 (10.4–384.2)
Time since last relapse on imatinib and/or sunitinib to study randomization (months)			
n	165	80	245
Mean (range)	2.9 (0.2–25.0)	4.8 (0.1–41.1)	3.5 (0.1–41.1)

ITT, intent-to-treat.

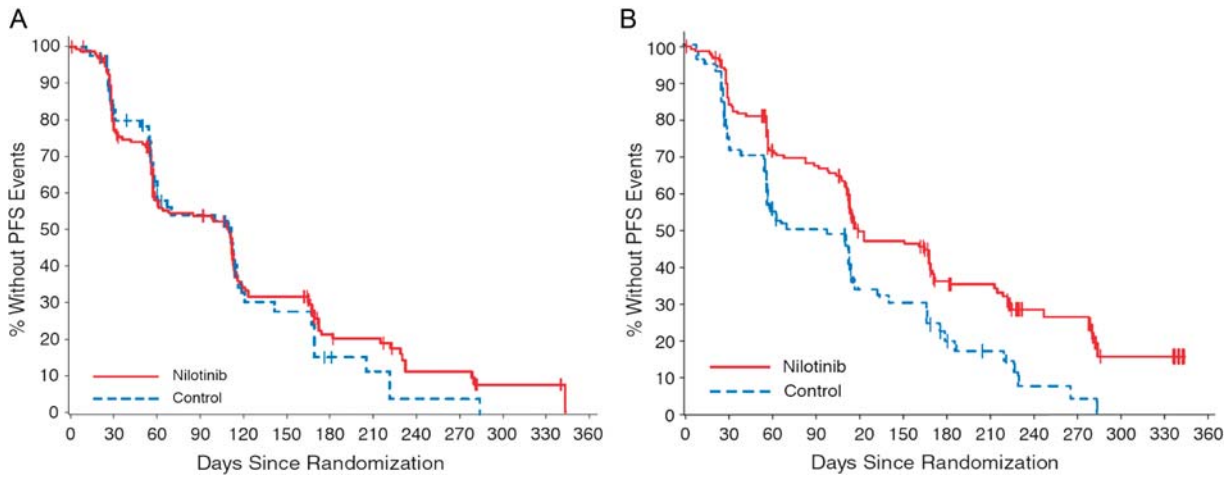


Figure 2. PFS based on central (A) and local (B) radiological review (intent-to-treat population). Data cut-off 27 June 2008. PFS, progression-free survival.

compared with the control arm [median 119 versus 70 days, respectively, HR 0.58, 95% CI (0.42–0.80); log-rank test $P = 0.0007$] (Figure 2B). High discordance was observed between the evaluations of PFS made by local assessment versus central review. The overall discordance rate was 25.4% for PFS status (event or censoring) and 47.6% for time to event (48.5% nilotinib, 45.8% control). In addition, the two independent blinded central readers displayed a high discordance rate when reading scans from the same subject, requiring the involvement of an adjudicator in 48.4% of cases.

Based on blinded CRR, one patient had a partial response (PR) in the nilotinib arm, and no patients achieved a complete response (CR) in either arm (supplemental Table A1, available at *Annals of Oncology* online). The overall clinical benefit rate (CBR = CR/PR/SD) in the nilotinib arm was 52.7% versus 44.6% in the control arm ($P = 0.28$). A CBR lasting >6 months was observed in 12 patients (7.3%) in the nilotinib arm and 1 patient (1.2%) in the control arm; this difference was not statistically significant ($P = 0.065$).

Although the study was not powered to detect statistically significant differences in OS in the ITT population, a nonstatistically significant trend in favor of the nilotinib arm was observed [median 332 versus 280 days; HR = 0.79, 95% CI (0.52–1.22); $P = 0.29$] (supplemental Figure 1A, available at *Annals of Oncology* online); this difference is particularly notable because 64 patients (77%) crossed over from the control arm to the nilotinib arm following progression; crossover usually occurred rapidly on control (median duration 70 days on control arm).

pharmacokinetics

The average minimum concentration (C_{min}) of nilotinib was 1037 ± 660 ng/ml, similar to previous findings [23]. Steady-state nilotinib concentrations were found to remain stable over the treatment course.

exploratory post hoc analyses

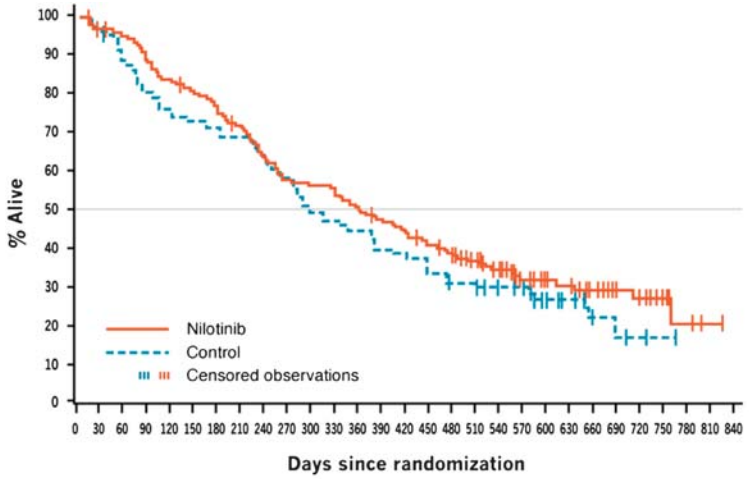
Recognizing that 41 patients (16.5%) in the ITT population had undergone treatment with more than two prior agents and 10 patients (4%) were accrued to the trial without well-documented progression on second-line treatment, an exploratory post hoc analysis was conducted to evaluate the true effect of nilotinib in a well-defined third-line patient population (true third line). This population ($n = 197$, 79.4% of total ITT) included all patients who had documented progression (or intolerance) after exactly one prior regimen each of imatinib and sunitinib. Progression on sunitinib was determined by RECIST within 14 weeks (~3 months for next assessment) of ceasing sunitinib. Based on the last survival follow-up (data cut-off 28 August 2009), patients in this subpopulation had a significantly longer OS on the nilotinib arm ($n = 132$) than those in the control arm [$n = 65$; median OS 405 versus 280 days, HR = 0.67, 95% CI (0.48, 0.95); $P = 0.02$] (Figure 3), a difference not observed in the ITT population using the same data cut-off [median 361 versus 300 days; HR = 0.84, 95% CI (0.62, 1.15); $P = 0.28$].

safety and tolerability

Median dose intensity was 800 mg/day for nilotinib, 669.5 mg/day for imatinib (BSC + I), and 33.3 mg/day for sunitinib (BSC + S). The median duration of exposure to treatment (including periods of temporary study drug interruption) was 113 days for the nilotinib arm and 70 days for the control arm (50 days BSC, 57.5 days BSC + I, 141 days BSC + S). Dose reduction was reported in 19 patients (7.7%) overall, including 15 (9.1%) in the nilotinib arm and 4 (4.8%) in the control arm (2 patients each in the BSC + I and BSC + S groups). Treatment interruption was reported in 68 patients (27.4%), including 49 (29.7%) in the nilotinib arm and 19 (22.9%) in the control arm [13 patients (24.1%) in the BSC + I group and 6 patients (26.1%) in the BSC + S group].

AEs were reported in 242 patients (97.6%); most AEs were gastrointestinal in origin. The most frequently reported AEs for nilotinib were abdominal pain (35.2%), nausea (29.7%), fatigue (26.7%), asthenia (25.5%), anorexia (23.6%), and anemia (21.2%) (Table 3).

Grade 3/4 drug-related AEs were reported in 39 patients (15.7%; Table 4). In the nilotinib arm, the most common grade 3/4 AEs were asthenia (3%), increased lipase (1.8%), abdominal



A

Overall survival, ITT population (N=248)	*P*=.28
Median (days) (nilotinib vs control)	361 vs 300
HR (95% CI)	0.84 (0.62, 1.15)

B

Overall survival, true-third-line–only (N=197)	*P*=0.02
Median (days) (nilotinib vs control)	405 vs 280
HR (95% CI)	0.67 (0.48, 0.95)

Figure 3. Overall survival in the intent-to-treat population (A) and the 'true third-line' only patient population (B). Data cut-off 28 August 2009. CI, confidence interval; HR, hazard ratio.

Table 3. Adverse events reported in at least 10% of patients (safety population)

Adverse event, *n* (%)	Nilotinib, *n* = 165	Control BSC + I, *n* = 54	Control BSC + S, *n* = 23	Control BSC, *n* = 6	Control total, *n* = 83	Total, *N* = 248
Any event	164 (99.4)	52 (96.3)	21 (91.3)	5 (83.3)	78 (94.0)	242 (97.6)
Nausea	49 (29.7)	29 (53.7)	3 (13.0)	0 (0)	32 (38.6)	81 (32.7)
Abdominal pain	58 (35.2)	13 (24.1)	6 (26.1)	3 (50.0)	22 (26.5)	80 (32.3)
Fatigue	44 (26.7)	10 (18.5)	4 (17.4)	1 (16.7)	15 (18.1)	59 (23.8)
Vomiting	33 (20.0)	22 (40.7)	3 (13.0)	0 (0)	25 (30.1)	58 (23.4)
Anorexia	39 (23.6)	15 (27.8)	0 (0)	2 (33.3)	17 (20.5)	56 (22.6)
Anemia	35 (21.2)	20 (37.0)	0 (0)	0 (0)	20 (24.1)	55 (22.2)
Peripheral edema	28 (17.0)	23 (42.6)	2 (8.7)	0 (0)	25 (30.1)	53 (21.4)
Asthenia	42 (25.5)	6 (11.1)	1 (4.3)	1 (16.7)	8 (9.6)	50 (20.2)
Constipation	34 (20.6)	6 (11.1)	0 (0)	1 (16.7)	7 (8.4)	41 (16.5)
Diarrhea	22 (13.3)	12 (22.2)	7 (30.4)	0 (0)	19 (22.9)	41 (16.5)
Headache	32 (19.4)	3 (5.6)	4 (17.4)	0 (0)	7 (8.4)	39 (15.7)
Pyrexia	28 (17.0)	6 (11.1)	2 (8.7)	0 (0)	8 (9.6)	36 (14.5)
Dyspnea	21 (12.7)	10 (18.5)	2 (8.7)	0 (0)	12 (14.5)	33 (13.3)
Rash	26 (15.8)	4 (7.4)	3 (13.0)	0 (0)	7 (8.4)	33 (13.3)
Back pain	25 (15.2)	4 (7.4)	0 (0)	1 (16.7)	5 (6.0)	30 (12.1)
Weight decreased	24 (14.5)	3 (5.6)	0 (0)	1 (16.7)	4 (4.8)	28 (11.3)
Upper abdominal pain	18 (10.9)	6 (11.1)	1 (4.3)	1 (16.7)	8 (9.6)	26 (10.5)
Cough	17 (10.3)	5 (9.3)	1 (4.3)	0 (0)	6 (7.2)	23 (9.3)
Myalgia	18 (10.9)	2 (3.7)	1 (4.3)	0 (0)	3 (3.6)	21 (8.5)
Pruritus	19 (11.5)	2 (3.7)	0 (0)	0 (0)	2 (2.4)	21 (8.5)

BSC, best supportive care; BSC + I, BSC plus imatinib; BSC + S, BSC plus sunitinib.

Table 4. Grade 3 or 4 drug-related adverse events reported in at least 1% of patients (safety population)

Adverse event, *n* (%)	Nilotinib, *n* = 165	Control BSC + I, *n* = 54	Control BSC + S, *n* = 23	Control total, *n* = 83	Total, *N* = 248
Any event	29 (17.6)	5 (9.3)	5 (21.7)	10 (12.0)	39 (15.7)
Anemia	2 (1.2)	4 (7.4)	0 (0)	4 (4.8)	6 (2.4)
Asthenia	5 (3.0)	0 (0)	0 (0)	0 (0)	5 (2.0)
Increased lipase	3 (1.8)	0 (0)	0 (0)	0 (0)	3 (1.2)
Abdominal pain	2 (1.2)	0 (0)	0 (0)	0 (0)	2 (0.8)
Increased alanine aminotransferase	2 (1.2)	0 (0)	0 (0)	0 (0)	2 (0.8)
Anorexia	2 (1.2)	0 (0)	0 (0)	0 (0)	2 (0.8)
Diarrhea	1 (0.6)	0 (0)	1 (4.3)	1 (1.2)	2 (0.8)
Fatigue	1 (0.6)	0 (0)	1 (4.3)	1 (1.2)	2 (0.8)
Headache	2 (1.2)	0 (0)	0 (0)	0 (0)	2 (0.8)
Myalgia	2 (1.2)	0 (0)	0 (0)	0 (0)	2 (0.8)
Neutropenia	0 (0)	0 (0)	2 (8.7)	2 (2.4)	2 (0.8)
Vomiting	2 (1.2)	0 (0)	0 (0)	0 (0)	2 (0.8)
Gastrointestinal hemorrhage	0 (0)	1 (1.9)	0 (0)	1 (1.2)	1 (0.4)
Septic shock	0 (0)	1 (1.9)	0 (0)	1 (1.2)	1 (0.4)
Thrombocytopenia	0 (0)	0 (0)	1 (4.3)	1 (1.2)	1 (0.4)

BSC + I, best supportive care plus imatinib; BSC + S, best supportive care plus sunitinib.

pain, increased alanine aminotransferase, anorexia, headache, anemia, vomiting, and myalgia (1.2% each). Grade 3/4 anemia (1.2% versus 4.8%) and neutropenia (0% versus 2.4%) were less frequent in the nilotinib arm compared with control. All cases of grade 3/4 neutropenia were reported in the BSC + S (8.7%) group of the control arm. Serious AEs (SAEs; grade 3/4) were reported in a total of 80 patients (32.3%), comprising 58 patients (35.2%) in the nilotinib arm and 22 (26.5%) in the control arm. The most common grade 3/4 SAEs involved the gastrointestinal tract (14.5%; 15.2% nilotinib, 13.3% control).

A total of 21 deaths were reported within 28 days after the last dose of study drug during the study period. Fourteen deaths (8.5%) occurred in the nilotinib arm and seven (8.4%) in the control arm [one patient (16.7%) in the BSC group and six patients (11.1%) in the BSC + I group].

discussion

This phase III study investigating the efficacy and safety of nilotinib versus BSC in patients with unresectable or metastatic GIST who progressed on or were intolerant of imatinib and sunitinib did not meet the primary end point according to CRR. However, for the same end point as assessed by local investigators, nilotinib provided a significant lengthening of median PFS compared with control.

The overall discordance rate between local and central reviews was 25.4% in PFS event status and 47.6% in time to event. In addition, high adjudication rates (48.4%) between central reviewers were observed, documenting the difficulty associated with use of RECIST in heavily treated patients who often have bulky and multifocal drug-resistant GIST. A significantly higher rate of nontarget lesions at baseline was identified by central review (91%) compared with local review (63%), and central reviewers determined disease progression much more frequently based solely on worsening of nontarget lesions (31 cases, 20.1% of all progression) than local reviewers (9 cases, 6.3% of all progression). Additional, exploratory, blinded radiological analyses were conducted, but high discordance between the two groups of reviewers was still observed. The discordance between blinded CRR and local investigator review in this population of patients with advanced GIST suggests that it may be difficult to assess efficacy by an imaging method alone, without taking into account clinical details to inform the status of disease in the patient.

There are several potential reasons for this discrepancy between local and central evaluations of PFS. As this was an open-label trial, investigator bias may be a factor; local investigators may also have had access to more robust patient information and clinical data to inform their clinical assessments. Advanced GIST also can be complex to assess by RECIST because of reported cases of 'false progressions' (i.e. volumetric progression despite clinical improvements and with metastases that can increase in size due to necrotic changes and perhaps intratumoral bleeding) [24, 25]. In fact, in the EORTC 62005 study, subjective progression (per the investigator) was associated with worse prognosis than progression defined by volumetric increase by RECIST alone [26].

The use of RECIST to evaluate PFS may be another explanation for the discrepancy in evaluations, as RECIST can underestimate the true rates of beneficial treatment response to molecularly targeted therapy, especially in GIST [27]. Size-based criteria included in RECIST were originally designed to measure responses to cytotoxic agents, and the limitations of these criteria have been extensively discussed [24, 28, 29]. Moreover, determining the types of changes that are indicative of a true response following TKI therapy can also be problematic. TKI-responsive GIST may initially increase in size but simultaneously become cystic, complicating the interpretation of whether a patient's tumor was truly progressing [27]. In this trial, the use of RECIST might have obscured the interpretation of results in certain patients by incorrectly declaring them as having progressive disease [24, 25].

Despite a high proportion of crossover from the control arm to the nilotinib arm, OS was nearly 2 months longer in the nilotinib arm compared with control. This trend was not statistically significant, partly given that this study was not powered to detect statistically significant differences in OS in the ITT population.

Given that 51 patients [21%; 33 (20%) nilotinib, 18 (22%) control] in the ITT population had undergone treatment with more than two prior regimens or were accrued to the trial without well-documented progression on prior sunitinib, a post hoc analysis was conducted to evaluate OS with longer follow-up in a 'true third-line' patient population. In this population, a significantly longer median OS of >4 months was observed in patients in the nilotinib arm compared with control. These findings suggest that true third-line patients with advanced GIST experienced a substantial clinical benefit following nilotinib treatment. In fact, in the later stages of GIST, OS may be a more objective end point, due to the limitations of RECIST in interpreting progression in patients with this disease.

In summary, although the study failed to meet its primary end point based on CRR, nilotinib was associated with a nonstatistically significant improvement in median OS in the ITT population, which is more clearly demonstrated in the significantly longer median OS (>4 months) in an exploratory post hoc analysis of a well-defined population of true third-line patients. Nilotinib was well tolerated; most AEs were manageable, nonhematologic, similar in frequency between treatment arms, and consistent with those reported in other clinical studies [30]. Based on its activity in this heterogeneous and extensively pretreated patient population, further evaluation of nilotinib in a well-defined population of patients with GIST is warranted. Other studies have been initiated in patients with advanced GIST, in the first-line setting, including a first-line pilot study and ENEST g1, a phase III open-label study of nilotinib versus imatinib as first-line therapy for advanced GIST [31, 32].

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disclosure

PR is a member of advisory boards and speakers bureaus for Novartis Oncology. JYB and MS conduct research for Novartis Oncology. GD has been a consultant for Novartis Pharmaceuticals, Pfizer, Ariad, Johnson & Johnson, PharmaMar, Genentech, Infinity Pharmaceuticals, EMD-Serono, GlaxoSmithKline, Amgen, Daiichi-Sankyo, ArQule, Enzon, Millenium/Takeda, ZipPharm, Champions Biotechnology, and Kolltan Pharmaceuticals. GD has conducted research for Novartis Pharmaceuticals, Pfizer, Ariad, Johnson & Johnson, PharmaMar, Infinity Pharmaceuticals, Amgen, and Daiichi-Sankyo. GD is a member of advisory boards for ZioPharm, Nereus, N-of-One, and Kolltan Pharmaceuticals and holds stock in Nereus, N-of-One, Champions Biotechnology, and Kolltan Pharmaceuticals. SY is employed by and holds stock in Novartis Pharmaceuticals. YH and IG are employed by Novartis Pharmaceuticals. Piotr Rutkowski has collected honoraria from Novartis Pharmaceuticals and Pfizer and is currently a member of an advisory board for Novartis Pharmaceuticals. All other authors do not have any conflicts of interest to disclose.

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Serial FDG–PET/CT for early outcome prediction in patients with metastatic colorectal cancer undergoing chemotherapy

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Background: The study purpose was to assess the predictive value of 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG)–positron emission tomography (PET)/computerized tomography (CT) metabolic response after a single course of chemotherapy in patients with metastatic colorectal cancer (mCRC).

Patients and methods: FDG–PET/CT scans were carried out at baseline and on day 14 in 41 patients with unresectable mCRC treated with a biweekly regimen of chemotherapy. Metabolic nonresponse was defined by <15% decrease in FDG uptake in the dominant proportion of the patient's lesions or if a lesion was found metabolically progressive. The PET-based response was correlated with radiological response (primary end point) and patient's outcome (secondary end points).

Results: RECIST response rate in metabolically responding patients was 43% (10 of 23) compared with 0% (0 of 17) in nonresponding patients ($P = 0.002$). The metabolic assessment's predictive performance for RECIST response was sensitivity 100% [95% confidence interval (CI) 69% to 100%], specificity 57% (95% CI 37% to 75%), positive predictive value 43% (95% CI 23% to 66%), and negative predictive value 100% (95% CI 80% to 100%). Comparing metabolically responding versus nonresponding patients, the hazard ratio (HR) was 0.28 (95% CI 0.10–0.76) for overall survival and 0.57 (95% CI 0.27–1.21) for progression-free survival.

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