Approval Summary: Imatinib Mesylate in the Adjuvant Treatment of Malignant Gastrointestinal Stromal Tumors

MARTIN H. COHEN, PATRICIA CORTAZAR, ROBERT JUSTICE, RICHARD PAZDUR

Office of Oncology Drug Products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, USA

Key Words. Imatinib • Gleevec • Kit • CD117 • Gastrointestinal stromal tumors

Disclosures: Martin H. Cohen: None; Patricia Cortazar: None; Robert Justice: None; Richard Pazdur: None.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the authors or independent peer reviewers.

ABSTRACT

On December 19, 2008, the U.S. Food and Drug Administration approved imatinib mesylate tablets for oral use (Gleevec®; Novartis Pharmaceuticals Corporation, East Hanover, NJ) for the adjuvant treatment of adult patients following complete gross resection of Kit⁺ (CD117⁺) gastrointestinal stromal tumor (GIST).

A randomized, double-blind, placebo-controlled study enrolling 713 patients was submitted. The primary objective of the clinical trial was to compare the recurrence-free survival (RFS) intervals of the two groups. Overall survival (OS) was a secondary endpoint. Eligible patients were ≥18 years of age with a histological diagnosis of GIST (Kit⁺), resected tumor size ≥3 cm, and a complete gross resection within 14–70 days prior to registration. Imatinib, 400 mg orally, was administered once daily for 1 year.

The study was terminated after completion of the

third protocol-specified interim analysis. At that time, 100 RFS events were confirmed by a blinded central independent review. With a median follow-up of 14 months, 30 RFS events were observed in the imatinib group and 70 were observed in the placebo group (hazard ratio, 0.398; 95% confidence interval, 0.259–0.610; two-sided *p*-value < .0001). OS results are immature.

Most patients in both groups experienced at least one adverse reaction, and 31% of the imatinib group and 18% of the placebo group experienced grade ≥3 adverse reactions. The most frequently reported adverse reactions (≥20%) were diarrhea, fatigue, nausea, edema, decreased hemoglobin, rash, vomiting, and abdominal pain. Drug was discontinued for adverse reactions in 17% and 3% of the imatinib and placebo-treated patients, respectively. *The Oncologist* 2010;15:300–307

INTRODUCTION

Imatinib mesylate has been proven to be highly efficacious for the treatment of advanced/metastatic gastrointestinal stromal tumors (GISTs) [1–3] and, based on early studies,

for the adjuvant treatment of GIST patients who have had complete gross resection of their primary neoplasms [4, 5].

The present report summarizes a large, double-blind, placebo-controlled, phase III trial to demonstrate the effi-

Correspondence: Martin H. Cohen, M.D., U.S. Food and Drug Administration, White Oak Campus, 10903 New Hampshire Avenue, Building 22, Room 2102, Silver Spring, Maryland 20993-0002, USA. Telephone: 301-796-1344; Fax: 301-796-9845; e-mail: martin.cohen@fda.hhs.gov Received June 18, 2009; accepted for publication February 5, 2010; first published online in *The Oncologist Express* on March 3, 2010. ©AlphaMed Press 1083-7159/2010/\$30.00/0 doi: 10.1634/theoncologist.2009-0120

cacy of imatinib adjuvant treatment of adult patients following complete gross resection of Kit⁺ (CD117⁺) GISTs. The primary objective of the clinical trial was to compare the recurrence-free survival (RFS) times of the two groups. Overall survival (OS) was a secondary endpoint.

PATIENTS AND METHODS

A single, phase III, randomized, double-blind study of adjuvant imatinib at 400 mg/day for 1 year versus matched placebo for 1 year in patients who had complete gross resection of their primary GIST was conducted by the American College of Surgeons Oncology Group. There were 234 study sites in the U.S. and Canada. The first patient was enrolled on July 31, 2002, and enrollment continued until April 12, 2007.

The primary study objective was to determine whether patients with resected primary GISTs who were randomized to the imatinib arm had a longer recurrence-free survival (RFS) interval than patients randomized to the placebo arm. Comparison of OS was a secondary endpoint. Scientific correlative analyses of tumor tissue and blood were also planned.

Major inclusion/exclusion criteria included: male or female, ≥ 18 years of age, having given informed consent, an Eastern Cooperative Oncology Group performance status score ≤ 2 , a histologic diagnosis of primary GIST (without peritoneal or distant metastasis) expressing Kit protein by immunochemistry and with a tumor size ≥ 3 cm in the maximum dimension, complete gross resection (i.e., including R0 [negative microscopic margins] and R1 [positive microscopic margins] resections) of the primary GIST within 70 days prior to registration, negative postoperative radiologic studies, appropriate laboratory values, a negative pregnancy test, no postoperative cancer therapy, no active infection, and no New York Heart Association class 3 or 4 cardiac disease.

Randomization was stratified according to tumor size (≥ 3 cm and < 6 cm, ≥ 6 cm and < 10 cm, ≥ 10 cm). A randomization error occurred over a 6-month period from November 14, 2003 to May 18, 2004, resulting in 60 patients apparently being assigned to the placebo arm without proceeding through the intended 1:1 randomization. In an attempt to correct the imbalance between arms, the treatment assignment program was reset from May 19, 2004 to June 9, 2004 at a 4:1 ratio favoring imatinib over placebo (11 patients). The intent-to-treat (ITT) population included all patients who were registered to the study prior to and including April 12, 2007, except the 60 patients who were unintentionally wrongly assigned because of a randomization system error. The safety population also excluded the

60 patients who were unintentionally wrongly assigned because of a system error.

The study was reviewed by the data monitoring committee every 6 months from August 2003 for safety and from June 2006 for efficacy also. All available patient data with regard to radiological, operative, and local pathology reports were included in the review, including records following the April 12, 2007 data cutoff. Prespecified statistical boundaries were employed at each efficacy interim analysis (IA) so that the trial could be stopped early for futility or for exceptional superiority of imatinib. The results of the third efficacy IA, including all information available up to January 22, 2007, led to the unblinding of the study on April 12, 2007. Upon unblinding of the study, patients still receiving placebo were eligible to cross over to 1 year of imatinib.

To assess the robustness of the analyses performed on the RFS endpoint, supportive sensitivity analyses were conducted with RFS adjusted for prognostic factors, with backdating of recurrence to a scheduled visit, with censoring at the last adequate assessment, with backdating to a midpoint of scheduled visits, with recurrence by definitive scan or biopsy, with recurrence by biopsy, with recurrence by investigator visit, by case report form documented recurrence, and with recurrence on the interim ITT population using the January 22, 2007 cutoff. The data for many of these analyses were obtained from the central independent medical review process.

RESULTS

The ITT population comprised 359 patients randomized to imatinib and 354 patients randomized to placebo. Table 1 summarizes the demographic characteristics of the study population and Table 2 summarizes the disease characteristics of the study population.

Thirty RFS events were noted in the imatinib treatment group and 70 events were noted in the placebo treatment group. There was a highly significant overall difference in the RFS probability estimate by first documented recurrence in favor of the imatinib group (overall hazard ratio [HR], 0.398; 95% confidence interval, 0.259–0.610; two-sided p -value $< .0001$). Figure 1 illustrates the Kaplan–Meier estimate of RFS by first documented recurrence in the ITT population. The median RFS follow-up time for the ITT population was 14.0 months.

Sensitivity analyses on RFS were highly consistent with all statistical tests except one, showing significance at the two-sided level with p -values $< .0001$; only the analysis of RFS based on biopsy was slightly above, with $p = .0002$. The analysis based on biopsies reduced the power because one third of the recurrences were not confirmed by biopsy.

Table 1. Patient demographics

Variable	Imatinib (n = 359)	Placebo (n = 354)	Total (n = 713)
Age (yrs)			
Mean $\pm$ SD	57.9 $\pm$ 12.94	58.3 $\pm$ 12.56	58.1 $\pm$ 12.75
Median	59.0	58.0	58.0
Age group, n (%)			
≤ 70 yrs	295 (82.2)	297 (83.9)	592 (83.0)
> 70 yrs	64 (17.8)	57 (16.1)	121 (17.0)
Gender, n (%)			
Female	189 (52.6)	163 (46.0)	352 (49.4)
Male	170 (47.4)	191 (54.0)	361 (50.6)
Race, n (%)			
White	290 (80.8)	271 (76.6)	561 (78.7)
Black or African-American	42 (11.7)	48 (13.6)	90 (12.6)
Native Hawaiian or other Pacific islander	1 (0.3)	2 (0.6)	3 (0.4)
Asian	20 (5.6)	24 (6.8)	44 (6.2)
American Indian or Alaska native	0	0	0
Other	1 (0.3)	0	1 (0.1)
Unknown	5 (1.4)	9 (2.5)	14 (2.0)
Ethnicity, n (%)			
Hispanic or Latino	14 (3.9)	16 (4.5)	30 (4.2)
Non-Hispanic	312 (86.9)	317 (89.5)	629 (88.2)
Unknown	33 (9.2)	21 (5.9)	54 (7.6)

Abbreviation: SD, standard deviation.

The HRs from all analyses were in the range of 0.304–0.398.

Of the 30 patients with events in the imatinib group, 25 recurred and five died as a result of causes other than GIST without prior recurrence. Of the 25 patients who recurred in the imatinib group, only two recurred while on treatment or within 30 days following the last dose; all others recurred > 30 days following withdrawal from treatment. In contrast, of the 70 patients with events in the placebo group, 62 recurred and remained alive at the cutoff date, seven recurred and subsequently died, and one died without prior recurrence.

The greatest therapeutic effect of imatinib was seen while on treatment up to 1 year following randomization. During this period, only six events were observed, compared with 51 events observed on placebo. Of the six events, two (discontinuation of imatinib treatment) were because of adverse events (AEs), two were because of death without recurrence, one was because of study ineligibility (*c-KIT*⁺), and one patient experienced a recurrence. The difference between the groups then decreased over time.

OS results are immature, with five deaths in the imatinib arm and eight deaths in the placebo arm.

At the time that the study was terminated, patients who were still receiving placebo (i.e., patients who were randomized < 1 year from study termination) were eligible to cross over to imatinib treatment. Patients who had been randomized prior to April 1, 2006 and who had therefore already completed the treatment phase by April 1, 2007 were not offered imatinib treatment.

SAFETY

Patients received either 400 mg imatinib or placebo orally once daily. If an AE occurred, the study medication could be interrupted and restarted at either 300 mg or 400 mg, as specified in the study protocol. The percentage of patient who took, on average, less than the protocol-planned 400-mg dose per day was higher in the imatinib group, at 18% (61 patients), versus 4% (13 patients) in the placebo group. Accordingly, the average daily doses were 387 ± 41 mg in the imatinib group and 397 ± 20 mg in the placebo group.

The median exposure to treatment was comparable between the treatment groups, at 11.1 months for imatinib and 11.5 months for placebo. The duration of imatinib exposure was 0 months to < 1 month for 6.5% of patients, 3 months to

Variable	Imatinib (n = 359)	Placebo (n = 354)	Total (n = 713)
Performance status score, n (%)			
0, asymptomatic and fully active	281 (78.3)	265 (74.9)	546 (76.6)
1, symptomatic, fully ambulatory	74 (20.6)	81 (22.9)	155 (21.7)
2, symptomatic, ambulatory	4 (1.1)	8 (2.3)	12 (1.7)
Time since resection of primary GIST (days)			
Mean $\pm$ SD	54.5 $\pm$ 13.61	55.3 $\pm$ 13.95	54.9 $\pm$ 13.78
Median	57.0	59.0	58.0
Range	20–74	15–96	15–96
≤ 50 days	134 (37.3)	118 (33.3)	252 (35.3)
51–70 days	220 (61.3)	228 (64.4)	448 (62.8)
≥ 71 days	5 (1.4)	8 (2.3)	13 (1.8)
Location of tumor, n (%)			
Stomach	209 (58.2)	234 (66.1)	443 (62.1)
Small intestine	2 (0.6)	4 (1.1)	6 (0.8)
Rectum	5 (1.4)	5 (1.4)	10 (1.4)
Other	141 (39.3)	111 (31.4)	252 (35.3)
Unknown	2 (0.6)	0	2 (0.3)
Tumor size, n (%)			
3 cm to <6 cm	143 (39.8)	149 (42.1)	292 (41.0)
6 cm to <10 cm	123 (34.3)	119 (33.6)	242 (33.9)
≥ 10 cm	93 (25.9)	86 (24.3)	179 (25.1)
Resection margins, n (%)			
R0	325 (90.5)	330 (93.2)	655 (91.9)
R1	34 (9.5)	23 (6.5)	57 (8.0)
Unknown	0	1 (0.3)	1 (0.1)
Tumor size 3 cm to <6 cm, n (%)			
Resection margins, R0	131 (36.5)	142 (40.1)	273 (38.3)
Resection margins, R1	12 (3.3)	6 (1.7)	18 (2.5)
Unknown	0	1 (0.3)	1 (0.1)
Tumor size 6 cm to <10 cm, n (%)			
Resection margins, R0	114 (31.8)	111 (31.4)	225 (31.6)
Resection margins, R1	9 (2.5)	8 (2.3)	17 (2.4)
Tumor size ≥ 10 cm, n (%)			
Resection margins, R0	80 (22.3)	77 (21.8)	157 (22.0)
Resection margins, R1	13 (3.6)	9 (2.5)	22 (3.1)

Abbreviation: GIST, gastrointestinal stromal tumor.

<6 months for 14.5% of patients, 6 months to <9 months for 9.2% of patients, 9 months to <11 months for 3.9% of patients, and ≥ 11 months for 52.5% of patients.

Most patients in both treatment groups experienced at least one AE during the treatment period (98.8% who received imatinib and 91.0% who received placebo) (Table 3). The gastrointestinal system was the most frequently affected system organ class in both treatment groups, in 90%

of patients in the imatinib group and 70% of patients in the placebo group. Periorbital and peripheral edema were reported for 47% and 27% of patients in the imatinib and placebo groups, respectively. AEs of grade ≥ 3 were reported in 104 imatinib-treated patients (31%) and in 63 patients in the placebo group (18%) (Table 3).

No unexpected AEs that were not previously known for imatinib were observed.

Figure 1. Recurrence-free survival.

Fifty-seven patients in the imatinib group stopped treatment early because of AEs, compared with 11 patients in the placebo group.

DISCUSSION

Adjuvant treatment of patients with malignant disease differs from the treatment of advanced/metastatic disease in that a percentage of the former patients are cured by surgical resection of their malignancy. Those patients experience toxicity but no therapeutic benefit from additional treatment.

If possible, therefore, it is important to more precisely define the subset of patients who will derive the most benefit from treatment. GIST may serve as a paradigm for this strategy. The discovery of constitutive Kit (and later platelet-derived growth factor α [PDGFA]) activation as the central mechanism of GIST pathogenesis [6, 7] suggested that inhibiting or blocking Kit and/or PDGFA signaling might be an important GIST treatment strategy. Indeed, imatinib mesylate inhibits kinase activity of both these molecules and represents the standard-of-care front-line drug for the treatment of unresectable and metastatic GISTs [1].

More recent data, from patients with advanced/metastatic GISTs, suggest that the site of the *KIT* gene mutation may affect the outcome of imatinib treatment. The most common *KIT* gene mutation occurs in exon 11, followed by exon 9 mutations [8]. The rate of response in patients with *KIT* exon 11 mutated GISTs is significantly higher than that in patients with *KIT* exon 9 mutated or wild-type genotype [9]. In addition, patients with *PDGFRA* exon 18 mutation D842V are resistant to imatinib therapy, whereas those with

mutation D842Y are sensitive [10, 11]. These data, if supported by future studies, may better define the resected GIST population who should receive adjuvant imatinib therapy.

Clinical prognostic variables have also been described. A GIST workshop, convened by the National Institutes of Health in 2001, defined the risk for aggressive clinical course by tumor size in the largest dimension and tumor mitotic count per 50 high power fields (HPF). Tumor size was classified as <2 cm, 2–5 cm, 5–10 cm, and >10 cm. Tumors <2 cm with mitotic counts <5 were classified as very low risk, whereas tumors 2–5 cm with mitotic counts <5 were classified as low risk [12]. Investigators at The Armed Forces Institute of Pathology evaluated 1,765 patients with gastric GISTs and 906 patients with jejunal or ileal GISTs for additional clinical prognostic factors. For gastric GISTs, tumor location in the fundus or gastroesophageal junction, coagulative necrosis, ulceration, and mucosal invasion were unfavorable factors ($p < .001$), whereas tumor location in the antrum was favorable ($p < .001$) [13]. For GISTs of the jejunum or ileum, outcome was strongly dependent on tumor size and mitotic activity, with an overall tumor mortality twice that for gastric GISTs. As with gastric GISTs, tumors <5 cm with ≤ 5 mitoses/50 HPF rarely metastasized whereas all other categories of tumor size and mitotic rate had moderate to high rates of metastasis [14]. Unfortunately, in the current report, the tumor size classification schema was different and mitotic rate was not determined.

The patient population entered into this trial was prog-

Table 3. Adverse reactions, regardless of relationship to study drug

Preferred term	All CTC grades		CTC grade ≥ 3	
	Imatinib (n = 337) %	Placebo (n = 345) %	Imatinib (n = 337) %	Placebo (n = 345) %
Diarrhea	59.3	29.3	3.0	1.4
Fatigue	57.0	40.9	2.1	1.2
Nausea	53.1	27.8	2.4	1.2
Periorbital edema	47.2	14.5	1.2	0
Hemoglobin decreased	46.9	27.0	0.6	0
Peripheral edema	26.7	14.8	0.3	0
Rash (exfoliative)	26.1	12.8	2.7	0
Vomiting	25.5	13.9	2.4	0.6
Abdominal pain	21.1	22.3	3.0	1.4
Headache	19.3	20.3	0.6	0
Dyspepsia	17.2	13.0	0.9	0
Anorexia	16.9	8.7	0.3	0
Weight increased	16.9	11.6	0.3	0
Liver enzymes (ALT) increased	16.6	13.0	2.7	0
Muscle spasms	16.3	3.3	0	0
Neutrophil count decreased	16.0	6.1	3.3	0.9
Arthralgia	15.1	14.5	0	0.3
WBC decreased	14.5	4.3	0.6	0.3
Constipation	12.8	17.7	0	0.3
Dizziness	12.5	10.7	0	0.3
Liver enzymes (AST) increased	12.2	7.5	2.1	0
Myalgia	12.2	11.6	0	0.3
Blood creatinine increased	11.6	5.8	0	0.3
Cough	11.0	11.3	0	0
Pruritus	11.0	7.8	0.9	0
Weight decreased	10.1	5.2	0	0
Hyperglycemia	9.8	11.3	0.6	1.7
Insomnia	9.8	7.2	0.9	0
Lacrimation increased	9.8	3.8	0	0
Alopecia	9.5	6.7	0	0
Flatulence	8.9	9.6	0	0
Rash	8.9	5.2	0.9	0
Abdominal distension	7.4	6.4	0.3	0.3
Back pain	7.4	8.1	0.6	0
Pain in extremity	7.4	7.2	0.3	0
Hypokalemia	7.1	2.0	0.9	0.6
Depression	6.8	6.4	0.9	0.6
Facial edema	6.8	1.2	0.3	0
Alkaline phosphatase increased	6.5	7.5	0	0
Dry skin	6.5	5.2	0	0
Dysgeusia	6.5	2.9	0	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTC, Common Terminology Criteria.

nistically heterogeneous. In order to identify the patient groups most likely to benefit from adjuvant treatment as opposed to those who are unlikely to benefit, subset analyses of clinical and laboratory risk factors predictive of recurrence are critical. Hopefully future subgroup analyses of this trial will address this issue.

Another feature of the current report that deserves comment is the shape of the RFS curve. The greatest therapeutic effect of imatinib is seen during the 1-year treatment period. The RFS difference between the groups then decreases over time, so that by 48 months the imatinib and placebo curves come together. A possible explanation for this outcome is that imatinib is cytostatic rather than cytotoxic. Evidence to support this hypothesis comes from imatinib therapeutic results in advanced/metastatic GIST patients, for whom complete remissions occur in only 0%–5% of treated patients and partial responses/stable disease occur in about 80% [1]. This is unlike the results of imatinib treatment of newly diagnosed chronic myeloid leukemia, for which complete hematologic response occurs in 97% of treated patients and complete cytogenetic response occurs in 76% [15]. Moreover, Liu and colleagues demonstrated that imatinib induces GIST tumor cell quiescence (withdrawal from the cell cycle) through the CDH1-SKP2-p27^{KIP1} signaling axis [16]. Whether a longer duration of admin-

istration of imatinib would increase apoptosis and cytotoxicity remains to be determined. Pertinent in this regard are preliminary results of a French Sarcoma Group trial in which patients with metastatic GISTs are being randomized to 1 year, 3 years, or 5 years of imatinib therapy. Although the continued and discontinued treatment groups are small, it was observed that, irrespective of imatinib treatment duration, there was near universal disease progression during the first year after imatinib discontinuation. Further, there was nearly complete disease control following reinstitution of imatinib therapy, and the OS times are comparable for all patient groups [17–19].

ACKNOWLEDGMENT

The views expressed are the result of independent work and do not necessarily represent the views and findings of the U.S. Food and Drug Administration.

AUTHOR CONTRIBUTIONS

Conception/Design: Martin H. Cohen

Administrative support: Patricia Cortazar, Robert Justice, Richard Pazdur

Collection and/or assembly of data: Martin H. Cohen

Data analysis and interpretation: Martin H. Cohen, Patricia Cortazar, Robert Justice, Richard Pazdur

Manuscript writing: Martin H. Cohen, Patricia Cortazar, Robert Justice, Richard Pazdur

Final approval of manuscript: Martin H. Cohen, Patricia Cortazar, Robert Justice, Richard Pazdur

REFERENCES

- 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;347:472–480.
- Blanke CD, Rankin C, Demetri GD et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. *J Clin Oncol* 2008;26:626–632.
- Cohen MH, Farrell AT, Justice R et al. Approval summary: Imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. *The Oncologist* 2009;14:174–180.
- Nilsson B, Sjölund K, Kindblom LG et al. Adjuvant imatinib treatment improves recurrence-free survival in patients with high-risk gastrointestinal stromal tumours (GIST). *Br J Cancer* 2007;96:1656–1658.
- Eisenberg BL. Combining imatinib with surgery in gastrointestinal stromal tumors: Rationale and ongoing trials. *Clin Colorectal Cancer* 2006;6(suppl 1):S24–S29.
- Hirota S, Isozaki K, Moriyama Y et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science* 1998;279:577–580.
- Isozaki K, Hirota S. Gain-of-function mutations of receptor tyrosine kinases in gastrointestinal stromal tumors. *Curr Genomics* 2006;7:469–475.
- Hornick JL, Fletcher CD. The role of KIT in the management of patients with gastrointestinal stromal tumors. *Hum Pathol* 2007;38:679–687.
- Heinrich MC, Owzar K, Corless CL et al. Correlation of kinase genotype and clinical outcome in the North American Intergroup phase III trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 Study by Cancer and Leukemia Group B and Southwest Oncology Group. *J Clin Oncol* 2008;26:5360–5367.
- 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;23:5357–5364.
- Lasota J, Miettinen M. Clinical significance of oncogenic KIT and PDGFRA mutations in gastrointestinal stromal tumours. *Histopathology* 2008;53:245–266.
- Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. *Hum Pathol* 2008;39:1411–1419.
- 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;29:52–68.
- Miettinen M, Makhlof H, Sobin LH et al. Gastrointestinal stromal tumors of the jejunum and ileum: A clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. *Am J Surg Pathol* 2006;30:477–489.
- Druker BJ. Translation of the Philadelphia chromosome into therapy for CML. *Blood* 2008;112:4808–4817.
- Liu Y, Perdreau SA, Chatterjee P et al. Imatinib mesylate induces quiescence in gastrointestinal stromal tumor cells through the CDH1-SKP2-p27Kip1 signaling axis. *Cancer Res* 2008;68:9015–9023.
- Chevreau C, Ray-Coquart IL, Bui B et al. Outcome of patients with advanced GIST achieving a complete remission (CR) with imatinib (IM) be-

- fore interruption: Pooled analysis of two consecutive prospective randomizations of the French Sarcoma Group BFR14 phase III trial [abstract 10549]. *J Clin Oncol* 2009;27(15 suppl):548s.
- 18 Pérol D, Dômont J, Ray-Coquard IL et al. Does interruption of imatinib (IM) in responding GIST patients after one year of treatment influence the secondary resistance to IM after its reintroduction? Updated results of the prospective French Sarcoma Group randomized phase III trial on long term survival [abstract 10556]. *J Clin Oncol* 2008;26(15 suppl):567s.
- 19 Adenis A, Cassier PA, Bui BN et al. Does interruption of imatinib (IM) in responding patients after three years of treatment influence outcome of patients with advanced GIST included in the BFR14 trial [abstract 10522]? *J Clin Oncol* 2008;26(15 suppl):558s.