

# OPTIMIZING THE DOSE OF IMATINIB FOR TREATMENT OF GASTROINTESTINAL STROMAL TUMOURS: Lessons from the Phase 3 trials

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by Shreyaskumar Patel and John R. Zalcberg.  
Published in *European Journal of Cancer*, March 2008.

*This article contains information that is outside the FDA-approved labeling for GLEEVEC.*

GLEEVEC® (imatinib mesylate) tablets are indicated for patients with KIT (CD117)-positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

**Please see Important Safety Information on inside flap and back cover and enclosed full Prescribing Information.**



**gleevec**®  
(imatinib mesylate) tablets  
100mg, 400mg

## Study Design

Two randomized, multinational, Phase 3 studies were conducted in patients on imatinib therapy with a diagnosis of unresectable or metastatic KIT+ GIST. The 2 study designs were similar, allowing a predefined combined analysis of safety and efficacy.<sup>1,2</sup>

## Study Objectives

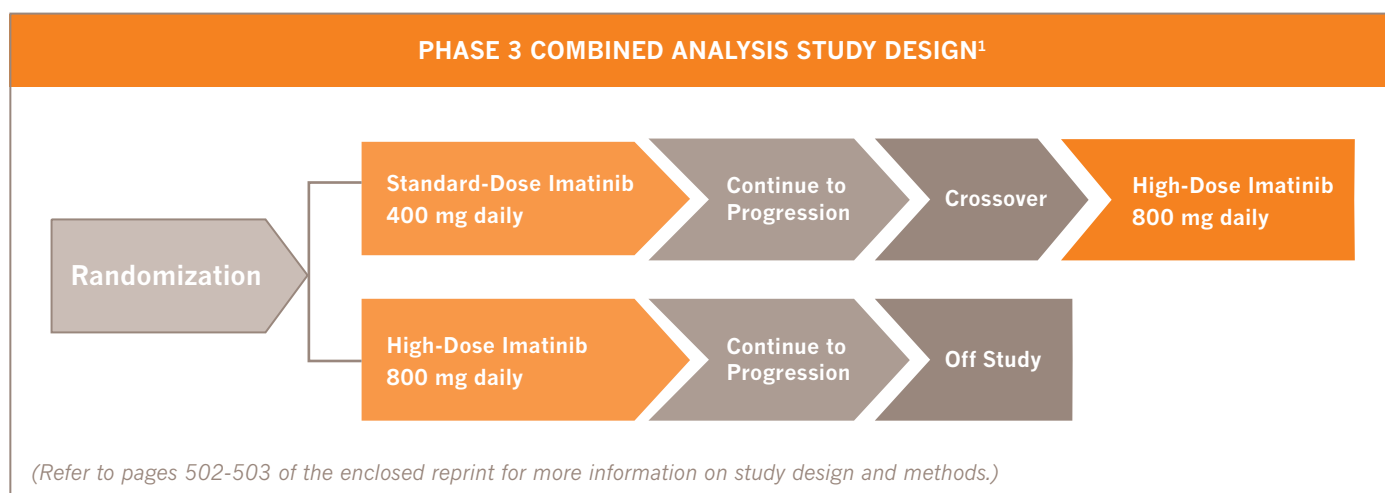
The European-Australasian study (Study 62005) was designed to assess progression-free survival (PFS) with overall survival (OS) as a secondary end point, whereas the North American Intergroup study (Study S0033) was designed to compare PFS and OS between high-dose and low-dose groups.<sup>1</sup>

METASTATIC GIST PATIENT POPULATIONS <sup>a</sup>		
Randomization arm	GLEEVEC PI <sup>2</sup> (N=1640)	Patel 2008 reprint <sup>1,b</sup> (N=1692)
400 mg/day (n)	818	849
800 mg/day (n)	822	843

<sup>a</sup>This table includes one data set from the approved label and another set from the analysis published by Patel and Zalberg.

<sup>b</sup>Based on combined eligible patient enrollment from Study 62005 and Study S0033.

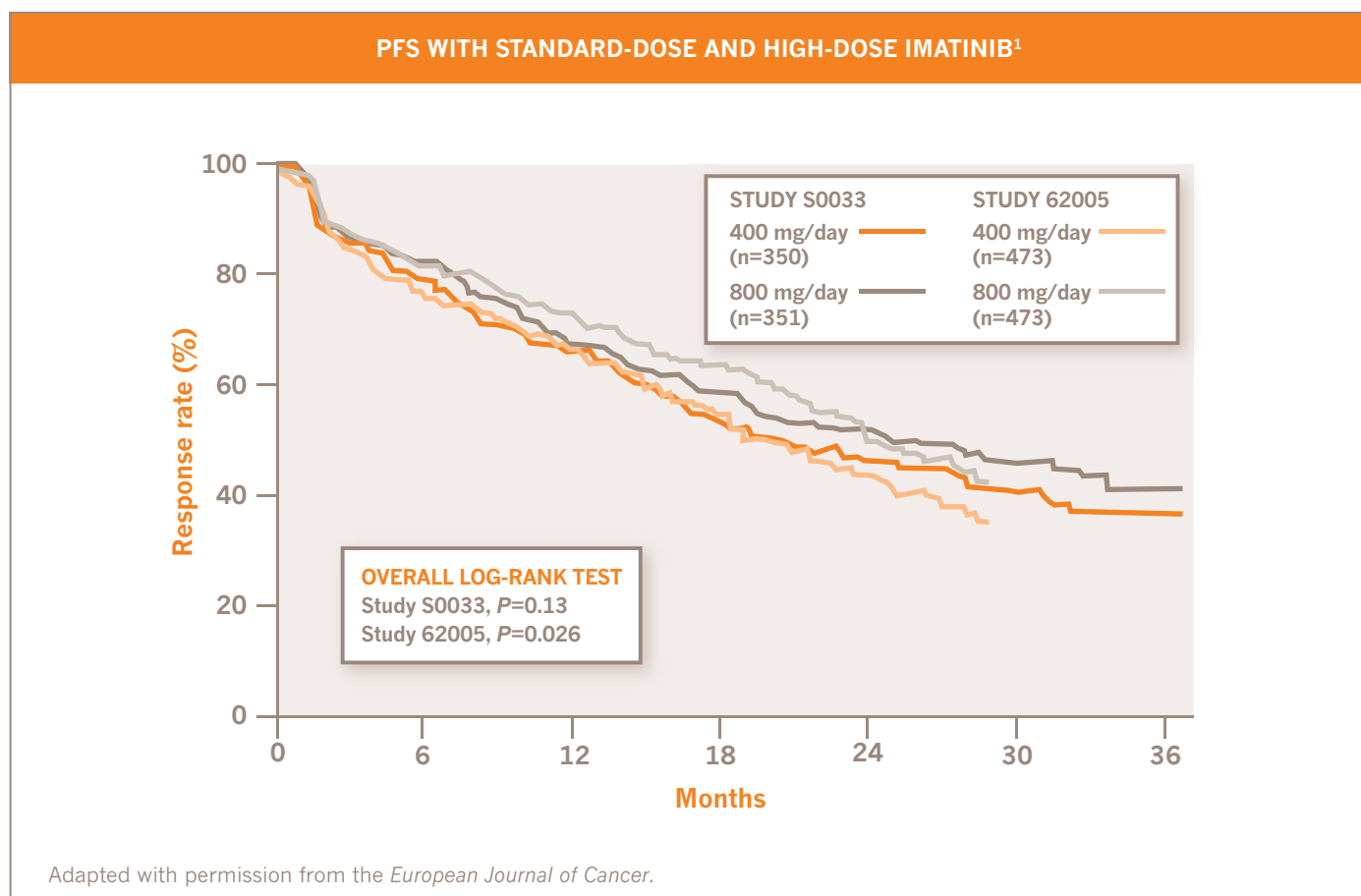
- Patients had a biopsy-proven diagnosis of unresectable or metastatic KIT+ GIST<sup>1</sup>
- In Study 62005, patient median age was 59 years in the standard-dose arm and 60 years in the high-dose arm<sup>1</sup>
- In Study S0033, patient median age was 61 years in both arms<sup>1</sup>
- Patients were randomized to receive imatinib 400 mg/day or 800 mg/day until disease progression or the development of unacceptable toxicity<sup>1,2</sup>
- Patients receiving imatinib 400 mg/day could cross over to 800 mg/day if disease progression occurred<sup>1,2</sup>



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## Results



- Approximately one-third of patients who progressed on standard-dose imatinib achieved partial response or stable disease with dose escalation to 800 mg/day<sup>1</sup>

**PFS AT APPROXIMATELY 24 MONTHS (PATEL 2008 REPRINT)<sup>1,c</sup>**

	Study 62005 <sup>d</sup>	Study S0033 <sup>e</sup>
400 mg/day	44% of patients	47% of patients
800 mg/day	50% of patients	52% of patients

**MEDIAN PFS (GLEEVEC PI)<sup>2,c</sup>**

400 mg/day	18.9 months (95% CI: 17.4-21.2)
800 mg/day	23.2 months (95% CI: 20.8-24.9)

<sup>c</sup>This table includes one data set from the label's FDA-approved analysis and another set from the analysis published by Patel and Zalcborg.

<sup>d</sup>CI values for these data not specified in this reprint;  $P=0.026$ .

<sup>e</sup>95% CI: 42%-53% for the 400-mg/day arm and 95% CI: 47%-57% for the 800-mg/day arm;  $P=0.13$ .

(Refer to pages 503-508 of the enclosed reprint for more information on key results.)

## Safety

- Severe toxicities occurred more frequently in the high-dose arm of both studies (50% vs 32% in Study 62005; 57% vs 38% in Study S0033;  $P < 0.0001$ )<sup>1</sup>
- Dose reductions were more likely in the high-dose arm of both studies and were usually due to nonhematologic toxicities<sup>1</sup>
- Incidence of dose reductions was significantly lower in patients who crossed over to high-dose imatinib than in patients who initially started with the higher dose<sup>1</sup>
- In Study 62005, anemia and fatigue were more severe after crossover, but neutropenia was less severe. All other toxicities did not differ significantly before and after crossover<sup>1</sup>

(Refer to pages 504-505 of the enclosed reprint for more information on safety.)

## Important Safety Information

- GLEEVEC is often associated with edema and occasionally serious fluid retention. Patients should be weighed and monitored regularly for signs and symptoms of fluid retention, which can be serious or life-threatening, and be advised to report any rapid, unexpected weight gain. The probability of edema tended to be increased among older patients (>65 years) or those taking higher doses of GLEEVEC. If severe fluid retention occurs, GLEEVEC should be withheld until the event has resolved and then resumed depending on the initial severity of the event
- Cytopenias have been reported. Complete blood counts should be performed weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (for example, every 2-3 months). Dose reduction or treatment interruption may be required for severe neutropenia or thrombocytopenia (see full Prescribing Information for dose adjustment recommendations)
- Severe congestive heart failure and left ventricular dysfunction have occasionally been reported. Most of the patients with reported cardiac events have had other comorbidities and risk factors, including advanced age and previous medical history of cardiac disease. Patients with cardiac disease or risk factors for cardiac failure should be monitored carefully, and any patient with signs or symptoms consistent with cardiac failure should be evaluated and treated
- Hepatotoxicity, occasionally severe, may occur. Assess liver function before initiation of treatment and monthly thereafter or as clinically indicated. Monitor liver function when combined with chemotherapy known to be associated with liver dysfunction. A 25% decrease in the recommended dose should be used for patients with severe hepatic impairment. If severe hepatotoxicity occurs, GLEEVEC should be withheld until the event has resolved and then resumed depending on the initial severity of the event
- In the Phase 3 unresectable or metastatic GIST studies, 13% of patients reported (NCI Grades 3/4)
- hemorrhage at any site. In the Phase 2 unresectable or metastatic GIST study, 5% of patients were reported to have severe gastrointestinal (GI) bleeds and/or intratumoral bleeds. GI tumor sites may have been the source of GI bleeds
- In patients with hypereosinophilic syndrome and cardiac involvement, cardiogenic shock and left ventricular dysfunction have been associated with initiation of GLEEVEC. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures, and temporarily withholding GLEEVEC
- Bullous dermatologic reactions (eg, erythema multiforme and Stevens-Johnson syndrome) have also been reported. In some cases, the reaction recurred upon rechallenge. Several postmarketing reports describe patients able to tolerate the reintroduction of GLEEVEC at a lower dose with or without concomitant corticosteroids or antihistamines following resolution or improvement of the bullous reaction
- Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levothyroxine replacement during treatment with GLEEVEC. TSH levels should be closely monitored in such patients
- Consider potential toxicities—specifically liver, kidney, and cardiac toxicity—and immunosuppression from long-term use
- Fetal harm can occur when administered to a pregnant woman; therefore, women of childbearing potential should be advised to not become pregnant while taking GLEEVEC tablets and to avoid breastfeeding while taking GLEEVEC tablets because of the potential for serious adverse reactions in nursing infants. Sexually active female patients taking GLEEVEC should use adequate contraception. If the patient does become pregnant while taking GLEEVEC, the patient should be advised of the potential hazard to the fetus
- In the Phase 2 unresectable or metastatic GIST trial (400 mg/day; 600 mg/day), severe (NCI Grades 3/4) lab abnormalities—including anemia (3%; 9%) and neutropenia (10%; 11%)—were reported among patients receiving GLEEVEC. In Phase 3 unresectable or metastatic GIST trials (400 mg/day; 800 mg/day), severe adverse reactions (NCI Grades 3/4/5), including abdominal pain (14%; 12%), edema (9%; 13%), fatigue (12%; 12%), nausea (9%; 8%), vomiting (9%; 8%), diarrhea (8%; 9%), rash (8%; 9%), and myalgia (6%; 4%), were reported among patients receiving GLEEVEC
- In the adjuvant treatment of GIST trials (GLEEVEC; placebo), severe (NCI Grades 3 and above) lab abnormalities—increased liver enzymes (ALT) (3%; 0%), (AST) (2%; 0%), decreased neutrophil count (3%; 1%), and decrease in hemoglobin (1%; 0%)—and severe adverse reactions (NCI Grades 3 and

Important Safety Information continued on back cover.

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## Conclusions

- Approximately half the patients in both studies did not experience disease progression at 2 years with high-dose imatinib<sup>1</sup>
  - Response rate included complete response and partial response
- Imatinib is effective in more than 80% of patients with unresectable or metastatic KIT+ GIST when administered at the starting dose of 400 mg/day<sup>1</sup>
- Approximately one-third of patients whose tumor progressed on the 400-mg/day initial dose had a partial response or stable disease after a dose increase to 800 mg/day<sup>1</sup>
- 800 mg/day was generally well tolerated after crossover from 400-mg/day therapy<sup>1</sup>

*(Refer to page 508 of the enclosed reprint for more information on study conclusions.)*

## Important Safety Information (cont'd)

above), including abdominal pain (3%; 1%), diarrhea (3%; 1%), rash (3%; 0%), fatigue (2%; 1%), nausea (2%; 1%), vomiting (2%; 1%), white blood cell count decreased (1%; 0%), and periorbital edema (1%; 0%), were reported among patients receiving adjuvant treatment with GLEEVEC

- There have also been reports, including fatalities, of cardiac tamponade, cerebral edema, acute respiratory failure, and GI perforation
- GLEEVEC is metabolized by the CYP3A4 isoenzyme and is an inhibitor of CYP3A4, CYP2D6, and CYP2C9. Significant reductions in imatinib concentrations may occur when GLEEVEC is administered concomitantly with agents that are strong CYP3A4 inducers such as rifampin, St. John's wort, and enzyme-inducing anti-epileptic drugs, eg, phenytoin. The use of concomitant strong CYP3A4 inducers should be avoided. If patients must be administered a strong CYP3A4 inducer, the dosage of GLEEVEC should be increased by at least 50% and clinical response should be carefully monitored. Caution is recommended when GLEEVEC is administered with CYP3A4 inhibitors such as ketoconazole, with CYP2D6 substrates that have a narrow therapeutic window, or with CYP3A4 substrates that have a narrow therapeutic window. Other examples of commonly used drugs that may significantly interact with GLEEVEC include acetaminophen, warfarin, erythromycin, and metoprolol. Grapefruit juice should also be avoided in patients taking GLEEVEC. (Please see full Prescribing Information for other potential drug interactions)
- Patients with moderate renal impairment (CrCL = 20-39 mL/min) should receive a 50% decrease in the recommended starting dose and future doses can be increased as tolerated. Doses greater than 600 mg are not recommended in patients with mild renal impairment (CrCL = 40-59 mL/min). For patients with moderate renal impairment, doses greater than 400 mg are not recommended. GLEEVEC should be used with caution in patients with severe renal impairment

## Common Side Effects of GLEEVEC Tablets

- Almost all patients who received GLEEVEC in the Phase 3 unresectable or metastatic GIST studies experienced adverse reactions at some time. Overall, the incidence of all grades of adverse reactions and the incidence of severe adverse reactions (CTC Grade 3 and above) were similar between the two treatment arms except for edema and rash/related terms, which were reported more frequently in the 800-mg group. The most

frequently reported adverse reactions (400 mg/day; 800 mg/day) (all Grades) were edema (77%; 86%), fatigue (69%; 75%), nausea (58%; 65%), abdominal pain (57%; 55%), diarrhea (56%; 58%), rash and related terms (56%; 70%), vomiting (37%; 41%), myalgia (32%; 30%), anemia (32%; 35%), anorexia (31%; 36%), and arthralgia (14%; 12%). Therapy with GLEEVEC was discontinued for adverse reactions in 5% of patients at both dose levels studied\*

- In the adjuvant treatment of GIST trials, almost all GLEEVEC- and placebo-treated patients experienced adverse reactions at some time. The most frequently reported adverse reactions were similar to those reported in other clinical studies in other patient populations and include (GLEEVEC; placebo) (all Grades) diarrhea (59%; 29%), fatigue (57%; 41%), nausea (53%; 28%), periorbital edema (47%; 15%), decreased hemoglobin (47%; 27%), peripheral edema (27%; 15%), rash (26%; 13%), vomiting (26%; 14%), abdominal pain (21%; 22%), anorexia (17%; 9%), arthralgia (15%; 15%), and myalgia (12%; 12%)\*
- In the adjuvant GIST trial, drug was discontinued for adverse events in 17% of GLEEVEC- and 3% of placebo-treated patients. Edema, GI disturbances (nausea, vomiting, abdominal distention, and diarrhea), fatigue, low hemoglobin, and rash were the most frequently reported adverse reactions at the time of discontinuation\*
- Supportive care may help management of some mild-to-moderate adverse reactions. However, in some cases, either a dose reduction or interruption of treatment with GLEEVEC may be necessary
- For daily dosing of 800 mg and above, dosing should be accomplished using the 400-mg tablet to reduce exposure to iron
- GLEEVEC tablets should be taken with food and a large glass of water to minimize GI irritation
- Patients should be informed to take GLEEVEC exactly as prescribed, and not to change their dose or stop taking GLEEVEC unless they are told to do so by their doctor. If patients miss a dose, they should be advised to take their dose as soon as possible unless it is almost time for their next dose, in which case the missed dose should not be taken. A double dose should not be taken to make up for any missed dose

\*For more detailed study information, please see full Prescribing Information.

**References:** 1. Patel S, Zalcberg JR. Optimizing the dose of imatinib for treatment of gastrointestinal stromal tumours: lessons from the phase 3 trials. *Eur J Cancer*. 2008;44(4):501-509. 2. GLEEVEC® (imatinib mesylate) tablets prescribing information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; February 2010.

**Please see enclosed full Prescribing Information.**



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East Hanover, New Jersey 07936-1080

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GLI-800436

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