

ADJUVANT IMATINIB MESYLATE AFTER RESECTION OF LOCALISED, PRIMARY GASTROINTESTINAL STROMAL TUMOUR: A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

by Ronald P. DeMatteo, Karla V. Ballman, Cristina R. Antonescu, et al.
Published in *The Lancet*, March 28, 2009.



GLIVEC® (imatinib) is indicated for the treatment of adult patients with KIT (CD 117)-positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST) and the adjuvant treatment of adult patients who are at significant risk of relapse following resection of KIT (CD 117)-positive GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment.

Please see Important Safety Information on back panel and enclosed Summary of Product Characteristics.

Study Design

A Phase III, multicenter, double-blind, randomized clinical trial was designed to compare 1 year of adjuvant therapy with GLIVEC versus placebo in patients with resected, localized primary KIT+ GIST.

Study Objectives

The primary end point was to compare recurrence-free survival (RFS) between the adjuvant GLIVEC and placebo arms. Secondary end points included overall survival (OS) and safety.

Patient Population

- 713 previously untreated patients with resected primary GIST were randomized*:
 - Patients had histologically proven diagnosis of localized primary GIST measuring ≥ 3 cm expressing KIT protein
 - Median age at randomization was 59 years (range 18-88) in the GLIVEC arm and 58 years (range 18-91) in the placebo arm
- Patients were randomized to receive either:
 - GLIVEC 400 mg/day (n=359)
 - Placebo (n=354)
- Patients received therapy for 1 year and were followed until year 5
- Patients were unblinded at the time of tumor recurrence and were then permitted to cross over to the GLIVEC arm
 - Patients who had completed the study therapy or were assigned to placebo crossed over to 400 mg/day
 - Patients receiving 400 mg/day during the study period could be crossed over to 800 mg/day in the event of recurrence

*65 patients of the 778 registered did not meet eligibility requirements.

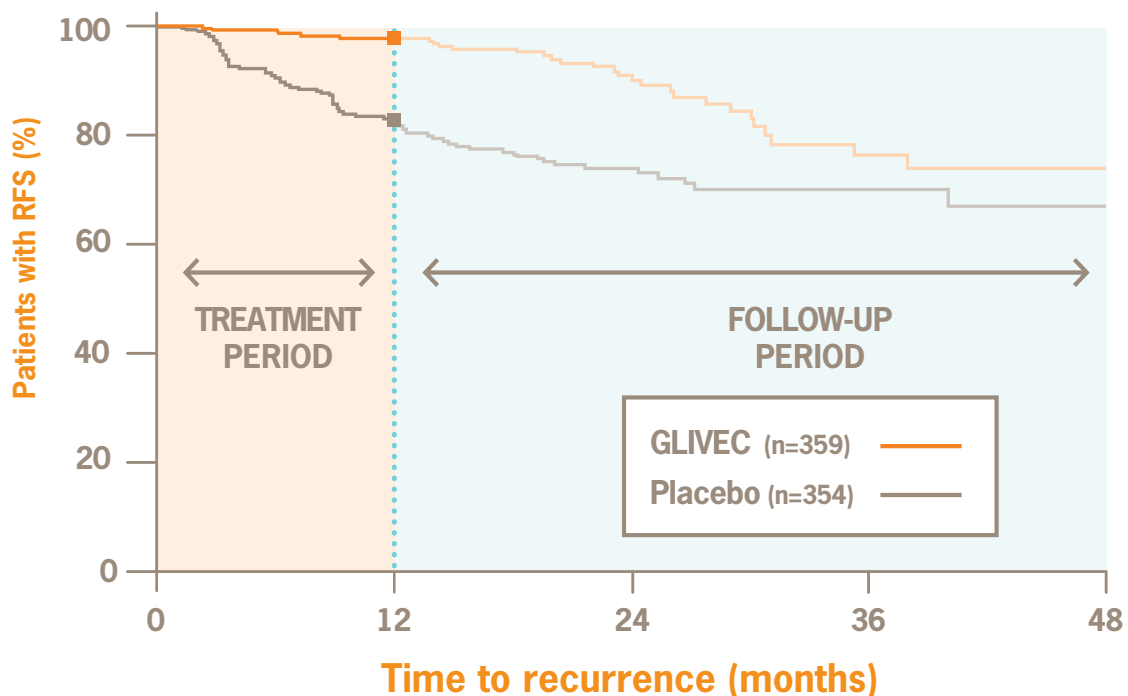
GLIVEC® (imatinib) is indicated for the treatment of adult patients with KIT (CD 117)-positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST) and the adjuvant treatment of adult patients who are at significant risk of relapse following resection of KIT (CD 117)-positive GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment.

Please see Important Safety Information on back panel and enclosed Summary of Product Characteristics.

Results

- GLIVEC significantly prolonged RFS compared with placebo at 1 year (overall hazard ratio 0.35; $P \leq 0.0001$)
 - GLIVEC arm: 98% RFS (95% CI: 0.96-1.00)
 - Placebo arm: 83% RFS (95% CI: 0.78-0.88)
- Disease recurrence was more frequent in patients treated with placebo (20%) versus patients treated with GLIVEC (8%)
 - During the 1 year of assigned therapy:
 - ◆ 41 recurrences occurred in the placebo arm compared with 1 recurrence in the GLIVEC arm
 - 6 months after stopping therapy:
 - ◆ The rate of recurrence in the GLIVEC arm began to increase
- GLIVEC prolonged RFS across all tumor size categories (>3 cm to >10 cm)
- No difference in OS was found due to the short follow-up time

Estimated Rate of Recurrence Over Time



Patients at risk:

Placebo:	354	188	89	34	8
GLIVEC:	359	207	105	33	6

Safety

- Discontinuation of treatment was more likely due to:
 - Adverse events in the GLIVEC arm ($P<0.0001$)
 - Tumor recurrence in the placebo arm ($P<0.0001$)
- Adjuvant GLIVEC was safe and well tolerated
 - Rate of adverse events overall was low and consistent with the use of GLIVEC in the CML* and metastatic GIST settings
- Grade 1 and 2 events were most common in both treatment arms and involved gastrointestinal effects, headache, rash, edema, fatigue, or myalgias/arthralgias

*Chronic myeloid leukemia.

Conclusions

- 98% of patients treated with adjuvant GLIVEC were recurrence-free at 1 year compared with 83% of patients treated with placebo
- The adverse event rate was low and consistent with the use of GLIVEC in the CML and metastatic GIST settings
- RFS may be prolonged with longer-duration adjuvant treatment

“Increased use of adjuvant imatinib could extend recurrence-free survival.”

—R.P. DeMatteo, *The Lancet*, 2009

GLIVEC® (imatinib) is indicated for the treatment of adult patients with KIT (CD 117)–positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST) and the adjuvant treatment of adult patients who are at significant risk of relapse following resection of KIT (CD 117)–positive GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment.

Important Safety Information

Contraindications: Hypersensitivity to imatinib or to any of the excipients

Precautions/Warnings: Should be taken with food and a large glass of water to minimize the risk of gastrointestinal disturbances. Beware of severe fluid retention. It is recommended that patients be weighed regularly. Regular monitoring of complete blood counts and liver function tests. Caution in patients with history of cardiac disease. Careful monitoring of patients with cardiac disease or risk factors for cardiac failure. Monitoring of TSH levels in thyroidectomy patients undergoing levothyroxine replacement. Should not be used during pregnancy unless clearly necessary. Should not be used by breast-feeding mothers

Interactions: Caution with CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin). Caution with CYP3A4 inducers (e.g. dexamethasone, rifampicin, phenytoin, carbamazepine, phenobarbital, St. John's Wort). Caution with substrates of CYP3A4 (e.g. triazolobenzodiazepines, dihydropyridine calcium channel blockers, simvastatin, cyclosporin, pimozide), CYP2C9 (e.g. warfarin) or CYP2D6 (e.g. metoprolol). Caution with concomitant use of paracetamol/acetaminophen

Adverse reactions: Very common: headache, nausea, vomiting, diarrhea, dyspepsia, abdominal pain, myalgia, arthralgia, muscle spasm or cramps, bone pain, dermatitis, eczema, rash, fatigue, weight increase

Common: anorexia, insomnia, dizziness, paresthesia, taste disturbance, hypoesthesia, flushing, photosensitivity reaction, weakness, pyrexia, chills, weight decrease, lacrimation increase, conjunctivitis, dry eye, blurred vision, dyspnea, epistaxis, cough, flatulence, abdominal distension, gastroesophageal reflux, constipation, dry mouth, gastritis, increased hepatic enzymes, pruritus, dry skin, erythema, alopecia, night sweats, joint swelling

Potentially serious: fluid retention, anasarca, edema (including brain, eye, pericard, abdomen, and lung), neutropenia, thrombocytopenia or anemia, pancytopenia, hemolytic anemia, hypokalemia, hyperkalemia, sepsis, cellulitis, fungal infection, upper respiratory tract infection, interstitial lung disease, pneumonia, pericardial/pleural effusion, pleuritic pain, pulmonary hypertension/hemorrhage/fibrosis, congestive heart failure, arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris, pericarditis, cardiac tamponade, thrombosis/embolism, ileus/intestinal obstruction, pancreatitis, hepatic failure/necrosis, hepatitis, exfoliative dermatitis, angioneurotic edema, Stevens-Johnson syndrome, erythema multiforme, leukocytoclastic vasculitis, Sweet's syndrome, lichenoid keratosis, lichen planus, toxic epidermal necrolysis, anaphylactic shock, syncope, hypotension, hematoma, acute respiratory failure, acute renal failure, hemorrhage (including brain, eye, kidney, and gastrointestinal tract), melena, hematemesis, diverticulitis, colitis, inflammatory bowel disease, gastrointestinal perforation, ascites, gastric ulcer, tumor hemorrhage/necrosis, hip osteonecrosis/avascular necrosis, sciatica, optic neuritis, cataract, papilledema, glaucoma, hearing loss, Raynaud's phenomenon, increased intracranial pressure, peripheral neuropathy, depression, convulsions

Note: Before prescribing, please read full Summary of Product Characteristics.

Source: DeMatteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2009;373(9669):1097-1104.