

CLINICAL TRIAL PROGRAM FOR ADJUVANT THERAPY WITH GLIVEC IN GIST*

*GIST, gastrointestinal stromal tumors.



GLIVEC® (imatinib) is indicated for the treatment of adult patients with KIT (CD117)-positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST) and for 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 cover.

LOOKING AHEAD IN GIST: ADJUVANT THERAPY WITH GLIVEC

The search for solutions

One in 2 patients experiences recurrence of GIST following surgery.¹

As the first therapy for GIST, GLIVEC changed the treatment landscape. Based on this success, 3 studies were undertaken to investigate the benefits of adjuvant therapy with GLIVEC in GIST.

1-year trial data

The landmark ACOSOG* Z9001 Phase III trial began a new chapter in the treatment of GIST²:

- At 1 year of treatment, 98% of patients had RFS in resected primary GIST with GLIVEC versus 83% with placebo
- These data support use of adjuvant therapy with GLIVEC in GIST

2-year trial underway

- The EORTC† 62024 trial will compare overall survival after 2 years of adjuvant therapy with GLIVEC with overall survival after no treatment³
- Enrollment is complete with interim results expected in 2010⁴

3-year trial underway

- The SSG‡ XVIII/AIO§ trial will compare RFS after 1 versus 3 years of adjuvant therapy with GLIVEC⁵
- Enrollment is complete with final analysis for RFS expected in 2010^{4,5}

*ACOSOG, American College of Surgeons Oncology Group.

†EORTC, European Organisation for Research and Treatment of Cancer.

‡SSG, Scandinavian Sarcoma Group.

§AIO, German Working Group on Medical Oncology.

Important Safety Information

Contraindications: Hypersensitivity to imatinib or to any of the excipients

Special warnings and precautions

Precautions/Warnings: GLIVEC should be taken with food and a large glass of water to minimize the risk of gastrointestinal disturbances. Severe fluid retention has occurred. It is recommended that patients be weighed regularly and undergo regular monitoring of complete blood counts and liver function tests. Caution should be exercised in patients with history of cardiac disease. Carefully monitor patients with cardiac impairment or risk factors for cardiac failure. Caution should be exercised in patients with severe renal disease. Monitor TSH levels in thyroidectomy patients undergoing levothyroxine replacement. GLIVEC should not be used during pregnancy unless clearly necessary. GLIVEC should not be used by breast-feeding mothers.

Interactions: Caution should be exercised with CYP3A4 inhibitors (eg, ketoconazole, clarithromycin), which may increase plasma concentrations of imatinib. Caution should be exercised with CYP3A4 inducers (eg, dexamethasone, rifampicin, phenytoin, carbamazepine, phenobarbital, St. John's Wort), which may decrease plasma concentrations of imatinib. Caution should be exercised with substrates of CYP3A4 (eg, triazolo-benzodiazepines, dihydropyridine calcium channel blockers, simvastatin, cyclosporin, pimozide), CYP2C9 (eg, warfarin) or CYP2D6 (eg, metoprolol). Caution should be exercised with concomitant use of paracetamol/acetaminophen.

Adverse reactions:

Very common (>1/10): Weight increase, neutropenia, thrombocytopenia, anemia, headache, nausea, diarrhea, vomiting, dyspepsia, abdominal pain, periorbital edema, dermatitis, eczema, rash, muscle spasm and cramps, musculoskeletal pain including myalgia, arthralgia, bone pain, fluid retention and edema, fatigue.

Common (>1/100, ≤1/10): Weight decrease, pancytopenia, febrile neutropenia, dizziness, paresthesia, taste disturbance, hypoesthesia, eyelid edema, lacrimation increase, conjunctival hemorrhage, conjunctivitis, dry eye, blurred vision, dyspnea, epistaxis, cough, flatulence, abdominal distension, gastroesophageal reflux, constipation, dry mouth, gastritis, GI bleeding, pruritus, facial edema, dry skin, erythema, alopecia, night sweats, photosensitivity reaction, joint swelling, anorexia, flushing, hemorrhage, weakness, pyrexia, anasarca, chills, rigors, increased hepatic enzymes, insomnia.

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

References: 1. National Comprehensive Cancer Network. Soft tissue sarcoma. Clinical Practice Guidelines in Oncology—V.1.2009. Accessed July 20, 2009. 2. 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. 3. National Cancer Institute. Phase III randomized study of adjuvant imatinib mesylate versus observation only in patients with completely resected localized gastrointestinal stromal tumor at intermediate- or high-risk of relapse. <http://www.cancer.gov/clinicaltrials/EORTC-62024>. Published January 24, 2005. Updated October 22, 2008. Accessed July 24, 2009. 4. Data on file. Novartis Pharmaceuticals Corporation. East Hanover, NJ. 5. Scandinavian Sarcoma Group and Sarcoma Group of the AIO, Germany. Short (12 months) versus long (36 months) duration of adjuvant treatment with the tyrosine kinase inhibitor imatinib mesylate of operable GIST with a high risk for recurrence: a randomized phase III study. Study protocol. http://www.ssg-organet/Documents/SSG%20XVIII_February2008.pdf. Accessed November 24, 2008.

RECURRENCE-FREE SURVIVAL IN RESECTED PRIMARY GIST*

A Phase III, randomized, double-blind study of adjuvant GLIVEC versus placebo for 12 months in patients following resection of primary GIST

STUDY OBJECTIVES

The primary end point of the study was recurrence-free survival (RFS), defined as the time from date of randomization to the date of recurrence or death from any cause.¹

STUDY DESIGN

A multicenter, double-blind, long-term, placebo-controlled, Phase III study (Z9001) was conducted to investigate the adjuvant use of GLIVEC in patients with completely resected GIST.¹

- 713 total patients were enrolled, and had^{1,2}:
 - A histologic diagnosis of primary GIST expressing KIT protein by immunohistochemistry
 - Tumor ≥ 3 cm in maximum dimension
 - Complete gross resection within 14 to 70 days prior to registration
 - Age range from 18 to 91 years
- Patients were randomized to 1 of 2 arms for 1 year^{1,2}:
 - GLIVEC at 400 mg/day (n=359)
 - Matching placebo (n=354)
- Patient randomization was stratified into 3 groups according to tumor size²:
 - ≥ 3 and < 6 cm
 - ≥ 6 and < 10 cm
 - ≥ 10 cm

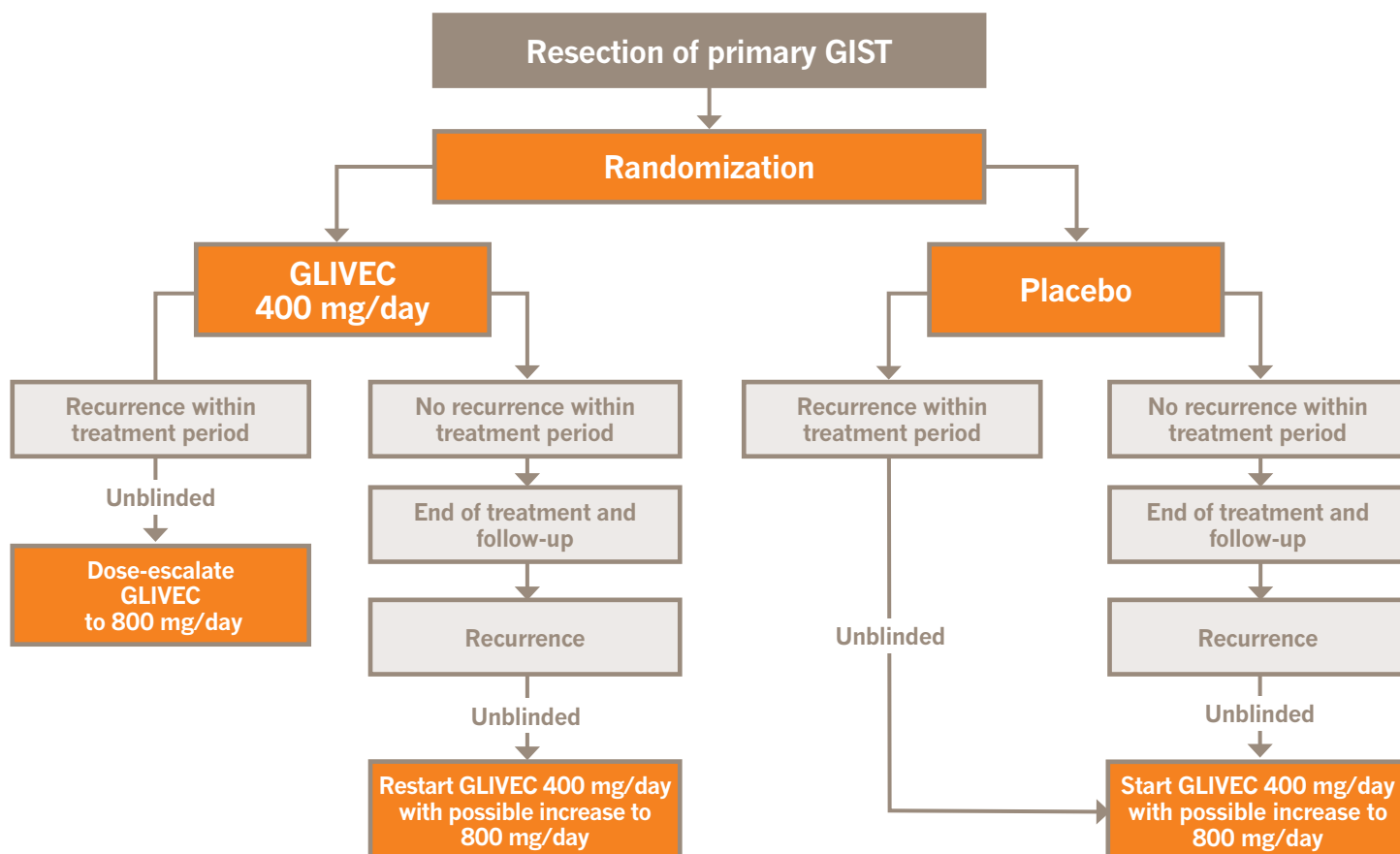
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Please see Important Safety Information on back page and enclosed Summary of Product Characteristics.

PHASE III STUDY DESIGN²



RESULTS

Efficacy

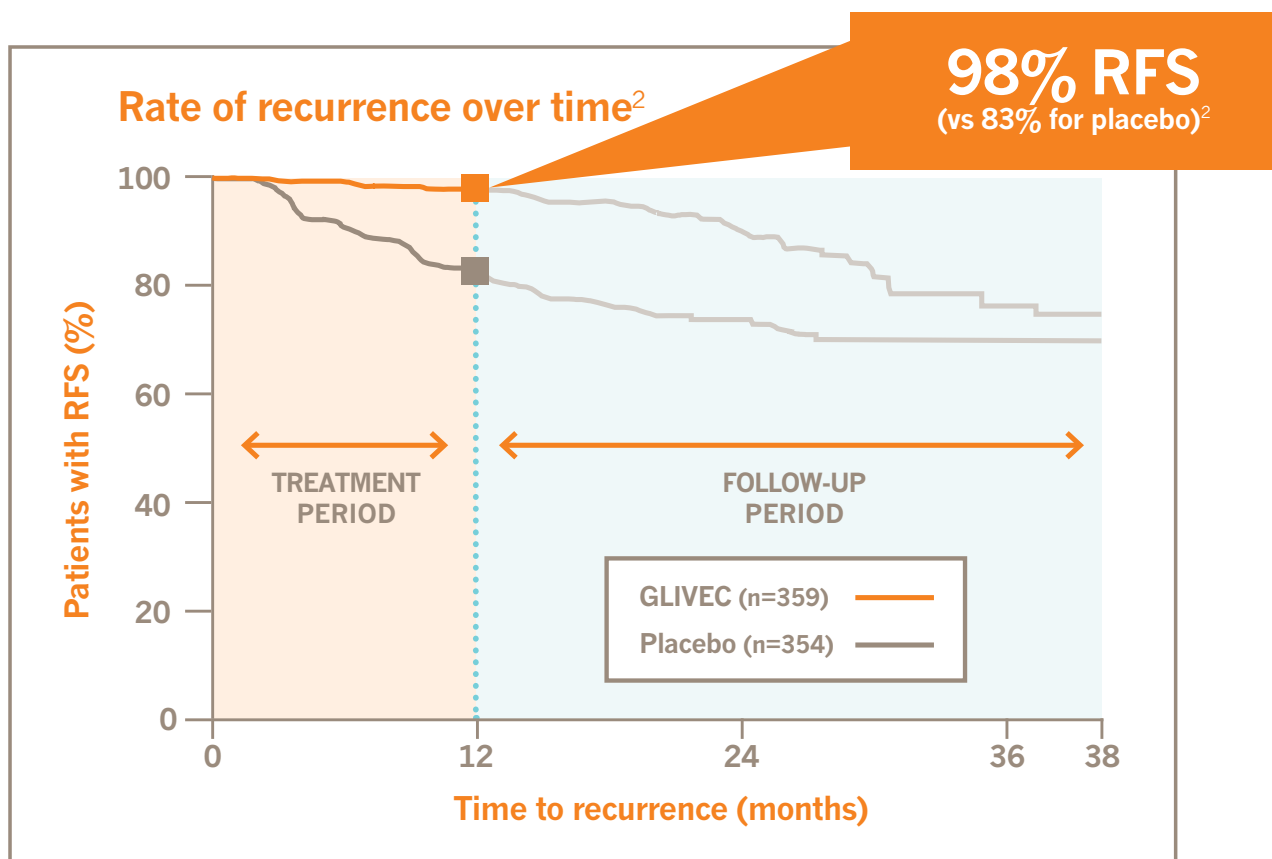
- Statistically significant clinical benefit with GLIVEC across all tumor size categories²
- After stopping therapy with GLIVEC, patients began to experience recurrence at a similar rate to placebo²

Safety

- The most frequently reported adverse reactions were diarrhea, fatigue, nausea, edema, decreased hemoglobin, rash, vomiting, and abdominal pain²
- 15% of patients (n=52) discontinued GLIVEC due to adverse reactions²
- No new adverse reactions that had not been previously reported in the unresectable and/or malignant metastatic setting²

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

GLIVEC Significantly Improved RFS¹



CONCLUSIONS

- **98%** of patients on GLIVEC achieved RFS at 1 year, versus 83% for those on placebo²
- Statistically significant clinical benefit with GLIVEC across all tumor size categories²
- Manage adverse reactions with supportive care whenever possible^{1,3}

Important Safety Information

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

References: 1. GLIVEC® (imatinib) Summary of Product Characteristics. Basel, Switzerland: Novartis Pharma AG; 2009. 2. 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. 3. Deininger MW, O'Brien SG, Ford JM, Druker BJ. Practical management of patients with chronic myeloid leukemia receiving imatinib. *J Clin Oncol*. 2003;21(8):1637-1647.

THE EORTC* 62024 TRIAL

A Phase III, randomized, open-label, multicenter study of adjuvant GLIVEC versus observation only for 24 months in patients following resection of primary GIST

STUDY OBJECTIVES¹

Primary end point

- Overall survival within the first 5 years in patients with intermediate- or high-risk GIST receiving either adjuvant treatment with GLIVEC for 24 months or no further therapy

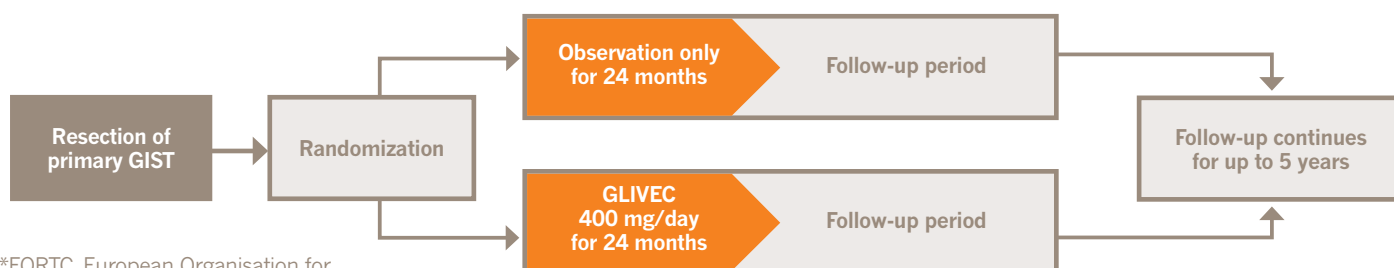
Secondary end points

- Relapse-free survival
- Relapse-free interval
- Time to imatinib failure
- Safety

STUDY DESIGN

An open-label, multicenter, multinational, randomized, Phase III study investigating the efficacy and safety of long-term adjuvant therapy with GLIVEC in patients with completely resected GIST who are estimated to be at an intermediate or high risk for disease recurrence.¹

- Patients are stratified by¹:
 - Risk recurrence (high vs intermediate)
 - Tumor site (gastric vs other)
 - Resection level (R0 vs R1)
- Patients were randomized to 1 of 2 arms for 2 years^{1,2}:
 - GLIVEC at 400 mg/day
 - Observation only (no antitumoral therapy)



*EORTC, European Organisation for Research and Treatment of Cancer.



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PATIENT POPULATION

An estimated 750 patients meeting the following criteria enrolled^{1*}:

- Histologically confirmed GIST
 - Localized disease
- One of the following categories of risk recurrence:
 - High risk, defined as meeting 1 of the following criteria:
 - ◆ Tumor >10 cm diameter
 - ◆ >10 mitoses per 50 high power field (HPF)
 - ◆ Tumor >5 cm diameter and mitotic count >5/50 HPF
 - Intermediate risk, defined as meeting 1 of the following criteria:
 - ◆ Tumor <5 cm diameter and mitotic count 6-10/50 HPF
 - ◆ Tumor 5 to 10 cm diameter and mitotic count <5/50 HPF
- A tumor that stained positive for KIT (CD117)
- Undergone complete resection at least 2 weeks but no more than 3 months prior to study entry
- No residual macroscopic disease after surgery
- No distant metastases
- Age ≥18 years

EXPECTED RESULTS

- 2010: interim results

FURTHER INFORMATION

For more information about this study, please visit www.eortc.be.

*A total of 900 patients were enrolled upon enrollment completion.

References: **1.** National Cancer Institute. Phase III randomized study of adjuvant imatinib mesylate versus observation only in patients with completely resected localized gastrointestinal stromal tumor at intermediate- or high-risk of relapse. <http://www.cancer.gov/clinicaltrials/EORTC-62024>. Published January 24, 2005. Updated October 22, 2008. Accessed July 24, 2009. **2.** 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(11):1656-1658.

THE SSG* XVIII/AIO† TRIAL¹

A Phase III, randomized, open-label, multicenter study of short (12-month) versus long (36-month) adjuvant treatment with GLIVEC in patients following resection for primary GIST

STUDY OBJECTIVES

Primary end point

- Recurrence-free survival in patients receiving adjuvant therapy with GLIVEC for either 12 or 36 months after primary resection of GIST

Secondary end points

- Overall survival
- GIST-specific survival
- Safety

STUDY DESIGN

An open-label, multicenter, multinational, prospective, randomized Phase III study investigating the efficacy and safety of adjuvant therapy with GLIVEC in patients with completely resected GIST who are estimated to be at a high risk for disease recurrence.

- Patients were randomized to 1 of 2 arms:
 - GLIVEC 400 mg/day for 12 months
 - GLIVEC 400 mg/day for 36 months



*SSG, Scandinavian Sarcoma Group. †AIO, German Working Group on Medical Oncology.



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PATIENT POPULATION

A total of 400 patients enrolled, meeting the following criteria:

- Histologically confirmed GIST
- GIST removed at open surgery
- Positive immunohistochemical documentation of KIT within 12 weeks of study entry
- High risk of tumor recurrence, defined as meeting 1 of the following criteria:
 - Tumor >10 cm diameter (with any mitotic count)
 - Any tumor size with mitotic count >10 mitoses per 50 high power field (HPF)
 - Tumor >5 cm diameter and mitotic count >5/50 HPF
 - Tumor rupture with spillage into the abdominal cavity at surgery
- Age ≥18 years

EXPECTED RESULTS

- 2010 (estimated): final analysis of the primary study end point performed after 100 recurrence events and all patients have completed the 15-month follow-up visit

FURTHER INFORMATION

For more information about this study, please visit www.ssg-org.net.

Reference: 1. Scandinavian Sarcoma Group and Sarcoma Group of the AIO, Germany. Short (12 months) versus long (36 months) duration of adjuvant treatment with the tyrosine kinase inhibitor imatinib mesylate of operable GIST with a high risk for recurrence: a randomized phase III study. Study protocol. http://www.ssg-org.net/Documents/SSG%20XVIII_February2008.pdf. Published February 2008. Accessed November 21, 2008.