Impact of Molecular Subtypes on Resistance to Therapy

Surgery in Metastatic GIST: Optimizing Outcomes

New Perspectives on Genetics of GIST Lacking KIT, PDGFRA Mutations
**Editorial Mission**
The GIST Cancer Journal is intended to serve as a comprehensive and authoritative resource of scientifically valid information for physicians and allied health care professionals regarding advances in the diagnosis and treatment of gastrointestinal stromal tumors. Editorial content focuses on the impact of translational research in oncology and gastroenterology relating specifically to GIST. As the official medical journal of the Life Raft Group, it also provides a forum for GIST patient advocacy. The GIST Cancer Journal is circulated to all medical oncologists and other selected medical professionals, and is available to members of the GIST community upon request.

**The Life Raft Group**
The mission of the Life Raft Group is to ensure the survival of gastrointestinal stromal tumor (GIST) patients through a comprehensive approach connecting individual patients’ needs, the worldwide community of GIST advocates and the global health and research environment. To do this, the group focuses on three key areas: research, patient support and education, and advocacy. (For additional information, please see Page 15.)

**Editor-in-Chief**
Jonathan C. Trent, MD, PhD
Co-Director, Musculoskeletal Center
Director, Sarcoma Medical Research Program
Professor of Medicine
University of Florida
Miami, Florida

**Medical Advisory Board**
Peter Reichenard, MD, PhD
Head of the Department of Interdisciplinary Oncology
Director of the Sarcoma Center Berlin-Brandenburg
Director, Cancer Center Berlin-Buch at HELIOS Klinikum
Berlin-Buch
Berlin, Germany

Matías Chacón, MD
Medical Oncologist
Instituto Médico Alexander Fleming
Buenos Aires, Argentina

Michael C. Heinrich, MD
Professor of Medicine (hematology and medical oncology)
Oregon Health and Science University School of Medicine
and the Portland Veterans Affairs Medical Center
Portland, Oregon

Andrew E. Rosenberg, MD
Professor of Pathology, Director of Bone and Soft Tissue Pathology
and Director of Surgical Pathology at the University of Miami
Miami, Florida

Yoon-Koo Kang, MD, PhD
Professor of Medicine
Department of Oncology, University of Ulsan College
of Medicine, Asan Medical Center,
Seoul, South Korea

**Nurse Advisory Board**
Monica Davey, RN BSN MEID MBA CCRP
Clinical Research Coordinator-Manager
Fox Chase Cancer Center
Philadelphia, Pennsylvania

**The Life Raft Group**
155 Route 46 West, Suite 202
Wayne, NJ 07470 USA
Phone 973-837-9092 ; Fax 973-837-9095
E-mail liferaft@liferaftgroup.org

**Publishing Staff**
Stu Chapman, Executive Editor and Publisher
Jenny Chapman, Assoc. Director, Editorial Services
Frank Iorio, Director of Advertising Sales and Business Development
Gloria Catalano, Production Director
Michael McClain, Design Director

**Editorial Office**
GUP Associates
160 Cabrini Blvd., Suite 95
New York, NY 10033
Tel: (516) 356-5006

Copyright 2014 GUP Associates.
All rights reserved. None of the contents may be reproduced in any form without the permission of the publisher.

**About the cover**
In this artist’s conceptual image of the abdomen, a gastrointestinal stromal tumor is depicted in a commonly found location near the small intestine as a bright, round mass near the center of the illustration. (Copyright ©, 2014, Cynthia Turner.)

---

**Table of Contents**

46 Clinical Imperatives in GIST: Impact of Molecular Subtypes on Resistance to Therapy
52 Surgery in Metastatic GIST in the TKI Era: Crucial Decisions to Optimize Outcomes
58 Current Concepts, New Perspectives on the Genetic Basis of GISTs Lacking KIT and PDGFRA Mutations
61 Nurse’s Corner: Clinical Trial Education Helps Patients Overcome Barriers to Enrollment
63 Life Raft Group Establishes First Pediatric GIST Virtual Tumor Board in Partnership with NIH

---

**Editor’s Memo**

ASCO 2014 and Beyond: How the Topics From Scientific Sessions Resonate in The GIST Cancer Journal

If you are like most of the 25,000 oncology professionals attending the 2014 annual meeting of the American Society of Clinical Oncology, you could only marvel at the most comprehensive agenda on cancer available worldwide. This is one of the most important oncology meetings of the year in a daunting venue designed to present cutting-edge scientific information and emerging trends. Despite the incredible breadth of the agenda, there were relevant presentations within the program devoted to gastrointestinal stromal tumor (GIST), topics that included sessions on the BRAF pathway in childhood cancer and DNA testing for KIT mutations, both areas of keen interest within the GIST community of investigators and practitioners.

Results from these sessions at ASCO and abstracts and posters on these and other GIST topics are excellent starting points as part of a road map to continuing progress in the identification of therapeutic targets and The unraveling of the pathophysiology in this disease. This second issue of The GIST Cancer Journal could not arrive on your desk at a better time. Fresh from ASCO, readers looking for amplification on topics covered at ASCO will find an in-depth discussion with our review articles on:

- New insights on the genetic basis of GISTs lacking KIT and PDGFRA mutations, with a special focus on SDH-deficient cases.
- Surgery in metastatic GIST in the TKI Era: an identification of crucial decisions to optimize outcomes.
- Clinical imperatives in GIST: assessing the impact of molecular correlates on resistance to therapy.

Like so much of the information presented at ASCO, the coverage of these topics in this issue may not always have translational impact to clinical practice but the findings from the literature are essential to our knowledge (continued on next page)
base and resonate with us as we build an expanding awareness of an array of factors impinging on clinical decision making. One area where there are implications for management concerns the use of surgery to prevent secondary resistance to imatinib. The review by Ricardo J. Gonzalez, MD, provides insights on special considerations when surgery is used as an adjuvant strategy. Two other GIST experts, Christopher L. Corless, MD, PhD, and Sosipatros A. Boikos, MD, contributed their observations as part of additional perspectives on a paradigm in their respective research areas.

We also welcome a new feature to the journal in this issue—the Nurse’s Corner with essential information for all oncology professionals engaged in the care of GIST patients. This highly practical section will help facilitate effective strategies; in this issue Jacquelyn C. Thomas, MPH, CHES, a Clinical Trial Educator, identifies barriers that need to be addressed as part of clinical trial enrollment for patients. Anyone needing additional information on this topic and related concerns and issues of patient advocacy should consult with the Life Raft Group and explore the broad spectrum of services offered by this organization.

Jonathan C. Trent, MD, PhD
Editor-in-Chief
Gleevec (imatinib mesylate) tablets are indicated for:
- Patients with KIT (CD117)-positive unresectable and/or metastatic gastrointestinal stromal tumors (GIST)
- Adjuvant treatment of adult patients following complete gross resection of KIT (CD117)-positive GIST

**Important Safety Information**

- **Gleevec** is often used in combination with edema, and occasionally, serious fluid retention. Severe fluid retention was reported in 9% to 13% of patients taking Gleevec for GIST. Patients who have undergone partial or complete resection of metastatic disease should be further studied for signs 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 in patients with GIST who received higher starting doses of Gleevec. Severe edema was observed in 182 patients (11.1%). If severe fluid retention occurs, manage with diuretic therapy and withhold Gleevec until the event has resolved, and then resume, depending on the initial severity of the event.

- Cytophenias have been reported. Complete blood counts should be performed weekly for the first month, bimonthly for the second month, and monthly thereafter as clinically indicated (eg, every 2 to 3 months). Dose reduction, treatment interruption, or in rare cases discontinuation of treatment may be required if severe cytopenias occur; see full prescribing information for dose adjustment recommendations.

- Severe congestive heart failure and left ventricular dysfunction have been reported. Most of the patients with reported cardiac events had 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 disease or history of renal failure should be monitored carefully, and any patient with signs or symptoms consistent with cardiac or renal toxicity should be evaluated immediately.

- Hepatotoxicity, occasionally severe, may occur. Cases of fatal liver failure and severe liver injury requiring liver transplants have been reported with both short-term and long-term use of Gleevec. Assess liver function before initiation of treatment, monthly during treatment, and as clinically indicated. 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. When Gleevec is given to patients with preexisting hepatitis, liver toxicity in the form of transient elevation and hyperbilirubinemia has been observed. Additionally, there have been reports of acute liver failure. Monitoring of hepatic function is recommended.

- In the Phase 3 unresectable or metastatic GIST studies, 13% of patients reported hemoptysis (NCI Grades 3/4) 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 and/or intratumoral bleeds. In other patient populations. In Study 1, comparing 12 months of Gleevec treatment with Gleevec treatment at the start of therapy, or as clinically indicated. 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.

- Bullous dermatologic reactions (eg, erythema multiforme and Stevens-Johnson syndrome) have also been reported. In some cases, the reaction recurred upon rechallenge. Several patients have been able to tolerate treatment with the reintroduction of Gleevec at a lower dose, with or without concurrent corticosteroids or antihistamines following resolution or improvement of the bullous reaction.

- Clinical cases of hypothyroidism have been reported in thyroidectomy patients undergoing levantinois 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 should be advised not to become pregnant while taking Gleevec and to avoid breastfeeding while taking Gleevec because of the potential for serious adverse reactions in nursing infants. Sexually active female patients should be advised not to become pregnant while taking Gleevec tablets and to avoid breastfeeding while taking Gleevec because of the potential hazard to the fetus.

- Growth retardation has been reported in children and preadolescents receiving Gleevec. The long-term effects of prolonged treatment with Gleevec and growth in children are unknown; therefore, monitoring of growth in children taking Gleevec is recommended.

- Cases of tumor lysis syndrome (TLS), including fatal cases, have been reported. Patients at risk for TLS should be managed with diuretics, alkalization, and hydration. High-dose rasburicase (500 mg/m²) or urate oxidase may be considered for the prevention of TLS. Two cases of TLS were reported in patients with metastatic GIST who received Gleevec. In Phase 3 unresectable or metastatic GIST trials (400 mg/day; 800 mg/day), the most frequently reported adverse reactions included abdominal pain (14%; 12%), edema (9%; 13%), fatigue (12%; 12%), nausea (5%; 8%), vomiting (9%; 8%), diarrhea (9%; 8%), rash (5%; 9%), myalgia (6%; 4%), anemia (9%; 5%), and anorexia (7%; 5%). The percentages listed represent NCI Grades 3 and above.

- In the adjuvant GIST study comparing 12 months of Gleevec to placebo treatment (Gleevec), 1.6% of patients experienced serious adverse reactions. Most serious adverse reactions included increase in liver enzymes (ALT) (3%; 0%), AST (2%; 0%), decreased neutrophil count (3%; 1%), and decrease in hemoglobin (1%; 0%) severe (NCI Grades 3/4) as reported above. Treatment-emergent adverse reactions associated with Gleevec included abdominal pain (3%; 1%), diarrhea (3%; 1%), rash (3%; 0%), fatigue (2%; 1%), vomiting (2%; 1%), decreased white blood cell count (1%; 0%), and periorbital edema (1%; 0%). The frequencies of these reported serious adverse reactions were similar to those reported in other studies 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 P-glycoprotein. The most commonly reported adverse reactions were similar in Study 1 comparing 12 vs 36 months of Gleevec treatment (12 mo; 36 mo), except for liver enzyme AST (2%; 3%), decreased neutrophil count (5%; 5%), decreased white blood cell count (2%; 3%), pain (1%; 3%), injection (2%; 3%), and blurring vision (1%; 1%), which were higher among patients receiving 36 months of adjuvant treatment with Gleevec than with Gleevec treatment.

- Patients with moderate renal impairment (CrCl=20-39 mL/min) should receive a 50% decrease in the recommended starting dose; future doses can be increased as tolerated. Doses greater than 600 mg are not recommended in patients with moderate renal impairment (CrCl=10-19 mL/min). For patients with severe 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 (NCI Grades 3 and above) adverse reactions were similar between the 2 treatment arms, except for edema and rash-related terms, which were reported more frequently during the Gleevec arm than the placebo arm (400 mg/day; 800 mg/day) (all grades) were edema (77%; 86%), fatigue (69%; 75%), nausea (58%; 65%), abdominal pain (57%; 59%), diarrhea (56%; 58%), rash and related terms (54%; 48%), vomiting (41%; 37%), and myalgia (38%; 30%), anemia (32%; 35%), anorexia (31%; 36%), and arthralgia (14%; 12%). Therapy with Gleevec was discontinued for adverse reactions in 5% of patients studied.

- In the adjuvant treatment of GIST studies, almost all Gleevec- and placebo-treated patients experienced adverse reactions at some time. In Study 1, comparing 12 months of Gleevec treatment with placebo (all grades), Gleevec was discontinued due to adverse reactions in 3% of patients receiving Gleevec and 2% of placebo patients. In Study 2, comparing 12 vs 36 months of Gleevec treatment (12 mo; 36 mo), therapy was discontinued due to adverse reactions in 7% (72%; 80%), peripheral edema (59%; 74%), muscle spasms (31%; 49%), decreased white blood cell count (35%; 47%), pain (26%; 46%), peripheral edema (33%; 41%), arthralgia (39%; 29%), and myalgia (9%; 15%), which were higher among patients receiving 36 months of adjuvant treatment with Gleevec. Adverse reactions listed represent the most frequently reported for Study 1 with the addition of adverse reactions with higher rates in Study 2.

- In the adjuvant GIST study comparing Gleevec vs placebo, drug was discontinued for adverse events in 17% of Gleevec- and 3% of placebo-treated patients. Edema, GI disturbances (nausea, vomiting, abdominal distension, and diarrhea), fatigue, low hematocrit, and rash were the most frequently reported adverse reactions at the time of discontinuation for drug. In the adjuvant GIST study comparing 12 vs 36 months of Gleevec treatment, drug was discontinued for adverse events in 8% of patients treated for 12 months and 14% of patients treated for 36 months.

- Supportive care may help reduce the severity of some mild to moderate adverse reactions. However, in some cases, either a dose reduction or interruption of treatment with Gleevec may be necessary.

- Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered at 400 mg twice a day. 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 instructed to take Gleevec exactly as prescribed and not to change the 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.*
If patients with **metastatic KIT+ GIST** progress on 400 mg/day and in the absence of severe adverse drug reactions,

**BUILD ON THE FOUNDATION OF GLEEVEC**

and increase the dose to 800 mg/day\(^1,2\)

---

**Treatment guidelines support dose escalation to 800 mg/day (given as 400 mg twice daily) if disease progression occurs on 400 mg/day and in the absence of severe adverse drug reactions\(^2\)**

- The GLEEVEC\(^\circledR\) (imatinib mesylate) metastatic trials included patients with unresectable and/or metastatic malignant KIT+ GIST randomized to receive 400 mg/day (N=818) or 800 mg/day (N=822)\(^1\)
- Approximately 1.5 to 2 years of progression-free survival and median overall survival (OS) of 4 years were achieved with GLEEVEC in clinical trials (median follow-up of 37.5 months in combined studies; N=1640)\(^1\)
  - Even in patients who crossed over to GLEEVEC 800 mg/day due to disease progression at 400 mg/day (n=347), median OS of 4 years was observed
- Adverse events were similar across both dosages in the metastatic trials, with the exception of edema and rash/related terms\(^1\)

---

**GLEEVEC\(^\circledR\) (imatinib mesylate) tablets are indicated for:**

- Patients with KIT (CD117)-positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST)

**Important Safety Information**

Serious adverse reactions may occur, including edema, cytopenias, severe congestive heart failure, left ventricular dysfunction, hepatotoxicity, hemorrhage. GI disorders, hypereosinophilic toxicity, dermatologic toxicities, hypothyroidism, toxicities from long-term use, fetal harm, and tumor lysis syndrome. Caution should be recommended when driving a car or operating machinery.

**References:** 1. GLEEVEC [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2013. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines\(^\circledR\)) for Soft Tissue Sarcoma V.1.2013. © National Comprehensive Cancer Network, Inc. 2013. All rights reserved. Accessed November 25, 2013. To view the most recent and complete version of the guideline, go online to www.nccn.org. NATIONAL COMPREHENSIVE CANCER NETWORK\(^\circledR\), NCCN\(^\circledR\), NCCN GUIDELINES\(^\circledR\), and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.
GLEEVEC (imatinib mesylate) tablets for oral use

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

1.1 Newly Diagnosed Philadelphia Positive Chronic Myeloid Leukemia (Ph+ CML)

Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia in chronic phase.

1.2 Ph+ CML in Blast Crisis (BC), Accelerated Phase (AP) or Chronic Phase (CP) After Interferon-alpha (IFN) Therapy

Patients with Philadelphia chromosome positive chronic myeloid leukemia in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.

1.3 Adult patients with Ph+ Acute Lymphoblastic Leukemia (ALL)

Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia.

1.4 Pediatric patients with Ph+ Acute Lymphoblastic Leukemia (ALL)

Pediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+-ALL) in combination with chemotherapy.

1.5 Myelodysplastic/Myeloproliferative Diseases (MDS/MPD)

Adult patients with myelodysplastic/myeloproliferative diseases associated with PDGFR (platelet-derived growth factor receptor) gene rearrangements.

1.6 Aggressive Systemic Mastocytosis (ASM)

Adult patients with aggressive systemic mastocytosis without the D816V c-Kit mutation or with c-Kit mutational status unknown.

1.7 Hypereosinophilic Syndrome (HES) and/or Chronic Eosinophilic Leukemia (CEL)

Urban patients with hypereosinophilic syndrome and/or chronic eosinophilic leukemia who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown.

1.8 Dermatofibrosarcoma Protubersans (DFSP)

Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protubersans.

1.9 Kit+ Gastrointestinal Stromal Tumors (GIST)

Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors.

1.10 Adjutant Treatment of GIST

Adjutant treatment of adult patients following complete gross resection of Kit (CD117) positive GIST.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Fluid Retention and Edema

Gleevec is often associated with edema and occasionally serious fluid retention [see Adverse Reactions (6.1)]. Patients should be weighed and monitored regularly for signs and symptoms of fluid retention. An unexpected rapid weight gain should be carefully investigated and appropriate treatment provided. The probability of edema was increased with higher Gleevec dose and age >65 years in the CML studies. Severe superficial edema was reported in 1.5% of newly diagnosed CML patients taking Gleevec, and in 2%-6% of other adult CML patients taking Gleevec. In addition, other severe fluid retention (e.g., pleural effusion, pericardial effusion, pulmonary edema, and ascites) reactions were reported in 1.3% of newly diagnosed CML patients taking Gleevec, and in 2%-6% of other adult CML patients taking Gleevec. Severe fluid retention was reported in 9% to 13.1% of patients taking Gleevec for GIST [see Adverse Reactions (6.11)].

5.2 Hematologic Toxicity

Treatment with Gleevec is associated with anemia, neutropenia, and thrombocytopenia. 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). In CML, the occurrence of these cytopenias is dependent on the stage of disease and is more frequent in patients with accelerated phase CML or blast crisis than in patients with chronic phase CML. In pediatric CML patients the most frequent toxicities observed were Grade 3 or 4 cytopenias including neutropenia, thrombocytopenia and anemia. These generally occur within the first several months of therapy [see Dosage and Administration (2.12) in the full prescribing information].

5.3 Severe Congestive Heart Failure and Left Ventricular Dysfunction

Severe congestive heart failure and left ventricular dysfunction have been reported in patients taking Gleevec. Most of the patients with reported cardiac reactions have had other co-morbidities and risk factors, including advanced age and previous medical history of cardiac disease. In an international randomized phase 3 study in 1,106 patients with newly diagnosed Ph+ CML in chronic phase, severe cardiac failure and left ventricular dysfunction were observed in 0.7% of patients taking Gleevec compared to 0.9% of patients taking IFN + Ara-C. Patients with cardiac disease or risk factors for cardiac or history of renal failure should be monitored carefully and any patient with signs or symptoms consistent with cardiac or renal failure should be evaluated and treated.

5.4 Hepatotoxicity

Hepatotoxicity, occasionally severe, may occur with Gleevec [see Adverse Reactions (6.3)]. Cases of fatal liver failure and severe liver injury requiring liver transplants have been reported with both short-term and long-term use of Gleevec. Liver function (transaminases, bilirubin, and alkaline phosphatase) should be monitored before initiation of treatment and monthly, or as clinically indicated. Laboratory abnormalities should be managed with Gleevec interruption and/or dose reduction [see Dosage and Administration (2.12) in the full prescribing information]. When Gleevec is combined with chemotherapy, liver toxicity in the form of transaminase elevation and hyperbilirubinemia has been observed. Additionally, there have been reports of acute liver failure. Monitoring of hepatic function is recommended.

5.5 Hemorrhage

In the newly diagnosed CML trial, 1.8% of patients had Grade 3/4 hemorrhage. In the Phase 3 unselectable or metastatic GIST studies 211 patients (12.9%) reported Grade 3/4 hemorrhage at any site. In the Phase 2 unselectable or metastatic GIST study 7 patients (5%) had a total of 8 CTC Grade 3/4 hemorrhages: gastrointestinal (GI) (3 patients), intratumoral (3 patients) or both (1 patient). Gastrointestinal tumor sites may have been the source of GI hemorrhages. Patients should therefore be monitored for gastrointestinal symptoms at the start of therapy.

5.6 Gastrointestinal Disorders

Gleevec is sometimes associated with GI irritation. Gleevec should be taken with or after a full glass of water to minimize this problem. There have been rare reports, including fatalities, of gastrointestinal perforation.

5.7 Hypereosinophilic Cardiac Toxicity

In patients with hypereosinophilic syndrome with occult infiltration of HES cells within the myocardium, cases of cardiogenic shock/left ventricular dysfunction have been associated with HES cell degranulation upon the initiation of Gleevec therapy. The condition was reported to be reversible with the administration of systemic steroids, circulatory support measures and temporarily withholding Gleevec. Myelodysplastic/myeloproliferative disease and systemic mastocytosis may be associated with high eosinophil levels. Performance of an echocardiogram and determination of serum troponin should therefore be considered in patients with HES/CEL, and in patients with MDS/MPD or ASM associated with high eosinophil levels. If either is abnormal, the prophylactic use of systemic steroids (1-2 mg/kg) for one to two weeks concomitantly with Gleevec should be considered at the initiation of therapy.

5.8 Dermatologic Toxicities

Bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome, have been reported with use of Gleevec. In some cases of bullous dermatologic reactions, including erythema multiforme and Stevens-Johnson syndrome reported during postmarketing surveillance, a recurrent dermatologic reaction was observed upon re-challenge. Several foreign post-marketing reports have described cases in which patients tolerated the reintroduction of Gleevec therapy after resolution or improvement of the bullous reaction. In these instances, Gleevec was resumed at a dose lower than that at which the reaction occurred and some patients also received concomitant treatment with corticosteroids or antihistamines.

5.9 Hypothyroidism

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.

5.10 Toxicities from Long-Term Use

It is important to consider potential toxicities suggested by animal studies, specifically, liver, kidney, and cardiac toxicity and immunosuppression. Severe liver toxicity was observed in dogs treated for 2 weeks, with elevated liver enzymes, hepatic necrosis, bile duct necrosis, and bile duct hyperplasia. Renal toxicity was observed in monkeys treated for 2 weeks, with focal mineralization and dilation of the renal tubules and tubular nephrosis. Increased BUN and creatinine were observed in several of these animals. An increased rate of opportunistic infections was observed with chronic imatinib treatment in laboratory animal studies. In a 39-week monkey study, treatment with imatinib resulted in worsening of normally suppressed malarial infections in these animals. Lymphopenia was observed in animals (as in humans). Additional long-term toxicities were identified in a 2-year rat study. Histopathological examination of the treated rats that died on study revealed cardiomyopathy (both sexes), chronic progressive...
nephropathy (females) and preputial gland papilloma as principal causes of death or reasons for sacrifice. Non-neoplastic lesions seen in this 2-year study which were not identified in earlier preclinical studies were the cardiovascular system, pancreas, endocrine organs and teeth. The most important changes included cardiac hypertrophy and dilatation, leading to signs of cardiac insufficiency in some animals.

5.11 Embryo-fetal Toxicity
Gleevec can cause fetal harm when administered to a pregnant woman. Imatinib mesylate was teratogenic in rats when administered during organogenesis at doses approximately equal to the maximum human dose of 800 mg/day based on body surface area. Significant post-implantation loss was seen in female rats administered imatinib mesylate at doses approximately one-half the maximum human dose of 800 mg/day based on body surface area. Sexually active female patients of reproductive potential taking Gleevec should use highly effective contraception. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [see Use in Specific Populations (8.1)].

5.12 Children and Adolescents
Growth retardation has been reported in children and pre-adolescents receiving Gleevec. The long term effects of prolonged treatment with Gleevec on growth in children are unknown. Therefore, close monitoring of growth in children under Gleevec treatment is recommended [see Adverse Reactions (6.13)].

5.13 Tumor Lysis Syndrome
Cases of Tumor Lysis Syndrome (TLS), including fatal cases, have been reported in patients with CML, GIST, ALL and eosinophilic leukemia receiving Gleevec. The patients at risk of TLS are those with tumors having a high proliferative rate or high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken. Due to possible occurrence of TLS, correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiation of Gleevec.

5.14 Driving and Using Machinery
Reports of motor vehicle accidents have been received in patients receiving Gleevec. While most of these reports are not suspected to be caused by Gleevec, patients should be advised that they may experience undesirable effects such as dizziness, blurred vision or somnolence during treatment with Gleevec. Therefore, caution should be recommended when driving a car or operating machinery.

6 ADVERSE REACTIONS
Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates on other clinical trials and may not reflect the rates observed in clinical practice.

6.1 Chronic Myeloid Leukemia
The majority of Gleevec-treated patients experienced adverse reactions at some time. Most reactions were of mild-to-moderate grade, but drug was discontinued for drug-related adverse reactions in 2.4% of newly diagnosed patients, 4% of patients in chronic phase after failure of interferon-alpha therapy, 4% in accelerated phase and 5% in blast crisis.

The most frequently reported drug-related adverse reactions were edema, nausea and vomiting, muscular cramps, musculoskeletal pain, diarrhea and rash (Table 2 for newly diagnosed CML, Table 3 for other CML patients). Edema was most frequently periorbital or in lower limbs and was managed with diuretics, other supportive measures, or by reducing the dose of Gleevec [see Dosage and Administration (2.12) in the full prescribing information]. The frequency of severe superficial edema was 1.5%-6%.

A variety of adverse reactions represent local or general fluid retention including pleural effusion, ascites, pulmonary edema and rapid weight gain with or without superficial edema. These reactions appear to be dose related, were more common in the blast crisis and accelerated phase studies (where the dose was 600 mg/day), and are more common in the elderly. These reactions were usually managed by interrupting Gleevec treatment and using diuretics or other appropriate supportive care measures. A few of these reactions may be serious or life threatening, and one patient with blast crisis died with pleural effusion, congestive heart failure, and renal failure.

Adverse reactions, regardless of relationship to study drug, that were reported in at least 10% of the Gleevec treated patients are shown in Tables 2 and 3.

### Table 2 Adverse Reactions Regardless of Relationship to Study Drug Reported in Newly Diagnosed CML Clinical Trial (≥10% of Patients Receiving Gleevec)[1]

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Gleevec (N=551)</th>
<th>IFN+ Ara-C (N=533)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>CTC Grades 3/4</td>
</tr>
<tr>
<td><strong>Fluid Retention</strong></td>
<td>61.7%</td>
<td>11.1%</td>
</tr>
<tr>
<td><strong>Superfical Edema</strong></td>
<td>59.9%</td>
<td>9.6%</td>
</tr>
<tr>
<td><strong>Other Fluid Retention Reactions</strong></td>
<td>6.9%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Nausea</td>
<td>49.5%</td>
<td>61.5%</td>
</tr>
<tr>
<td>Muscle Cramps</td>
<td>49.2%</td>
<td>11.8%</td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
<td>47.0%</td>
<td>44.8%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45.4%</td>
<td>43.3%</td>
</tr>
<tr>
<td>Rash and Related Terms</td>
<td>40.1%</td>
<td>26.1%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>38.8%</td>
<td>67.0%</td>
</tr>
<tr>
<td>Headache</td>
<td>37.0%</td>
<td>43.3%</td>
</tr>
<tr>
<td>Joint Pain</td>
<td>31.4%</td>
<td>38.1%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>36.5%</td>
<td>25.9%</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>30.5%</td>
<td>8.8%</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>28.9%</td>
<td>21.2%</td>
</tr>
<tr>
<td>- GI Hemorrhage</td>
<td>1.6%</td>
<td>1.1%</td>
</tr>
<tr>
<td>- CNS Hemorrhage</td>
<td>0.2%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>24.1%</td>
<td>38.8%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22.5%</td>
<td>27.8%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>18.9%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Cough</td>
<td>20.0%</td>
<td>23.1%</td>
</tr>
<tr>
<td>Pharyngolaryngeal Pain</td>
<td>18.1%</td>
<td>11.4%</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>21.2%</td>
<td>8.4%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>19.4%</td>
<td>24.4%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>17.5%</td>
<td>42.6%</td>
</tr>
<tr>
<td>Weight Increased</td>
<td>15.6%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>14.7%</td>
<td>18.6%</td>
</tr>
<tr>
<td>Depression</td>
<td>14.9%</td>
<td>35.8%</td>
</tr>
<tr>
<td>Influenza</td>
<td>13.8%</td>
<td>6.2%</td>
</tr>
<tr>
<td>Bone Pain</td>
<td>11.3%</td>
<td>15.6%</td>
</tr>
<tr>
<td>Constipation</td>
<td>11.4%</td>
<td>14.4%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>11.4%</td>
<td>6.0%</td>
</tr>
</tbody>
</table>

1. All adverse reactions occurring in ≥10% of Gleevec treated patients are listed regardless of suspected relationship to treatment.

2. Other fluid retention reactions include pleural effusion, ascites, pulmonary edema, pericardial effusion, anasarca, edema aggravated, and fluid retention not otherwise specified.

### Table 3 Adverse Reactions Regardless of Relationship to Study Drug Reported in Other CML Clinical Trials (≥10% of All Patients in any Trial)[1]

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>All Grades</th>
<th>Grade 3/4</th>
<th>All Grades</th>
<th>Grade 3/4</th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloid Blast Crisis (n=260)</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluid Retention</td>
<td>72.9%</td>
<td>76%</td>
<td>69%</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Superfical Edema</td>
<td>66.6%</td>
<td>74%</td>
<td>67%</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Other Fluid Retention Reactions</td>
<td>22.6%</td>
<td>26%</td>
<td>62%</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>71.5%</td>
<td>73%</td>
<td>63%</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle Cramps</td>
<td>28.1%</td>
<td>47%</td>
<td>62%</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>54.4%</td>
<td>58%</td>
<td>36%</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>43.4%</td>
<td>57%</td>
<td>48%</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>53.1%</td>
<td>49%</td>
<td>30%</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- CNS Hemorrhage</td>
<td>9.7%</td>
<td>3%</td>
<td>2%</td>
<td>1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- GI Hemorrhage</td>
<td>8.4%</td>
<td>6%</td>
<td>5%</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
<td>42.9%</td>
<td>49%</td>
<td>38%</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>30.4%</td>
<td>46%</td>
<td>48%</td>
<td>1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin Rash</td>
<td>36.5%</td>
<td>47%</td>
<td>47%</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>41.7%</td>
<td>41%</td>
<td>21%</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>25.5%</td>
<td>34%</td>
<td>40%</td>
<td>1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(continued)
### Table 3 Adverse Reactions Regardless of Relationship to Study Drug Reported in Other CML Clinical Trials (≥10% of All Patients in Any Trial)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Grades</th>
<th>Grade 3/4</th>
<th>Grade 3/4</th>
<th>Grade 3/4</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>27</td>
<td>5</td>
<td>32</td>
<td>2</td>
<td>36</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>30</td>
<td>6</td>
<td>33</td>
<td>4</td>
<td>32</td>
</tr>
<tr>
<td>Weight Increased</td>
<td>5</td>
<td>1</td>
<td>17</td>
<td>5</td>
<td>32</td>
</tr>
<tr>
<td>Cough</td>
<td>14</td>
<td>0.8</td>
<td>27</td>
<td>0.9</td>
<td>20</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12</td>
<td>0</td>
<td>22</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>Malaise</td>
<td>9</td>
<td>0</td>
<td>24</td>
<td>2</td>
<td>27</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>10</td>
<td>0</td>
<td>17</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>Asthenia</td>
<td>18</td>
<td>5</td>
<td>21</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>15</td>
<td>4</td>
<td>21</td>
<td>7</td>
<td>12</td>
</tr>
</tbody>
</table>

### Table 4 Lab Abnormalities in Newly Diagnosed CML Clinical Trial

<table>
<thead>
<tr>
<th>CTC Grades</th>
<th>Gleevec N=551</th>
<th>IFN+Ara-C N=533</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3</td>
<td>Grade 4</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Hematology Parameters*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Neutropenia*</td>
<td>13.1</td>
<td>3.6</td>
</tr>
<tr>
<td>- Thrombocytopenia*</td>
<td>8.5</td>
<td>0.4</td>
</tr>
<tr>
<td>- Anemia</td>
<td>3.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Biochemistry Parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Elevated Creatinine</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>- Elevated Bilirubin</td>
<td>0.9</td>
<td>0.2</td>
</tr>
<tr>
<td>- Elevated Alkaline Phosphatase</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>- Elevated SGOT/SGPT</td>
<td>4.7</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*p<0.001 (difference in Grade 3 plus 4 abnormalities between the two treatment groups)
Table 6 Adverse Reactions Reported More Frequently in Patients Treated with Study Drug (>5%) or in Cycles with Study Drug (>1%)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Per Patient Incidence With Gleevec</th>
<th>Per Patient Incidence With Gleevec*</th>
<th>Per Patient Incidence With Gleevec**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ph+ ALL</td>
<td>No Gleevec</td>
<td>Ph+ ALL</td>
</tr>
<tr>
<td>Grade 3 and 4 Adverse Events</td>
<td>N = 92</td>
<td>N = 65</td>
<td>N = 778</td>
</tr>
<tr>
<td>Nausea and/or Vomiting</td>
<td>15 (16%)</td>
<td>6 (9%)</td>
<td>28 (4%)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>31 (34%)</td>
<td>16 (25%)</td>
<td>72 (9%)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>7 (8%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>6 (7%)</td>
<td>0</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>8 (9%)</td>
<td>2 (3%)</td>
<td>9 (1%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>10 (11%)</td>
<td>3 (5%)</td>
<td>19 (2%)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>11 (12%)</td>
<td>6 (9%)</td>
<td>17 (2%)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>5 (5%)</td>
<td>3 (5%)</td>
<td>12 (2%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>5 (5%)</td>
<td>0</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>8 (9%)</td>
<td>12 (2%)</td>
<td>23 (3%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (5%)</td>
<td>4 (5%)</td>
<td>12 (2%)</td>
</tr>
<tr>
<td>Rash / Skin Disorder</td>
<td>3 (3%)</td>
<td>0</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>49 (53%)</td>
<td>32 (49%)</td>
<td>131 (17%)</td>
</tr>
</tbody>
</table>

Myelosuppression

<table>
<thead>
<tr>
<th>Hematological Parameters</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia (&lt;750/µL)</td>
<td>92 (100%)</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;75,000/µL)</td>
<td>90 (92%)</td>
</tr>
</tbody>
</table>

* Defined as the frequency of AEs per patient per treatment cycles that included Gleevec (includes patients with Ph+ ALL that received cycles with Gleevec).

** Defined as the frequency of AEs per patient per treatment cycles that did not include Gleevec (includes patients with Ph+ALL that received cycles without Gleevec as well as all patients with Ph- ALL who did not receive Gleevec in any treatment cycle).

6.5 Adverse Reactions in Other Subpopulations

In older patients (≥65 years old), with the exception of edema, where it was more frequent, there was no evidence of an increase in the incidence or severity of adverse reactions. In women there was an increase in the frequency of neutropenia, as well as Grade 1/2 superficial edema, headache, nausea, rigors, vomiting, rash, and fatigue. No differences were seen that were related to race but the subsets were too small for proper evaluation.

6.6 Acute Lymphoblastic Leukemia

The adverse reactions were similar for Ph+ ALL as for Ph+ CML. The most frequently reported drug-related adverse reactions reported in the Ph+ ALL studies were mild nausea and vomiting, diarrhea, myalgia, muscle cramps and rash, which were easily manageable. Superficial edema was a common finding in all studies and were described primarily as periorbital or lower limb edemas. These edemas were rarely severe and may be managed with diuretics, other supportive measures, or in some patients by reducing the dose of Gleevec.

6.7 Myelodysplastic/Myeloproliferative Diseases

Adverse reactions, regardless of relationship to study drug, that were reported in at least 10% of the patients treated with Gleevec for MDS/MPD in the phase 2 study, are shown in Table 7.

6.8 Aggressive Systemic Mastocytosis

All ASM patients experienced at least one adverse reaction at some time. The most frequently reported adverse reactions were diarrhea, nausea, ascites, muscle cramps, dyspnea, fatigue, peripheral edema, anemia, pruritus, rash and lower respiratory tract infection. None of the 5 patients in the phase 2 study with ASM discontinued Gleevec due to drug-related adverse reactions or abnormal laboratory values.

6.9 Hypereosinophilic Syndrome and Chronic Eosinophilic Leukemia

The safety profile in the HES/CEL patient population does not appear to be different from the safety profile of Gleevec observed in other hematologic malignancy populations, such as Ph+ CML. All patients experienced at least one adverse reaction, the most common being gastrointestinal, cutaneous and musculoskeletal disorders. Hematological abnormalities were also frequent, with instances of CTC Grade 3 leukopenia, neutropenia, lymphopenia, and anemia.

6.10 Dermatofibrosarcoma Protubersans

Adverse reactions, regardless of relationship to study drug, that were reported in at least 10% of the 12 patients treated with Gleevec for DFSP in the phase 2 study are shown in Table 8.

Table 8 Adverse Reactions Regardless of Relationship to Study Drug Reported in DFSP Patients in the Phase 2 Study (≥10% All Patients) All Grades

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=12 n (%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Periorbital Edema</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Face Edema</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>Edema Periipheral</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>Eye Edema</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Lacrimation Increased</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Dyspnea Exertional</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>2 (16.7)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2 (16.7)</td>
</tr>
</tbody>
</table>

Clinically relevant or severe laboratory abnormalities in the 12 patients treated with Gleevec for DFSP in the phase 2 study are presented in Table 9.

Table 9 Laboratory Abnormalities Reported in DFSP Patients in the Phase 2 Study

<table>
<thead>
<tr>
<th>CTC Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology Parameters</td>
<td>17%</td>
<td>0%</td>
</tr>
<tr>
<td>- Anemia</td>
<td>17%</td>
<td>0%</td>
</tr>
<tr>
<td>- Neutropenia</td>
<td>0%</td>
<td>8%</td>
</tr>
<tr>
<td>Biochemistry Parameters</td>
<td>- Elevated Creatinine</td>
<td>0%</td>
</tr>
</tbody>
</table>

1CTC Grades: neutropenia (Grade 3 ≥0.5-1.0 x 10⁹/L, Grade 4 ≥0.5 x 10⁹/L), thrombocytopenia (Grade 3 ≥10 - 50 x 10⁹/L, Grade 4 ≥10 x 10⁹/L), anemia (Grade 3 ≥65-80 g/L, Grade 4 ≥65 g/L), elevated creatinine (Grade 3 >3-6 x upper limit normal range [ULN], Grade 4 ≥6 x ULN).

6.11 Gastrointestinal Stromal Tumors

In the Phase 3 trials the majority of Gleevec-treated patients experienced adverse reactions at some time. The most frequently reported adverse reactions were edema, fatigue, nausea, abdominal pain, diarrhea, rash, vomiting, myalgia, anemia, and anorexia. Drug was discontinued for adverse reactions in a total of 89 patients (5.4%). Superficial edema, most frequently periorbital or lower extremity edema was managed with diuretics, other supportive measures, or by reducing the dose of Gleevec [see Dosage and Administration (2.12) in the full prescribing information]. Severe (CTC Grade 3/4) edema was observed in 182 patients (11.1%).

Adverse reactions, regardless of relationship to study drug, that were reported in at least 10% of the patients treated with Gleevec are shown in Table 10.

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, which was reported more frequently in the 800 mg group.
### Table 10 Number (%) of Patients with Adverse Reactions Regardless of Relationship to Study Drug where Frequency is ≥10% in any One Group (Full Analysis Set) in the Phase 3 Unresectable and/or Malignant Metastatic GIST Clinical Trials

<table>
<thead>
<tr>
<th>Imatinib 400 mg</th>
<th>Imatinib 800 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=818</td>
<td>N=822</td>
</tr>
<tr>
<td><strong>Reported or Specified Term</strong></td>
<td><strong>All Grades</strong></td>
</tr>
<tr>
<td>Edema</td>
<td>76.7</td>
</tr>
<tr>
<td>Fatigue/lethargy, malaise, asthenia</td>
<td>69.3</td>
</tr>
<tr>
<td>Nausea</td>
<td>58.1</td>
</tr>
<tr>
<td>Abdominal pain/cramping</td>
<td>57.2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>56.2</td>
</tr>
<tr>
<td>Rash/desquamation</td>
<td>38.1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>37.4</td>
</tr>
<tr>
<td>Myalgia</td>
<td>32.6</td>
</tr>
<tr>
<td>Anemia</td>
<td>32.0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>31.1</td>
</tr>
<tr>
<td>Other G1 toxicity</td>
<td>25.2</td>
</tr>
<tr>
<td>Headache</td>
<td>22.0</td>
</tr>
<tr>
<td>Other pain (excluding tumor related pain)</td>
<td>20.4</td>
</tr>
<tr>
<td>Other dermatological/skin toxicity</td>
<td>17.6</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>17.0</td>
</tr>
<tr>
<td>Other constitutional symptoms</td>
<td>16.7</td>
</tr>
<tr>
<td>Cough</td>
<td>16.1</td>
</tr>
<tr>
<td>Infection (without neutropenia)</td>
<td>15.5</td>
</tr>
<tr>
<td>Pruritus</td>
<td>15.4</td>
</tr>
<tr>
<td>Other neurological toxicity</td>
<td>15.0</td>
</tr>
<tr>
<td>Constipation</td>
<td>14.8</td>
</tr>
<tr>
<td>Other renal/genitourinary toxicity</td>
<td>14.2</td>
</tr>
<tr>
<td>Arthralgia (joint pain)</td>
<td>13.6</td>
</tr>
<tr>
<td>Dyspnea (shortness of breath)</td>
<td>13.6</td>
</tr>
<tr>
<td>Fever in absence of neutropenia (ANC&lt;1.0 x 10^9/L)</td>
<td>13.2</td>
</tr>
<tr>
<td>Sweating</td>
<td>12.7</td>
</tr>
<tr>
<td>Other hemorrhage</td>
<td>12.3</td>
</tr>
<tr>
<td>Weight gain</td>
<td>12.0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>11.9</td>
</tr>
<tr>
<td>Dyspepsia/heartburn</td>
<td>11.5</td>
</tr>
<tr>
<td>Neutropenia/granulocytopenia</td>
<td>11.5</td>
</tr>
<tr>
<td>Rigors/chills</td>
<td>11.0</td>
</tr>
<tr>
<td>Dizziness/lightheadedness</td>
<td>11.0</td>
</tr>
<tr>
<td>Creatine increase</td>
<td>10.8</td>
</tr>
<tr>
<td>Flatulence</td>
<td>10.0</td>
</tr>
<tr>
<td>Stomatitis/pharyngitis (oral/pharyngeal mucositis)</td>
<td>9.2</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>6.0</td>
</tr>
</tbody>
</table>

Clinically relevant or severe abnormalities of routine hematologic or biochemistry laboratory values were not reported or evaluated in the Phase 3 GIST trials. Severe abnormal laboratory values reported in the Phase 2 GIST trial are presented in Table 11.

### Table 11 Laboratory Abnormalities in the Phase 2 Unresectable and/or Malignant Metastatic GIST Trial

#### 400 mg (n=733)
- **CTC Grades**
  - Grade 3: 65-80 g/L, Grade 4 >80 g/L
  - Elevated Creatinine: 0, 3, 0
  - Reduced Albumin: 3, 0, 4
  - Elevated Bilirubin: 1, 1, 0
  - Elevated Alkaline Phosphatase: 0, 0, 3
  - Elevated SGOT (AST): 4, 0, 3
  - Elevated SGPT (ALT): 6, 0, 7

#### 600 mg (n=745)
- **CTC Grades**
  - Grade 3: 65-80 g/L, Grade 4 >80 g/L
  - Elevated Creatinine: 0, 3, 0
  - Reduced Albumin: 3, 0, 4
  - Elevated Bilirubin: 1, 1, 0
  - Elevated Alkaline Phosphatase: 0, 0, 3
  - Elevated SGOT (AST): 4, 0, 3
  - Elevated SGPT (ALT): 6, 0, 7

**Adjuvant Treatment of GIST**

In Study 1, the majority of both Gleevec and placebo treated patients experienced at least one adverse reaction at some time. The most frequently reported adverse reactions were similar to those reported in other clinical studies in other patient populations and include diarrhea, fatigue, nausea, edema, decreased hemoglobin, rash, vomiting, and abdominal pain. No new adverse reactions were reported in the adjuvant GIST treatment setting that had not been previously reported in other patient populations including patients with unresectable and/or malignant metastatic GIST. Drug was discontinued for adverse reactions in 57 patients (17%) and 11 patients (3%) of the Gleevec and placebo treated patients respectively. Edema, gastrointestinal disturbances (nausea, vomiting, abdominal distention and diarrhea), fatigue, low hemoglobin, and rash were the most frequently reported adverse reactions at the time of discontinuation.

In Study 2, discontinuation of therapy due to adverse reactions occurred in 15 patients (8%) and 27 patients (14%) of the Gleevec 12-month and 36-month treatment arms, respectively. As in previous trials the most common adverse reactions were diarrhea, fatigue, nausea, edema, decreased hemoglobin, rash, vomiting, and abdominal pain.

Adverse reactions, regardless of relationship to study drug, that were reported in at least 5% of the patients treated with Gleevec are shown in Table 12 (Study 1) and Table 13 (Study 2). There were no deaths attributable to Gleevec treatment in either trial.

### Table 12: Adverse Reactions Regardless of Relationship to Study Drug Reported in Study 1 (≥5% of Gleevec Treated Patients)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>All CTC Grades</th>
<th>CTC Grade 3 and above</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diarrhea</strong></td>
<td>59.3</td>
<td>29.3</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>57.0</td>
<td>40.9</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>53.1</td>
<td>27.8</td>
</tr>
<tr>
<td><strong>Periobital Edema</strong></td>
<td>47.2</td>
<td>14.5</td>
</tr>
<tr>
<td><strong>Hemoglobin Decreased</strong></td>
<td>46.9</td>
<td>27.0</td>
</tr>
<tr>
<td><strong>Peripheral Edema</strong></td>
<td>26.7</td>
<td>14.8</td>
</tr>
<tr>
<td><strong>Rash (Exfoliative)</strong></td>
<td>26.1</td>
<td>12.8</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>25.5</td>
<td>13.9</td>
</tr>
<tr>
<td><strong>Abdominal Pain</strong></td>
<td>21.1</td>
<td>22.3</td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>19.3</td>
<td>20.3</td>
</tr>
<tr>
<td><strong>Dyspepsia</strong></td>
<td>17.2</td>
<td>13.0</td>
</tr>
<tr>
<td><strong>Anorexia</strong></td>
<td>16.9</td>
<td>8.7</td>
</tr>
<tr>
<td><strong>Weight Increased</strong></td>
<td>16.9</td>
<td>11.6</td>
</tr>
<tr>
<td><strong>Lever enzymes (ALT)</strong></td>
<td>16.6</td>
<td>13.0</td>
</tr>
</tbody>
</table>

#### Hematology Parameters
- **Anemia**
  - Grade 3: 3, 0, 8, 1
- **Thrombocytopenia**
  - Grade 3: 0, 0, 1, 0
- **Neutropenia**
  - Grade 3: 7, 3, 8, 3

(continued)
### Table 12: Adverse Reactions Regardless of Relationship to Study Drug
#### Reported in Study 1 (≥5% of Gleevec Treated Patients)\(^{(1)}\)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>All CTC Grades</th>
<th>CTC Grade 3 and above</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gleevec (n=337)</td>
<td>Placebo (n=345)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>12.2</td>
<td>11.6</td>
</tr>
<tr>
<td>Blood Creatinine Increased</td>
<td>11.6</td>
<td>5.8</td>
</tr>
<tr>
<td>Cough</td>
<td>11.0</td>
<td>11.3</td>
</tr>
<tr>
<td>Pruritus</td>
<td>11.0</td>
<td>7.8</td>
</tr>
<tr>
<td>Weight Decreased</td>
<td>10.1</td>
<td>5.2</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>9.8</td>
<td>11.3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>9.8</td>
<td>7.2</td>
</tr>
<tr>
<td>Lacrimation Increased</td>
<td>9.8</td>
<td>3.8</td>
</tr>
<tr>
<td>Alopecia</td>
<td>9.5</td>
<td>6.7</td>
</tr>
<tr>
<td>Flatulence</td>
<td>8.9</td>
<td>9.6</td>
</tr>
<tr>
<td>Rash</td>
<td>8.9</td>
<td>5.2</td>
</tr>
<tr>
<td>Abdominal Distension</td>
<td>7.4</td>
<td>6.4</td>
</tr>
<tr>
<td>Back Pain</td>
<td>7.4</td>
<td>8.1</td>
</tr>
<tr>
<td>Pain in Extremity</td>
<td>7.4</td>
<td>7.2</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>7.1</td>
<td>2.0</td>
</tr>
<tr>
<td>Depression</td>
<td>6.8</td>
<td>6.4</td>
</tr>
<tr>
<td>Facial Edema</td>
<td>6.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Blood Alkaline Phosphatase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>6.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Dry skin</td>
<td>6.5</td>
<td>5.2</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>6.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Abdominal Pain Upper</td>
<td>6.2</td>
<td>6.4</td>
</tr>
<tr>
<td>Neuropathy Peripheral</td>
<td>5.9</td>
<td>6.4</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>5.6</td>
<td>1.7</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>5.0</td>
<td>2.6</td>
</tr>
<tr>
<td>Platelet Count Decreased</td>
<td>5.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>5.0</td>
<td>1.7</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>5.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Vision Blurred</td>
<td>5.0</td>
<td>2.3</td>
</tr>
</tbody>
</table>

\(^{(1)}\)All adverse reactions occurring in ≥5% of patients are listed regardless of suspected relationship to treatment. A patient with multiple occurrences of an adverse reaction is counted only once in the adverse reaction category.

### Table 13: Adverse Reactions Regardless of Relationship to Study Drug by Preferred Term All Grades and 3/4 Grades
#### (≥5% of Gleevec Treated Patients) Study 2\(^{(1)}\)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>All CTC Grades</th>
<th>CTC Grades 3 and above</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myalgia</td>
<td>12.2</td>
<td>11.6</td>
</tr>
<tr>
<td>Blood Creatinine Increased</td>
<td>11.6</td>
<td>5.8</td>
</tr>
<tr>
<td>Cough</td>
<td>11.0</td>
<td>11.3</td>
</tr>
<tr>
<td>Pruritus</td>
<td>11.0</td>
<td>7.8</td>
</tr>
<tr>
<td>Weight Decreased</td>
<td>10.1</td>
<td>5.2</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>9.8</td>
<td>11.3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>9.8</td>
<td>7.2</td>
</tr>
<tr>
<td>Lacrimation Increased</td>
<td>9.8</td>
<td>3.8</td>
</tr>
<tr>
<td>Alopecia</td>
<td>9.5</td>
<td>6.7</td>
</tr>
<tr>
<td>Flatulence</td>
<td>8.9</td>
<td>9.6</td>
</tr>
<tr>
<td>Rash</td>
<td>8.9</td>
<td>5.2</td>
</tr>
<tr>
<td>Abdominal Distension</td>
<td>7.4</td>
<td>6.4</td>
</tr>
<tr>
<td>Back Pain</td>
<td>7.4</td>
<td>8.1</td>
</tr>
<tr>
<td>Pain in Extremity</td>
<td>7.4</td>
<td>7.2</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>7.1</td>
<td>2.0</td>
</tr>
<tr>
<td>Depression</td>
<td>6.8</td>
<td>6.4</td>
</tr>
<tr>
<td>Facial Edema</td>
<td>6.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Blood Alkaline Phosphatase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>6.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Dry skin</td>
<td>6.5</td>
<td>5.2</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>6.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Abdominal Pain Upper</td>
<td>6.2</td>
<td>6.4</td>
</tr>
<tr>
<td>Neuropathy Peripheral</td>
<td>5.9</td>
<td>6.4</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>5.6</td>
<td>1.7</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>5.0</td>
<td>2.6</td>
</tr>
<tr>
<td>Platelet Count Decreased</td>
<td>5.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>5.0</td>
<td>1.7</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>5.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Vision Blurred</td>
<td>5.0</td>
<td>2.3</td>
</tr>
</tbody>
</table>

\(^{(1)}\)All adverse reactions occurring in ≥5% of patients are listed regardless of suspected relationship to treatment. A patient with multiple occurrences of an adverse reaction is counted only once in the adverse reaction category.

### 6.12 Additional Data from Multiple Clinical Trials
The following adverse reactions have been reported during clinical trials of Gleevec.

- **Cardiac Disorders:**
  - Estimated 0.1%-1%: congestive cardiac failure, tachycardia, palpitations, pulmonary edema
  - Estimated 0.01%-0.1%: arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris, pericardial effusion

- **Vascular Disorders:**
  - Estimated 1%-10%: flushing, hemorrhage
  - Estimated 0.1%-1%: hypertension, hypotension, peripheral coldness, Raynaud's phenomenon, hemoptoma, subdural hematoma

- **Clinical Laboratory Tests:**
  - Estimated 0.1%-1%: blood CPK increased, blood LDH increased
  - Estimated 0.01%-0.1%: blood amylase increased

- **Dermatologic:**
  - Estimated 1%-10%: dry skin, alopecia, face edema, erythema, photosensitivity reaction
  - Estimated 0.1%-1%: exfoliative dermatitis, bullous eruption, nail disorder, purpura, psoriasis, rash pustular, contusion, sweating increased, urticaria, ecchymosis, increased tendency to bruise, hypotrichosis, skin hypopigmentation, skin hyperpigmentation, onycholysis, folliculitis, petechiae
  - Estimated 0.01%-0.1%: vesicular rash, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, acute febrile neutrophilic dermatosis (Sweet's syndrome), nail discoloration, angioneurotic edema, erythema multiforme, leucocytoclastic vasculitis
Digestive: Estimated 1%-10%: abdominal distention, gastroesophageal reflux, dry mouth, gastritis
Estimated 0.1%-1%: gastric ulcer, stomatitis, mouth ulceration, eructation, melena, esophagitis, ascites, hematemesis, chelitis, dysphagia, pancreatitis
Estimated 0.01%-0.1%: colitis, ileus, inflammatory bowel disease

General Disorders and Administration Site Conditions: Estimated 1%-10%: weakness, anasarca, chills
Estimated 0.1%-1%: malaise

Hematologic:
Estimated 1%-10%: pancytopenia, febrile neutropenia
Estimated 0.1%-1%: thrombocytopenia, lymphopenia, bone marrow depression, eosinophilia, lymphopenopathy
Estimated 0.01%-0.1%: hemolytic anemia, aplastic anemia

Hepatobiliary:
Estimated 0.1%-1%: hepatitis, jaundice
Estimated 0.01%-0.1%: hepatic failure and hepatic necrosis

Hypersensitivity:
Estimated 0.01%-0.1%: angioedema

Infections:
Estimated 0.1%-1%: sepsis, herpes simplex, herpes zoster, cellulitis, urinary tract infection, gastroenteritis
Estimated 0.01%-0.1%: fungal infection

Metabolic and Nutritional:
Estimated 1%-10%: weight decreased
Estimated 0.1%-1%: hypophosphatemia, dehydration, gout, increased appetite, decreased appetite, hyperuricemia, hypercalcaemia, hyperglycaemia, hyponatraemia
Estimated 0.01%-0.1%: hyperkalaemia, hypomagnesaemia

Musculoskeletal:
Estimated 1%-10%: joint swelling
Estimated 0.1%-1%: joint and muscle stiffness
Estimated 0.01%-0.1%: muscular weakness, arthritis

Nervous System/Psychiatric:
Estimated 1%-10%: paresthesia, hypesthesia
Estimated 0.1%-1%: syncope, peripheral neuropathy, somnolence, migraine, memory impairment, libido decreased, sciatrica, restless leg syndrome, tremor
Estimated 0.01%-0.1%: increased intracranial pressure, confusional state, convulsions, optic neuritis

Respiratory:
Estimated 0.1%-1%: respiratory failure, acute, urinary frequency increased, hematuria, renal pain

Reproductive:
Estimated 0.1%-1%: breast enlargement, menorrhagia, sexual dysfunction, gynecomastia, erectile dysfunction, menstruation irregular, nipple pain, scrotal edema

Special Senses:
Estimated 1%-10%: conjunctivitis, vision blurred, eyelid edema, conjunctival hemorrhage, dry eye
Estimated 0.1%-1%: vertigo, tinnitus, eye irration, eye pain, orbital edema, scleral hemorrhage, retinal hemorrhage, blepharitis, macular edema, hearing loss
Estimated 0.01%-0.1%: papilledema, glaucoma, cataract

Eye disorders: vitreous hemorrhage
Cardiac disorders: pericarditis, cardiac tamponade

Vascular disorders: thrombosis/embolism, anaphylactic shock

Respiratory, thoracic and mediastinal disorders: acute respiratory failure, interstitial lung disease

Gastrointestinal disorders: ileus/intestinal obstruction, tumor hemorrhage/tumor necrosis, gastrointestinal perforation (see Warnings and Precautions (5.6)), diverticulitis

Skin and subcutaneous tissue disorders: lichenoid keratosis, lichen planus, toxic epidermal necrolysis, palmar-plantar erythrodysesthesia syndrome

Musculoskeletal and connective tissue disorders: avascular necrosis/hip osteonecrosis, rhabdomyolysis/myopathy, growth retardation in children

Reproduction disorders: hemorrhagic corpus luteum/hemorrhagic ovarian cyst

Including some fatalities

7 DRUG INTERACTIONS

7.1 Agents Inducing CYP3A4 Metabolism
Pretreatment of healthy volunteers with multiple doses of rifampin followed by a single dose of Gleevec, increased Gleevec oral-dose clearance by 3.8-fold, which significantly (p<0.05) decreased mean Cmax and AUC.

Similar findings were observed in patients receiving 400-1200 mg/day Gleevec concomitantly with enzyme-inducing anti-epileptic drugs (EIAED) (e.g., carbamazepine, oxcarbamazepine, phenytoin, fosphenytoin, phenobarbital, and primidone). The mean dose normalized AUC for imatinib in the patients receiving EIAED’s decreased by 73% compared to patients not receiving EIAED.

Concomitant administration of Gleevec and St. John’s Wort led to a 30% reduction in the AUC of imatinib.

Consider alternative therapeutic agents with less enzyme induction potential in patients when rifampin or other CYP3A4 inducers are indicated. Gleevec doses up to 1200 mg/day (600 mg BID) have been given to patients receiving concomitant strong CYP3A4 inducers (see Dosage and Administration (2.11) in the full prescribing information).

7.2 Agents Inhibiting CYP3A4 Metabolism
There was a significant increase in exposure to imatinib (mean Cmax and AUC increased by 26% and 40%, respectively) in healthy subjects when Gleevec was co-administered with a single dose of ketoconazole (a CYP4A4 inhibitor). Caution is recommended when administering Gleevec with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, neflinavir, ritonavir, saquinavir, telithromycin, and voriconazole). Grapefruit juice may also increase plasma concentrations of imatinib and should be avoided. Substances that inhibit the cytochrome P450 isoenzyme (CYP3A4) activity may decrease metabolism and increase imatinib concentrations.

7.3 Interactions with Drugs Metabolized by CYP3A4
Gleevec increases the mean Cmax and AUC of simvastatin (CYP3A4 substrate) 2- and 3.5-fold, respectively, suggesting an inhibition of the CYP3A4 isoform.

Similar findings were observed in patients receiving 400-1200 mg/day Gleevec concomitantly with enzyme-inducing anti-epileptic drugs (EIAED) (e.g., carbamazepine, oxcarbamazepine, phenytoin, fosphenytoin, phenobarbital, and primidone), which may increase plasma concentrations of imatinib and should be avoided. Substances that inhibit the cytochrome P450 isoenzyme activity may decrease metabolism and increase imatinib concentrations.

7.4 Interactions with Drugs Metabolized by CYP2D6
Gleevec increased the mean Cmax and AUC of warfarin by approximately 23% suggesting that Gleevec has a weak inhibitory effect on CYP2D6-mediated metabolism. No dose adjustment is necessary; however, caution is recommended when administering Gleevec with CYP2D6 substrates that have a narrow therapeutic window.

7.5 Interaction with Acetaminophen
In vitro, Gleevec inhibits the acetaminophen O-glucuronidate pathway (IC50 58.5 μM). Co-administration of Gleevec (400 mg/day for eight days) with acetaminophen (1000 mg single dose on day eight) in patients with CML did not result in any changes in the pharmacokinetics of acetaminophen. Gleevec pharmacokinetics were not altered in the presence of single-dose acetaminophen. There is no pharmacokinetic or safety data on the concomitant use of Gleevec at doses >400 mg/day or the chronic use of concomitant acetaminophen and Gleevec.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category D (see Warnings and Precautions (5.11)).
similar to adult values (11.0 L/hr/m² in children vs. 10.0 L/hr/m² in adults), with normal hepatic function. At steady state, the mean Cmax/dose and AUC/dose for CGP74588 increased by about 56% and 55%, respectively, in patients with severe hepatic impairment compared to patients with normal hepatic function [see Dosage and Administration (2.11) in the full prescribing information].

### Table 14 Liver Function Classification

<table>
<thead>
<tr>
<th>Liver Function Test</th>
<th>Normal (n=14)</th>
<th>Mild (n=30)</th>
<th>Moderate (n=20)</th>
<th>Severe (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Bilirubin</td>
<td>≤ULN</td>
<td>&gt;1.0-1.5x ULN</td>
<td>&gt;1.5-3x ULN</td>
<td>&gt;3-10x ULN</td>
</tr>
<tr>
<td>SGOT</td>
<td>≤ULN</td>
<td>&gt;ULN (can be normal if Total Bilirubin is &gt;ULN)</td>
<td>Any</td>
<td>Any</td>
</tr>
</tbody>
</table>

ULN=upper limit of normal for the institution

### 8.7 Renal Impairment

The effect of renal impairment on the pharmacokinetics of imatinib was assessed in 59 cancer patients with varying degrees of renal impairment (Table 15) at single and steady state imatinib doses ranging from 100 to 800 mg/day. The mean exposure to imatinib (dose normalized AUC) in patients with mild and moderate renal impairment increased 1.5- to 2-fold compared to patients with normal renal function. The AUCs did not increase for doses greater than 600 mg in patients with mild renal impairment. The AUCs did not increase for doses greater than 400 mg in patients with moderate renal impairment. Two patients with severe renal impairment were dosed with 100 mg/day and their exposures were similar to those seen in patients with normal renal function receiving 400 mg/day. Dose reductions are necessary for patients with moderate and severe renal impairment [see Dosage and Administration (2.11) in the full prescribing information].

### Table 15 Renal Function Classification

<table>
<thead>
<tr>
<th>Renal Dysfunction</th>
<th>Renal Function Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>CrCL = 40-59 mL/min</td>
</tr>
<tr>
<td>Moderate</td>
<td>CrCL = 20-39 mL/min</td>
</tr>
<tr>
<td>Severe</td>
<td>CrCL = &lt;20 mL/min</td>
</tr>
</tbody>
</table>

CrCL = Creatinine Clearance

### 10 OVERDOSAGE

Experience with doses greater than 800 mg is limited. Isolated cases of Gleevec overdose have been reported. In the event of overdosage, the patient should be observed and appropriate supportive treatment given.

#### Adult Overdose

1.200 to 1,600 mg (duration varying between 1 to 10 days): Nausea, vomiting, diarrhea, rash, erythema, edema, swelling, fatigue, muscle spasms, thrombocytopenia, pancytopenia, abdominal pain, headache, decreased appetite.

1.800 to 3,200 mg (as high as 3,200 mg daily for 6 days): Weakness, myalgia, increased CPK, increased bilirubin, gastrointestinal pain.

6,400 mg (single dose): One case in the literature reported one patient who experienced nausea, vomiting, abdominal pain, pyrexia, facial swelling, neutrophil count decreased, increased transaminases.

8 to 10 g (single dose): Vomiting and gastrointestinal pain have been reported.

A patient with myeloid blast crisis experienced Grade 1 elevations of serum creatinine. Grade 2 asches and elevated liver transaminase levels, and Grade 3 elevations of bilirubin after inadvertently taking 1,200 mg of Gleevec daily for 6 days. Therapy was temporarily interrupted and complete reversal of all abnormalities occurred within 1 week. Treatment was resumed at a dose of 400 mg daily without recurrence of adverse reactions. Another patient developed severe muscle cramps after taking 1,600 mg of Gleevec daily for 6 days. Complete resolution of muscle cramps occurred following interruption of therapy and treatment was subsequently resumed. Another patient that was prescribed 400 mg daily, took 800 mg of Gleevec on Day 1 and 1,200 mg on Day 2. Therapy was interrupted, no adverse reactions occurred and the patient resumed therapy.

#### Pediatric Overdose

One 3 year-old male exposed to a single dose of 400 mg experienced vomiting, diarrhea and anorexia and another 3 year-old male exposed to a single dose of 980 mg experienced decreased white blood cell count and diarrhea.

Distributed by: Novartis Pharmaceuticals Corporation

East Hanover, New Jersey 07936

© Novartis

T2013-100

October 2013
Assessment of GIST genotypes is essential for the optimal use of molecularly-targeted therapies. Distinct mutations require different dosing of the tyrosine kinase inhibitor (TKI) imatinib. In cases of TKI resistance, the choice of second- or third-line therapies is similarly dictated by the specific tumor genotype. Thus, routine genotyping is essential in the management of GIST, and further elucidation of the molecular mechanisms that underlie TKI resistance should point the way to improved personalized therapies.

The paradigm of kinase-targeted therapy was first established when the small molecule inhibitor imatinib was found to inhibit the BCR-ABL fusion kinase that is the pathogenic driver of chronic myeloid leukemia. Imatinib also inhibits mutant forms of KIT tyrosine kinase that are responsible for the growth of most gastrointestinal stromal tumors (GISTs). As a result, imatinib has completely transformed the treatment of this disease.1 This review considers factors that influence the response to – as well as resistance to – imatinib and related TKIs in the management of GIST.

About 80% of GISTs have mutations in the KIT gene that cause activation of the kinase and stimulate signaling through downstream pathways that support tumor growth. Mutations in a KIT homologue, platelet-derived growth factor receptor alpha (PDGFRA), account for another 10% of GISTs. The remaining 10% of GISTs, commonly referred to as wild-type GIST (WT GIST), are a heterogeneous group that harbor mutations in other genes within the MAP kinase pathway (NF1, RAS, BRAF), or have defects in succinate dehydrogenase activity related to mutation of genes encoding this complex (SDHA, SDHB, SDHC or SDHD). As a group, WT GISTs are less sensitive to imatinib and other KIT/ PDGFRA TKIs. Thus, the diversity of molecular subtypes of GIST has direct implications for TKI treatment.

While imatinib has revolutionized the treatment of patients with advanced GISTS, clinical resistance to the drug has proved to be a daunting challenge in the management of this disease. Multiple secondary resistance mutations may arise in more than one lesion within the same patient, and this heterogeneity complicates treatment considerably. The correlation of GIST genotype with patient responses in clinical trials has enabled substantial progress toward the elucidation of the molecular mechanisms that drive drug resistance. Further understanding of this process will foster improved drug development and treatment strategies.

Tumor Genotype versus Imatinib Dose

In the original phase II trial of imatinib for the treatment of advanced GIST it was noted that the partial response rate using RECIST criteria was much higher for patients with a KIT exon 11 mutant-tumor (83.5%) than for those with an exon 9-mutant tumor (47.8%) or a tumor with no detected KIT mutation (0.0%). This correlated with longer progression-free survival in the exon 11-mutant group. The relationship between tumor genotype and imatinib response was further established through two, large international phase III trials of imatinib therapy. The SWOG S0033 study2 and the EORTC trial3 compared 400 mg versus 800 mg daily imatinib doses, and evaluated responses with respect to KIT and PDGFRA mutation status. A meta-analysis of the results from trials for 772 patients showed that the 800 mg dose significantly improved progression-free survival compared to the 400 mg dose for patients with a KIT exon 9 mutation. In contrast, there was no benefit of the increased dose for patients with a KIT exon 11 mutation or no mutation.4 For this reason, tumor genotyping is now recommended by the NCCN for all GIST cases in which imatinib treatment is under consideration.

Use of Imatinib in the Adjuvant Setting

Soon after it was established that imatinib has activity in patients with advanced GIST, the Z9001 trial was initiated to determine whether adjuvant use of imatinib following surgi-
You are invited to celebrate the 1st Annual worldwide GIST Awareness Day.

GIST Awareness Day was created by The Life Raft Group to help address the lack of education and recognition surrounding GIST and help break down the barriers to funding, research, treatment and diagnosis that this causes.

We need your help to spread the word!
- Get your medical center involved: Promotional materials including banners and pamphlets are available upon request to set up a GIST Awareness Day booth in your lobby
- Highlight GIST and GIST Awareness Day as a featured part of July's Sarcoma Awareness Month
- Send in pictures and videos of your team participating in our origami boat Guinness World Record attempt
- Bring attention to GIST Awareness Day on social media by using hashtags #GISTAwarenessDay and #GISTKeepFolding
- Hold a GIST Awareness Day celebration of your own!

To register your institution visit: www.gistawarenessday.org

For questions about or assistance in planning an event at your institution please contact Mildred Menos at mmenos@liferaftgroup.org
cal resection of a primary GIST would delay, or perhaps prevent, recurrence of disease. This trial of 713 patients compared the recurrence-free survivals (RFS) of patients treated with 12 months of imatinib (400 mg) versus placebo. The trial was closed early when an interim analysis showed that there was a clear benefit of imatinib, which reduced recurrences at 12 months by 17%. Interestingly, upon completion of 12 months of adjuvant treatment, disease recurrences began to appear in the imatinib-treated group at a rate that paralleled that in the placebo group, and during long-term follow-up the RFS was identical in the imatinib and placebo groups. This important observation suggested that 12 months of adjuvant treatment was not sufficient to cure patients.

The Scandinavian-SSG trial addressed the question of whether 3 years of adjuvant imatinib would further reduce the risk of recurrence over 1 year. Indeed, patients receiving 36 months of imatinib had a longer RFS compared to those treated for 12 months (hazard ratio [HR], 0.46; 0.32 0.65; 5-year RFS, 65.6% vs 47.9%). Moreover, the overall survival was higher in the 36-month arm (HR 0.45; 0.22-0.89; 5-year survival 92% vs 81.7%).

Given the potential side effects of prolonged imatinib treatment, it is essential to accurately assess the risk of recurrence in order to identify which patients will most likely derive benefit from adjuvant therapy. The placebo arm of the Z9001 trial provided a unique opportunity to assess pathologic and genotypic features that correlate with RFS in a prospectively followed population. Based on a median follow-up of 74 months, the key findings from this study were that tumor size, location, and mitotic rate, but not tumor genotype were factors that independently correlated with disease recurrence. Similarly, results from the imatinib arm of the Z9001 trial and the Scandinavian-SSG trial associated five factors (high mitotic rate, non-gastric location, large tumor size, tumor rupture, and adjuvant imatinib for 12 months) with disease recurrence. The two strongest predictive factors were mitotic rate (Figure) and tumor location, with gastric location and low mitotic rate at the favorable end of the spectrum. The decision to administer adjuvant imatinib therapy requires careful assessment of these risk factors for each patient.

Responses to Imatinib Therapy Persistent versus Resistant Disease

An interesting trial conducted in France examined the question as to what is the optimal duration of imatinib therapy for advanced, unresectable GIST. Patients who had taken imatinib for 3 years and had continuous control of their disease were randomized to either continue or to discontinue treatment. For those continuing treatment, progression-free survival over the next 2 years remained high at 80%, but for those who stopped therapy it was only 16%. The rapid relapse after the discontinuation of therapy reflected persistent disease; that is, viable GIST cells were derepressed after 3 years of control under imatinib. In contrast, among the patients who maintained imatinib therapy on the trial there were some who showed renewed growth of their tumor, indicating disease that had become truly resistant to imatinib.

Primary Resistance

Resistance to treatment with KIT/PDGFRA inhibitors such as imatinib can be divided into two types: primary and secondary. Approximately 10% of patients with GIST have primary resistance, defined as progression within the first 6 months of treatment. The probability of primary resistance varies with GIST genotype, ranging from 5% for tumors with KIT exon 11, to 16% for KIT exon 9 and 23% for wild-type GISTs. Differences in underlying sensitivity to imatinib are thought to account for this. Whereas exon 11-mutant KIT is highly sensitive to imatinib (IC50 of <100 nM), exon 9-mutant KIT and wild-type KIT are less sensitive to the drug (IC50 ~1000 nM for each). As discussed above, doubling the imatinib dose for patients with exon 9 mutations helps to overcome this relative resistance, allowing longer progression-free survival.

Another cause for primary imatinib resistance is the PDGFRA mutation D842V. It is the most common mutation in this kinase and is fully resistant to the effects of imatinib in vitro. Correspondingly, patients with PDGFRA D842V-mutant GIST have low response rates and very short progression-free- and overall-survivals during imatinib treatment. Crenolanib is a TKI that has activity versus D842V and is now being tested in a clinical trial. It is important to note, however, that other PDGFRA mutations are sensitive to imatinib in vitro and patients with these mutations have shown durable responses to imatinib.

Among the wild-type GISTs there are tumors with mutations downstream of KIT that might be better managed with other targeted agents. For example, pediatric/SDH-deficient GISTs appear to respond better to sunitinib than imatinib, and a BRAF-mutant GIST was recently reported to respond well to the BRAF inhibitor dabrafenib after failing to respond to imatinib.

Secondary Resistance

After an initial response to imatinib, approximately 90% of patients eventually develop disease progression. This secondary resistance may manifest as a growing nodule within a pre-existing, clinically quiescent lesion, the development of one or more new lesions, or as widespread disease throughout the liver or abdominal cavity. Acquired mutations in KIT or PDGFRA account for most secondary resistance.

In a phase II imatinib study for advanced GIST, 67% of the patients whose tumor showed imatinib resistance had a new, or secondary, mutation in KIT. Interestingly, these secondary mutations were common among tumors with a primary exon 11 mutation, but were not observed in wild-type GISTs. The secondary mutations were concentrated in two regions of the KIT kinase domain: the ATP binding pocket (exons 13 and 14), and the activation loop (exons 17 and 18). Mutations in the ATP pocket interfere directly with drug binding, while the activation loop mutations stabilize KIT in an active conformation that favors imatinib interaction.
Drug resistance has also been observed in PDGFRA-mutant GISTs, in which the most common acquired mutation is D842V mutation.

Additional studies using more sensitive assays have identified secondary mutations in more than 80% of drug-resistant GIST lesions.21-23 Notably, there is significant heterogeneity of resistance across different tumor sites within a patient, and even within different areas of the same site. In one study there were up to 5 different drug resistance mutations in different portions of a single lesion and up to 7 different secondary resistance mutations across multiple tumors in the same patient.21 This heterogeneity of resistance is the main cause for disease progression, not only on imatinib, but on subsequent kinase inhibitors.

Approaches to Imatinib-resistant GIST

The majority of GIST patients who develop secondary resistance to imatinib are not responsive to dose escalation, so that alternative inhibitors are needed to target KIT and PDGFRA. A number of drugs have been evaluated for GIST treatment, including sunitinib, sorafenib, dasatinib, pazopanib, regorafenib, masitinib, and nilotinib. Unlike imatinib, several of these agents also inhibit vascular endothelial growth factor receptors (VEGFR) 1 and 2 in addition to targeting KIT and PDGFRA.24 Inhibitory effects on tumor growth observed with these salvage agents could therefore be due to antagonism of VEGFR1/2 and consequent decreased angiogenesis.

Sunitinib is FDA approved as a second-line therapy for GIST patients who progress on (or are intolerant of) imatinib, but its activity varies across secondary KIT mutations. In a phase I/II study of 97 patients,25 approximately half of the patients obtained clinical benefit from sunitinib, and in a phase III trial of 312 patients, the median time to tumor progression was more than four times as long with sunitinib compared to placebo treatment (27.3 weeks compared to 6.4 weeks).26 Notably, the median progression-free survival with sunitinib was significantly longer for patients who had secondary KIT mutations in the ATP-binding pocket than for the patients who had activation loop mutations (33.9 weeks compared to 10.0 weeks), consistent with the in vitro sunitinib sensitivity of exon 13-14 variants and comparative resistance of exon 17-18 variants.12 Given the approximately equal frequency of these different classes of mutations in imatinib-resistant lesions and the multiplicity of lesions in a typical patient, it is not surprising that mixed responses to sunitinib therapy are common.2

Over time, the majority of patients treated with imatinib and sunitinib will develop resistance, so that third-line therapy is needed. To this end, regorafenib, which targets KIT and PDGFR α, as well as a number of angiogenic factors (VEGFR1/2/3, TIE2) and oncogenic signaling proteins (BRAF, MAPK), has recently been approved by the FDA. In a phase II trial of 34 patients with imatinib + sunitinib resistant GIST, regorafenib yielded a remarkable 10 month median progression-free survival (PFS). Biopsies from patients pre- and post-regorafenib showed a marked inhibition of KIT activation loop mutants which are imatinib- and sunitinib- resistant.27 A five-fold improvement in median PFS compared to placebo (4.9 months vs 0.9 months), and 73% reduction in risk of disease progression were subsequently achieved in a phase III trial of 199 imatinib + sunitinib resistant GIST pa-
patients. But even with newer drugs like regorafenib, resistance develops over time, suggesting that escape from ATP- competitive inhibitors of KIT and PDGFRA is inevitable.

Future Directions
A key challenge in the treatment of kinase inhibitor-resistant GIST is that a single patient may harbor multiple lesions, often with many different resistance mutations. Active areas of investigation are focused on improved methods to identify these mutations and treat these complex lesions. Tumor-specific mutations can be detected in circulating cell-free DNA in the plasma of GIST patients. If this methodology can afford the needed sensitivity, then this may provide a means to non-invasively detect the full spectrum of resistance mutations within a patient. Appropriate kinase inhibitors, or combinations thereof, could then be administered based on the mutations identified. In addition, a new class of non-ATP mimetic kinase inhibitors (switch pocket kinase inhibitors) has shown high potency when tested in vitro and represents promise in the fight against drug resistance. It is also possible to broaden the search for new drug targets. A high-throughput in vitro screen of FDA-approved anti-cancer agents has identified transcriptional inhibitors and topoisomerase II inhibitors as potential new therapies in GIST. Finally, immune-based therapies may be able to circumvent TKI resistance by stimulating the host anti-tumor immune response. Agents that target CTLA-4 and PD-1, negative regulators of the immune response, have shown efficacy against a number of solid tumors including melanoma, non-small cell lung cancer and renal-cell cancer. These may prove effective in GIST as well. Collectively, these new avenues provide substantial optimism for the improved therapy of GIST.

Conclusions
Substantial progress in the clinical management of GIST has been made possible by the understanding of the underlying molecular alterations that drive tumor growth. Identification of the key roles of primary KIT and PDGFRA mutations in GIST led to the FDA approval of imatinib in advanced disease as well as in the adjuvant setting. Notably, GIST genotyping is essential to determine the optimal dosing of imatinib for each patient. KIT exon 9 mutations require a higher imatinib dose that other mutations, while some GIST molecular subtypes may be unresponsive to imatinib and thus require treatment with other agents. In addition, risk assessment, based upon tumor size, location and mitotic index, is essential to identify patients most likely to benefit from imatinib after primary tumor resection. Despite initial responses to imatinib, secondary resistance mutations will develop in the majority of cases of advanced GIST. While sunitinib has been FDA-approved as second-line therapy after development of imatinib resistance, and regorafenib has shown promise as a third-line therapy after failure of imatinib and sunitinib, the development of drug resistance remains a challenge. Ongoing innovations to improve methods to detect the diverse secondary mutations, to develop improved kinase inhibitors, to identify other potential drug targets, and to develop immune-based therapies hold considerable promise for improved GIST patient care.

References


---

**trail·blaz-er**

Someone who makes, does, and discovers something new and makes it acceptable or popular and marks or prepares a trail through a forest or field for other people to follow.

---

**Introducing The GIST Cancer Journal, a trailblazer for medical oncologists and gastroenterologists**

Follow *The GIST Cancer Journal* as it carves its way through the oncology literature and points toward new insights, approaches, and trends in the diagnosis and treatment of gastrointestinal stromal tumor. Covering a broad spectrum of topics, issues and unresolved questions, the journal will explore essential information, all evidence-based for health care professionals. Here are some of the topics the journal will address in future issues:

- The clinical necessity of molecular diagnostics in GIST
- The role of surgery in metastatic GIST
- Pediatric/SDH deficient GIST
- Clinical case reports: patients with other cancers, response to therapies not approved by the FDA, metastatic sites, novel mutations in KIT, PDGF, and other genes

The journal will also highlight a range of patient advocacy issues and relevant topics for nurses, including the management of common side effects, problems and solutions in acquiring off-label therapeutics, the greatest hurdles to evaluation at GIST referral centers, and patient barriers to participation in clinical trials.
As GIST has become a model for targeted therapy with tyrosine kinase inhibitors, new perspectives have emerged on the use of multimodal strategies, particularly with regard to the adjuvant use of surgery in the metastatic setting. When resection is a viable option, clinicians are confronted with a range of options and factors. A review of current literature suggests how these factors impinge on clinical decision making and what approaches help to optimize management in advanced disease.

It has been called one of the critical areas of assessment in the management of advanced gastrointestinal stromal tumor (GIST). The critical area concerns the need for clear guidelines on the use of surgery in the TKI era and how they should be built into the treatment algorithm. Although surgery is a well established part of the paradigm in management of advanced GIST, many issues still need to be addressed and a host of factors need to be considered in deciding when to use surgery, which patients are most likely to benefit, how mutational status could affect decision making, what strategies are appropriate in imatinib-resistant disease, and how management can be individualized when clinicians are confronted by secondary resistance to TKI agents.

These are essential considerations for treatment of metastatic GIST because medical management is only part of the optimal treatment strategy. Lifelong treatment with imatinib is recommended in patients with responsive GIST due to the increased likelihood of disease progression when the drug is stopped. Even in the setting of progressive disease on imatinib, the NCCN task force recommends continued therapy as a component of best supportive care to limit the growth of sensitive clones or tumors sensitive to imatinib. Other studies with alternative TKIs, including sunitinib and regorafenib, have outlined a role for these agents in the setting of imatinib resistance.

**Rationale for Surgery**
Numerous studies offer data on the rationale for surgery although surgery alone is of limited value in treating recurrent or metastatic GIST with curative intent. As early as 2000, for example, prior to the imatinib era, a study reported that complete gross resection was possible in only 30% of patients and the median survival of those treated with surgery alone was 19 months. Although 80% of patients with metastatic disease show some response or stable disease on imatinib, a complete pathologic response is reported less than 5% of the time. Thus, the opportunity for combining imatinib with surgery has emerged as a key strategy.

Surgery can also be of benefit for another reason: most patients with advanced GIST respond initially to imatinib, but the majority develops resistance, with the median time to resistance being 2 years with the mechanism primarily being through secondary mutations in KIT. Thus, the rationale for using surgery—now increasingly deployed as an adjuvant to TKI therapy—goes far beyond the traditional role it had at one time as a palliative option in metastatic or local advanced GIST. With the advent of drugs that target the underlying molecular pathophysiology of GIST, surgical resection following imatinib or sunitinib therapy may be curative in some patients with advanced disease. Recent studies are delineating in a more precise fashion how surgery can be optimized as an adjuvant tool and new data suggest ways in which the treatment algorithm has evolved.

**Post-imatinib Surgery: When is it Worthwhile?**
To address this question, Mussi et al pursued two directions:

1. One rationale for carrying out surgery upon best clinical response to imatinib is that a reduction of tumor load might decrease the risk of secondary resistance.
2. The alternative is that one might consider an operation only in case of local progression with the aim of resecting lesions that have already developed secondary resistance.
A retrospective analysis included 80 patients who underwent surgery for metastatic GIST after imatinib therapy and were divided into 2 groups: (1) those with surgery at best clinical response and (2) those with surgery at focal progression. At 2 years, progression-free survival (PFS) was 64.4% in the first group and 9.7% in the second group. Median disease-specific survival from the time of imatinib onset was not reached in either group. At 5 years DSS was significantly shorter in the second group (82.9% in the first group vs 67.6% in the second group).

The clear difference in survival between the groups who underwent surgery raises implications for the timing of surgery as well as clinical consequences, particularly in view of the fact that secondary resistance to imatinib is the main complication that limits the long-term efficacy of the drug. Such resistance is related, at least in part, to acquired mutations that become clinically relevant after prolonged exposure to the drug, a phenomenon that validates the utility of surgery as part of a multimodal approach to treatment of metastatic GIST. Mussi et al postulate that the worst consequence of this disease persistence is that GISTs frequently develop secondary resistance likely the result of evolution of mutant cells. Thus, surgery could conceivably prevent this event or remove resistant tumor tissue if carried out upon clinical progression. However, the timing when Mussi carried out their study was still not clear.

Identifying a Limited Role for Surgery: What Subsets?
The authors observed that secondary progression usually occurs after 2 years. In this study the median time from the beginning of imatinib treatment to surgery was 15 months in the clinical response group and 21 months in the group with progressive disease, suggesting that progression frequently occurred between 15 and 21 months. Based on this observation, the authors postulate that surgery should not take place much later than 1 year after imatinib onset if a clinical response is achieved. The authors acknowledge a key limitation of their findings: it is difficult to tell whether the survival advantage seen in patients who had surgery upon clinical response was due to the timing of the surgery or selection bias. This question needs to be answered in randomized studies.

Overall, 2 conclusions can be drawn from this report:
• Patients who undergo surgery for focal progressive disease have a limited benefit in terms of disease control. Surgery does not seem to prevent generalized progression in this group and may be best relegated to second-line or third-line treatment.
• Surgery for residual disease upon best clinical response does convey a survival benefit compared with patients historically treated with imatinib alone. It is uncertain, however, to what extent the study’s nonrandomized design and possible selection bias (patients with a better prognosis had a higher chance of being selected for surgery) were confounding factors.

Distinguishing which subsets of patients may experience prolonged survival after aggressive treatment with a combination of surgery and kinase-directed therapy has also been a focus of other studies, including a report by Raut et al who also observed a very limited role for surgery in treating patients with generalized disease progression. Categorizing patients based on extent of disease before surgery, these authors noted the following in their series of 69 patients:
• Patients with advanced GISTs exhibiting limited progression while receiving kinase inhibitors have prolonged overall survival after debulking procedures. Those with limited disease progression usually progressed within 12 months of surgery.
But in the setting of generalized progression, surgery had little to offer. All patients with generalized progression of metastatic GISTs despite systemic therapy died within 12 months of surgery. Hence, surgery should be considered in this group in the context of symptom palliation.

Criteria for Patient Selection and the Need for an RCT
One of the conundrums of assessing whether surgery is truly of benefit in the setting of metastatic GIST is that a randomized clinical trial is still needed. Yet, retrospective data have helped to propose a treatment algorithm for carefully selected patients who show stable disease or limited radiographic progression. The Raut paper, for example, arrived at the aforementioned conclusions with a categorization of patients in 3 groups: those with stable disease, defined as lesions that appear unchanged or decreasing on serial CT scans; limited progression which includes few lesions that are increasing in size but still appear resectable on imaging; and generalized progression which includes multiple enlarging sites of disease and therefore only possible in circumstances of surgical palliation.

The accumulating data suggest that using these criteria to carefully select patients with stable or responsive disease on imatinib would be optimal in do the data simply reflect selection of patients with better biology that would have fared just as well with medical therapy alone? We need a randomized clinical trial along these lines: after a defined period (say, 6-9 months or at least after maximum response) patients with resectable disease considered stable or responding by cross sectional imaging should be randomized to surgery or continued medical therapy. Surgical patients would resume TKIs as soon as possible after surgery. The endpoints would include PFS and OS. Such a trial would also need to consider differences in development of secondary resistance to TKIs, including a second line agent like sunitinib. There is a phase 2 trial that has studied the pre-operative use of imatinib in advanced GIST (conducted by the RTOG 0132), but it is small and nonrandomized. Nevertheless, it has confirmed the criteria of the aforementioned retrospective studies.

Sunitinib
Surgery in patients with advanced disease on sunitinib is less well defined. Raut et al enrolled 50 patients who underwent surgery for metastatic disease while on second line sunitinib. But unlike the experience with imatinib, the preoperative response to sunitinib did not correlate with resectability or outcomes after surgery. Although PFS and OS were relatively high (15.6 and 26 months, respectively) the question still remains as to whether this is more an indication of careful patient’s selection. Thus, Bamboat et al conclude that cytorreductive surgery in patients on second line sunitinib needs to be individualized and weighed against associated morbidity and alternative treatments.

Regorafenib
There is also interest in the use of regorafenib in metastatic and/or unresectable GIST after failure of imatinib and sunitinib. As a Phase 2 trial notes, regorafenib is a structurally unique inhibitor of multiple cancer associated kinases, including KIT and PDGFR. Because KIT and PDGFR remain drivers of GIST after resistance to imatinib and sunitinib, George et al explored its use in 33 patients who received at least 2 cycles of regorafenib. Median PFS was 10 months, an encouraging result that will be further studied in an ongoing international Phase 3 trial to determine whether regorafenib is a uniquely active agent in managing GIST after resistance to imatinib and sunitinib.

Mutation Status
An early evaluation for mutation status is a key part of the algorithm in patients being considered for metastasectomy following treatment with imatinib because the presence and mutation status of KIT and PDGFRA provides prognostic information and can alter the treatment algorithm. Primary resistance to imatinib is defined as radiographic tumor progression (changes in tumor size and density by CT scan) during the first 6 months of therapy. Secondary resistance occurs later (more than 6 months) and is often the result of a second mutation in a different region within the kinase domain of KIT and PDGFR. Most GISTs that develop secondary resistance to imatinib have a primary mutation in KIT exon 11 and then develop an exon 13, 14, or 17 mutation.

This issue was also addressed by Chun-Nan et al who observed that secondary mutations were found more frequently in GIST patients with local progression after surgery.
than in those with response. Thus, surgery may prevent potential development of secondary\textsuperscript{16} mutation in GIST patients with response. Secondary KIT mutations were also found more often in patients with primary exon 11 mutation than in those with exon 9 mutation (38.7\% vs 16.7\%).

Evidence from Phase 3 trials show that compared with exon 9 mutant or wild-type GIST, patients who have the more commonly seen KIT exon 11 mutation benefit more from imatinib and have higher rates of PFS and OS.\textsuperscript{17,18} WT GIST that lacks a mutation in KIT and PDGFRA has a worse outcome and limited response to imatinib. In the absence of an exon 17 mutation, the dose of imatinib is an important factor to consider in patients with advanced small bowel disease. An exon 9 mutation is often present and these tumors are more responsive to higher doses of imatinib. These tumors seem to be more responsive to 400 mg twice daily when compared with 400 mg daily.\textsuperscript{11} This confirms evidence from other studies indicating that 800 mg seems to afford more benefit.

There is further evidence that response rates among patients receiving sunitinib are also affected by mutation status. A study by Heinrich et al\textsuperscript{19} in 78 patients found that the clinical activity of sunitinib is influenced by both the primary and secondary mutation status in three of the most commonly seen mutations, PFS and OS were highest in patients with exon 9 mutations vs exon 11 and WT/PDGFRA mutations. These response rates were also greater for patients with secondary KIT exon 13 or 14 mutations than those with exon 17 or 18 mutations.

### Hepatic resection in the TKI era

One of the issues not yet sufficiently explored relates to the use of multimodal therapy consisting of hepatectomy and TKIs for metastatic GIST. There is still controversy with respect to the timing of combined systemic and locoregional (hepatic resection) therapies.\textsuperscript{20} The National Comprehensive Cancer Network recommends surgery for limited disease progression refractory to systemic therapy or locally advanced or previously unresectable tumors after a favorable response to imatinib.\textsuperscript{21}

Turley et al\textsuperscript{22} cover some critical issues with regard to strategies currently in vogue for minimizing the development of secondary KIT mutations, which lead to TKI resistance. This multi-institutional study of hepatic resection reported a 3-year overall survival rate of 67.4\% with a median survival not reached at 5 years for those receiving combination therapy. This is in contrast to data in other reports indicating a median survival of 36 to 47 months and 48 months for patients who underwent liver resection alone or TKI monotherapy, respectively. Turley et al then address the relevance of their findings to the 2 current strategies for treating metastatic GIST. The first, from Haller et al\textsuperscript{23}:

- Treat recurrence of GIST with systemic TKIs and reserve surgery for patients who demonstrate early signs of TKI resistance such as “stagnation of tumor shrinkage” on radiographic imaging.
- The second, from DeMatteo et al\textsuperscript{24} from MSKCC emphasizes surgery for recurrent disease within 6 months of initiating TKI therapy to minimize the risk of acquiring secondary mutations responsible for TKI resistance. Underlying this strategy is that since the response of GISTs to imatinib generally will plateau after 6 months of exposure to therapy, tumor debulking will delay the development of secondary KIT mutations.

This guideline proposed by DeMatteo et al is generally a good one since the response to imatinib generally does plateau at 6-9 months. However, in some cases, resistance may not appear until 18-24 months so some patients may still be responding after that time when they are predicted to “plateau.” Turley et al recommend that all patients with hepatic GISTs metastases be treated aggressively with both surgery and postoperative TKI therapy before clinical signs of TKI resistance become apparent.

### Liver Metastases: Additional Considerations

One might assume that patients with a greater disease burden would be expected to have a poorer prognosis. A study
by de la Fuente et al., however, debunks this notion as it compared OS in patients presenting with isolated hepatic metastases with that of patients with synchronous metastatic disease to the liver and sarcomatosis on a background of GISTs. Treatment with TKI therapy was similar in both groups. Based on results in 193 patients (43 with isolated hepatic metastases and 16 with synchronous metastases to the liver and sarcomatosis) overall survival was similar.

It is also important to identify patients who could benefit from the use of hepatic chemoembolization. This is an area where data have been scarce, and the true efficacy of HACE for improving OS could be difficult to determine because of the concomitant use of other therapies, according to Kobayashi et al. Their report on 110 patients found that HACE produced a favorable tumor response or disease stabilization in a majority of patients. Patients who appear to benefit from HACE are those in whom conventional systemic therapy has failed. Multiple HACE procedures and the use of imatinib can produce improved PFS-liver and OS; factors adversely affecting prognosis are a large burden of liver disease and the presence of extrahepatic disease.

The Role of Radiofrequency Ablation
HACE, along with radiofrequency ablation, might be considered, for lack of better terminology “salvage methods” in metastatic GIST. They may be tenable options for patients who are not able to undergo resection to a margin-negative status or cannot be completely resected. Resection may not be tenable because of comorbidity or technically the resection is not appropriate because of the extent of disease. A recent study by Yamanaka27 concluded that RFA is feasible, safe and effective for the treatment of GIST liver metastases.

Conclusion
A multimodal approach for the treatment of metastatic GIST, including a rationale for the use of surgery in conjunction with TKI therapy, is an important feature of the emerging treatment algorithm in this setting. GISTs frequently develop secondary resistance and surgery could either prevent this event if performed early or remove resistant tumor tissue if used upon clinical progression. The timing of surgery should be individualized but in most cases it should not be much later than one year after initiation of imatinib, depending on the response to medical therapy. Prospective randomized trials are needed to further delineate the role surgery in metastatic GIST.

References
Science For A Better Life

Bayer Oncology is committed to working with patients, caregivers, scientists, and clinicians to bring effective therapeutic options to patients with cancer.

Visit us at www.pharma.bayer.com

Bayer HealthCare
Gastrointestinal stromal tumors (GIST) are the most common mesenchymal neoplasm of the gastrointestinal tract and KIT or PDGFRA mutations are identified as central tumor-initiating events in many cases. However, 85% of GISTs occurring in children and 15% of GISTs occurring in adults lack these mutations; these are known as Wild Type (WT) GISTS. Tyrosine kinase inhibitors, including imatinib, sunitinib and regorafenib have primarily activity in KIT or PDGFRA mutated GIST, while currently we have no effective treatments for Wild-Type GISTs. A detailed characterization of the different subgroups of wild-type GIST and their tumorigenic pathways is urgently needed, in order to identify novel effective treatments. In this report we will attempt to summarize the most recent advantages in Wild-Type GIST.

SDH Deficient Wild-Type GIST

It was recently reported by the “Pediatric and Wild-Type GIST Clinic at the National Institutes of Health”, at the annual meeting of the Connective Tissue Oncology Meeting in New York, USA that although wild-type GIST remains heterogeneous, the vast majority of these tumors have SDHB deficiency detected by immunohistochemistry (IHC). Succinate dehydrogenase (SDH) is a heteroligomer, composed of subunits A, B, C and D and it participates in both the Krebs cycle and the electron transfer chain located in the mitochondrial inner membrane. The epidemiology of SDH-deficient GIST has been studied to some extent. It constitutes half of all gastric GIST in patients under 40, and it is less common in older adults and children in their first decade of life. SDH-deficient tumors are more common in girls. SDH-Deficient GIST can be either syndromic (Carney Triad, Carney-Stratakis Syndrome) or sporadic.

Carney Triad

Carney Triad (CTr) was first described in 1977 and was named because of the association of 3 tumors: gastric epithelioid leiomyosarcoma (subsequently called GIST), extra-adrenal paraganglioma, and pulmonary chondroma. Zhang et al highlighted how gastric stromal tumors in CTr are different clinically, pathologically, and behaviorally from sporadic gastric GIST. Their study of 104 patients with the syndrome revealed that most patients with Carney Triad were young women (mean age 22 years). Features of the usual KIT or PDGFRA mutant GIST included occurrence in older patients (>50 years), equal sex distribution, single tumor occurrence, infrequent metastasis and not to lymph nodes, a generally favorable response to imatinib and usually a benign natural history with infrequent mortality. Although the report by Zhang et al included a large cohort, other reports suggest how the view of the triad has evolved over the years, reflecting new data. For example, in 1999, more than 20 years after the initial report, Carney reviewed findings in another 79 cases, reporting that only 20% of these patients had all 3 tumors. A clear etiology of CTr remains currently elusive. Exploring the genetics of CTr, Matyakhina et al. performed one of the most comprehensive analyses, by performing comparative genomic hybridization...
in 37 patients with CTr and showed genetic alterations in the 14q, 1p, and 22q chromosomal loci.\(^8\) Their paper concludes that CTr is not due to SDH-inactivating or KIT/ PDGFRA—activating mutations.

**Carney-Stratakis Syndrome**

The Carney-Stratakis syndrome (CSS) is an inherited predisposition to GIST and paraganglioma that is caused by inactivating germline mutations in SDHB, -C or D.\(^9,\text{10,11}\) Carney et al first described the syndrome in 2002 as a separate condition. In this report, they described 12 patients (7 male and 5 female) with an average age of 23 years from 5 unrelated families that manifested paraganglioma and gastric stromal sarcoma.\(^7\) The tumors were inherited in an apparent autosomal dominant manner, with incomplete penetrance.

This report noted that 7 patients had paraganglioma, 4 had paraganglioma and gastric stromal sarcoma and 1 had gastric stromal sarcoma. The paraganglioma was multicentric and the gastric stromal sarcoma multifocal. Because of the rarity of gastric stromal sarcoma and its multifocality, the young age of the patients, and the unlikely possibility of coincidental co-occurrence of paragangliomas and gastric stromal sarcomas, Carney et al suggested that a new syndrome exists with these two main components. Therefore, the familial condition is distinct from the Carney Triad and has been called the Carney-Stratakis Syndrome.

Two other reports\(^12,13\) further clarified diagnostic aspects of the syndrome, noting that these patients have negative staining for SDHB on immunohistochemistry. The distribution appears to be equal for females and males; patients tend to be older than in CTr, have epithelioid histology, gastric location, and frequent lymph node metastases.

**Sporadic SDH-Deficient GIST**

A report by Janeway et al\(^14\) offered insight on the role of defective cellular respiration in sporadic GIST lacking mutations in Wild-Type GIST. In this series, 34 patients with Wild-Type GIST without a personal or family history of paraganglioma were tested for SDH germline mutations; 4 of these patients (12%) had germline mutations in SDHB or SDHC. Wild-Type GIST that lacked somatic mutations or deletions in SDH had either complete loss of or substantial reduction in SDHB protein expression. In contrast, most KIT mutant GISTs had strong SDHB expression. One unresolved issue, according to the results from Janeway et al is whether these isolated SDH-deficient GIST can be categorized as sporadic GIST or whether they might be a precursor of the CTr or CSS.

In summary, SDH-Deficient GIST, with or without SDHx mutations, has unique clinical features, very distinct from the KIT/PDGFRA mutated GIST. These tumors have mainly gastric location with primarily epithelioid histology, showing lymphovascular invasion and a plexiform phenotype, are multifocal and tend to metastasize to the lymph nodes. While CTr patients are primarily young females, patients with CSS have not clear female predominance. SDH-Deficient GIST tends to metastasize early but it has overall a more indolent course.

**SDHB positive by IHC Wild-Type GIST**

**NF1 mutated GIST**

The study by Wang et al\(^15\) evaluated SDHB expression in a significant number of NF1-associated cases. In doing so, the authors proposed that a lack of SDHB expression is not involved in pathogenesis of NF1-associated GISTs. Results were based on 22 NF1-associated GISTs obtained from a repository of nearly 30 years. All 22 NF1-associated GISTs showed staining for SDHB expression; 21 tumors were located in the small intestine and one in the colon. It is unclear what the exact frequency of these mutations is. GIST reportedly occurs 150 times more often in NF1 patients than in the general population.

**BRAF mutated GIST**

BRAF mutations are detected in more than half of melanoma cases and they have become an area of focus in GIST. BRAF is a member of the RAF family of serine/threonine protein kinases that are important effectors of RAS activation; BRAF is involved in the RAS-RAF-ERK signaling pathway, which connects extracellular signals to transcriptional regulation. In a recent study it was shown that 13% of patients with wild-type GIST carry a V600E mutation.\(^16\) In another study 3 out of 61 GIST patients were found to have a V600E mutation.\(^17\) BRAF mutations have been also described in KIT/PDGFRA mutated GIST, as a mechanism of resistance to imatinib.\(^18\)

In summary, SDHB positive Wild-Type GIST is located primarily at the small bowel; it is not usually multifocal and has primarily spindle histology. Unfortunately the small studies that we have for these types of tumors do not allow good estimates of other clinical and histological characteristics. Although BRAF or NF1 mutated GIST has similarities with the phenotype of KIT/PDGFRA mutated GIST, there is no
evidence supporting that it has the same sensitivity to tyrosine kinase inhibitors. Larger studies are needed to characterize this heterogeneous genetically group of GIST.

Discussion

This is an exciting time for the exploration of mechanisms that drive tumorigenesis in Wild-Type GIST—with a special focus on the SDH-Deficient GIST. This is very important, since tyrosine kinase inhibitors seem to have limited activity in SDH-Deficient GIST. IGF1R pathway has been studied as a promising target in Wild-Type GIST. IGF1R has been shown to be over-expressed in Wild-Type GIST compared to the KIT/PGFRA mutated GIST. Results from an ongoing study using linsitinib, a multi-kinase inhibitor, approved currently for medullary thyroid carcinoma. Another study opened recently at NIH, using vandetanib, a multi-kinase inhibitor, approved currently for medullary thyroid carcinoma. This study is ongoing and has no results yet.

It is not entirely clear how SDH deficiency leads to tumorigenesis in GIST. It is known that dysfunction of Succi-nate Dehydrogenase enzyme is leading to accumulation of succinogen in GIST. It is known that dysfunction of Succi-nate Dehydrogenase enzyme is leading to accumulation of succinogen in GIST. It is known that dysfunction of Succinate Dehydrogenase enzyme is leading to accumulation of the succinate, an oncometabolite that inhibits demethylation of DNA and Histones; this phenomenon is leading gradually into a hypermethylator phenotype while KIT/PGFRA mutated GIST has a normal methylation pattern. Although it is too early to suggest implications of this mechanism for therapy, it would make sense to evaluate demethylating agents in patients with SDH-Deficient GIST.

Although patients with CTR, CSS or sporadic SDH-Deficient GIST have a similar phenotype: gastric location, mut-lifocality, epithelioid histology, early metastasis, with an indolent overall course, testing for SDHx mutations is important, in order to define if the GIST is part of an inherited syndrome. Subsequently, relatives of the patients should be screened for the same pathogenic mutations. Although there are no established guidelines currently how to follow asymptomatic carriers of SDHx mutations, this population is at risk to develop GIST or paragangliomas and should be screened with MRI, CT or PET CT if they develop symptoms. In case that they have additional findings like hypertension, palpitation or sweating, measurement of plasma cate-cholamines should be done to rule out a functional paragang-lioma.

Conclusions

The majority of Wild-Type GIST is characterized by SDH deficiency and it can be either sporadic (CTR or CSS) or syn-dromic. Long term follow up is important in these patients, to monitor them for the development of paragangliomas, while relatives of patients with SDHx mutations should be screened for the same mutations. The term SDH-Deficient GIST should be used in these patients, instead of the term Wild-Type GIST that is inaccurate.
How patients are made to feel will dramatically impact their willingness to consider, initiate, and continue clinical trial participation. They have barriers that keep them from joining or staying in a clinical trial. As healthcare providers, we are charged with the duty to address these barriers, but many of us are not aware of the trials and tribulations that patients are faced with. On the other hand, some of us are all too familiar with the barriers that patients face but do not know how to address them. Many patients:

Do not know about clinical trials
Most people have never heard of the term “clinical trial.” They may be aware of some medical research studies, but they have no idea that all medications they take are part of a protocol at the first stages of a clinical trial. Not only are patients not aware of clinical trials, clinical trials are not being offered as a treatment option when they are being seen by their healthcare provider. Some patients are more proactive about their health than others and take the time to do research and ask questions, but most people coming in for care are too preoccupied to ask about a clinical trial.

Do not have access to trials
Patients living in rural areas do not have access to trials that are sometimes offered to big name institutions in big cities. Sometimes, studies are not offered to the local hospital in an urban area, where research is not the main focus. Many times, patients are forced to travel hours to get access to new and innovative studies. This can deter anyone from wanting to participate in a research study that may or may not work for them.

May be afraid or suspicious of research
It has been made very clear by patients that they do not want to be treated like a guinea pig. They are sick and do not want to become a science project. Patients do not want to be the cause of physicians receiving financial kickbacks for their participation in a clinical trial. Even after the establishment of protocols, informed consent, institutional review boards (IRBs) and the Healthcare Insurance Portability and Accountability Act (HIPPA), there is still medical mistrust, especially among minority populations.

Cannot afford to participate
Many are under the assumption that participating in a clinical trial will cost more than standard treatment. They believe that insurance will not cover the cost of this new experimental drug and are not willing to participate. For others, if they are willing to participate, outside costs deter them. This means extra costs for travel, lodging, food, child care, copays, etc.

May not want to go against physician's wishes
The rule has always been to “follow the doctor’s orders.” This is the mantra that some live by. A patient is less likely to take the word of a healthcare provider who is not their primary care physician. They have built a bond and a certain level of trust. In a delicate situation as this, what the doctor says goes.

At the other end of the spectrum, physicians can be the cause of some of the barriers that prohibit patients from participating in a clinical trial.

Lack awareness of appropriate clinical trials
At most comprehensive cancer centers and teaching hospitals, continuing research is a job requirement. At smaller institutions, clinical research may not be a priority. In this case, if a patient mentions a clinical trial, the physician may not be aware of what research is going on at their institution or even how to direct the patient to find the answer.

May be unwilling to “lose control” of a person’s care and believe that standard therapy is best
The added stress of working with another healthcare team does not make a clinical trial look too appealing to a primary care physician who has history with a particular patient. If a primary care physician feels like they do not have an active voice in their patient's care, he or she will be less likely to
encourage patients to participate. Also, if they do not believe or wholeheartedly support the idea of clinical research, then the patient will most likely agree and decide not to participate.

**May be concerned that clinical trials add administrative burdens**
Due to the added stress of extra paperwork and extra clinic hours, many physicians are not keen on clinical research studies. To some, it’s more time consuming for their already overworked staff, more meetings, and more paperwork without the addition of more time in their already tight schedules.

**Benefits of clinical trial education**
Most patients say no because they do not have the tools to say yes. There are many benefits to providing clinical trial education to patients. Giving patients vital information that they were not equipped with before they walked in the door can make a world of difference in their care and overall attitude towards their disease and treatment.

**Addresses myths**
In this age of modern technology, it is vital to a patient’s health that we as healthcare providers are giving patients the most accurate health information. It can be very difficult when Google and WebMD seem to trump what the healthcare provider tells a patient. Even after addressing these myths, one must address what a parent, sister or neighbor has said about medical research and clinical trials. Providing clinical trial education can help to dispel these myths and encourage patients to ask more questions.

**Aids in informed decision-making**
Clinical trial education gives patients the tools to make a well-informed decision about participating in a clinical trial. Typically, patients rely on the opinions of family members, friends and their doctor to make their decisions. They personally may not understand the informed consent process, placebos or randomization, but feel that they must say yes due to urging from others. The clinical trial educator (CTE) should make it a point to fully explain all aspects of the trial, no matter how simple or complicated. Using the teach-back method to make sure patients fully understand all aspects of clinical trial participation is helpful for both the patient and the CTE. Instead of asking, “Do you understand?” saying “Now, can you tell me what we just discussed?” shows what aspects of trial participation need more clarification.

**Builds trust**
Most patients put all their trust in the hands of their healthcare provider. Having support from a primary care physician makes the discussion about participation in a clinical trial go a little easier. The suggestion from their primary care physician puts patients at ease, and they are more willing to listen and take the trial participation seriously, as opposed to reading a pamphlet that they see on a table in a waiting room. A level of trust is also formed between the patient and the clinical trial educator. A patient may feel intimidated by their doctor and may be willing to voice more of their fears to someone that they feel they can relate to. The educator may not be a physician but they are more likely to use lay terms and be able to answer general questions about clinical trials that patients may not even be aware of.

**Creates consistency**
The use of clinical trial education during a patient’s visit at a cancer center can create consistency among the patient’s care team. If the health care provider mentions a trial to a patient to peak their interests, the CTE can be the next person to provide the pertinent information about trial participation. Based on the patient’s reaction, the CTE can hand the patient off to the next person on their health care team who may be able to provide trial specific information to the patient. Working together and having open communication among health care providers can be beneficial for the patient and their overall healthcare.

**Time efficient**
Using a CTE can be very time efficient and ease the patient flow. As we all know, a physician has numerous patients to see and relay very sensitive information as well. Patients have numerous questions and the introduction of a clinical trial as a treatment option will only add to the time spent with patients. The use of a CTE can ease some of the administrative burdens that are sometimes inevitable. In an ideal situation, questions about clinical trial participation are general in nature and can be answered with a quick yes or no. Unfortunately, it does not happen that way. During a patient’s visit, the CTE can utilize the time a patient spends waiting to be seen by a physician. It may require the CTE to be on call at times, but it is the best utilization of the patient and physician’s time. This down time can occur prior to the healthcare provider walking in to see the patient, after the visit, after being triaged, or at the patient’s discretion. Having an open line of communication with the healthcare team is essential to making this particular method flow successfully. Afterwards, patients feel informed, engaged, empowered, and optimistic. There is no right or wrong answer to the question of whether clinical trial participation is a good choice because each participant’s situation is different. The decision is personal. At the end of the discussion, try to leave potential participants with this information so they are able to make an informed decision that they feel content with.

62 The GIST Cancer Journal
In 2008, the National Institutes of Health (NIH) launched an in-person clinic for the Pediatric GIST and Wild-type GIST community which brought together clinicians and scientific researchers from across the world to collaborate and learn more about this rare disease with each other as well as to meet patients and their families firsthand. Through this effort, a core team of multidisciplinary experts was formed who meet regularly to discuss cases that come to the clinic. Tumor and blood samples are collected from patients for the purpose of research and have already yielded several important breakthroughs.

One project the team is involved with is the investigation of germline mutations in the succinate dehydrogenase complex (SDH). This is an important area of study since SDH mutations may help physicians to understand how wild-type GISTs are formed and wild-type GIST patients with SDH germline mutations are at risk of developing paragangliomas. In fact, due in large part to the research produced by this clinic, it is now understood that Pediatric GIST can be diagnosed after age 18 and should more appropriately be titled SDH-deficient GIST.

Despite the surge of knowledge researchers have gained from this clinic, decreases in government funding have now reduced the number of in-person meetings held to once per year, with much needed additional staffing and resources becoming difficult to find.

The Life Raft Group has responded to the funding cuts and partnered with the NIH to supplement the loss of an in-person clinic by launching the first Pediatric GIST Virtual Tumor Board.*

The process is an augmentation of how virtual tumor review boards work. If selected, doctors of GIST patients log on and review their de-identified patient case with a panel of experts by using the internet, secure servers, and state-of-the-art video conferencing software.

The purpose of the Pediatric GIST Virtual Tumor Board is to bring together leading experts to discuss pediatric/wild-type (SDH-deficient) GIST cases, while serving as an educational resource for local physicians. The Board also provides valuable access for patients and doctors who would not ordinarily be able to attend an in-person clinic due to resources or distance. The Virtual Tumor Board will not only inform the local doctors of the most up to date treatment options, trials, and studies, it will also encourage a collaborative effort of GIST experts from around the world, thus ensuring the best care possible is offered to these patients.

The LRG will use cutting-edge technology to connect the local treating physicians and their team with key opinion leaders in the field of Pediatric (SDH-deficient) GIST. Participants will virtually access radiology films such as CT scans and other necessary medical reports to help review particular cases and provide advice. The objective is to help improve patient outcomes by connecting local treating physicians with leading GIST experts.

The first Pediatric GIST Virtual Tumor Board will take place on June 27th from 2:00-3:30 pm. If you have a case that you would like to have reviewed by a team of experts and you would like to apply to the Virtual Tumor Board, please contact Sara Rothschild at srothschild@liferaftgroup.org or 973-837-9092 ext 118. We will provide you with the application to get started.

*Note: Despite the change in definitions for this subtype of GIST cancer, we will refer to the term “Pediatric GIST”. Please note that pediatric and wild-type tumors are now being classified as SDH-deficient GIST. Anyone who fits this classification is welcome to have their case reviewed.
The New ‘Go-To’ Website in GIST

www.thegistcancerjournal.org

The GIST Cancer Journal will make this address your favorite educational site for in-depth information on the diagnosis and treatment of gastrointestinal stromal tumors.

Visit the journal’s website frequently for:
• Regular News Alerts on late-breaking developments in clinical trials and translational research
• Important links to other sources related to GIST diagnosis and treatment
• Valuable and practical advice on patient advocacy issues
• The complete and easily accessed archive of past issues of The GIST Cancer Journal
• News on upcoming scientific sessions