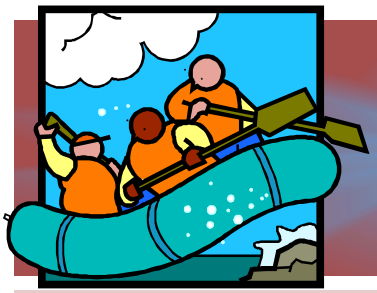
Battling GIST with Gleevec (STI571)



LIFE RAFT GROUP

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# Medicare's anti-oral drug policy would be updated

WASHINGTON, D.C. – U.S. Representative Deborah Pryce (R-Ohio) has introduced the "Access to Cancer Therapies Act" to update Medicare's anti-cancer oral drug policy to make sure that people with cancer have access to all anti-cancer oral drugs.

"New oral drug therapies are being developed to treat cancer in less invasive, more effective ways," Pryce said. "This good news about cancer therapies could mean bad news for seniors if the Medicare program is not updated."

U.S. Rep. Deborah Pryce with the 2001 Horizon Congressional Cancer Award for legislative leadership in the fight against cancer.

Currently, Medicare covers anti-cancer oral drugs, but only if the drug is equivalent to drug therapies provided under physician services, that is administered intravenously in a doctor's office or in an outpatient department. Today, this policy covers 90 to 95 percent of cancer drug therapy.

There are many new oral cancer drugs in the pipeline that will not fall under Medicare's strict definitions for coverage. Oral drugs make up only five percent of the oncology market today, but that will increase to 25 percent or more in the next decade.

"If we do not update Medicare's policy to accommodate new, cutting-edge cancer drugs, the existing level of coverage that seniors rely on will be diminished," Pryce said. "We cannot

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# Gleevec OK'd by FDA; effectiveness hailed

**By Richard Palmer**

Relatively few people had heard of the orange pills known as Gleevec (or Glivec or STI-571) before this month.

That all changed Thursday, May 10, when U.S. Health and Human Services Secretary Tommy G. Thompson held a press conference to announce the federal Food and Drug Administration had approved Gleevec for the treatment of chronic myeloid leukemia.

Novartis Pharmaceuticals, the maker of Gleevec, had applied for approval exactly 10 weeks before approval came - one of the fastest reviews ever for a cancer drug. The FDA action came after it reviewed three separate studies involving more than 1,000 patients.

As details of the effectiveness of Gleevec and its implications became known, the announcement became Big News. CNN cycled the story every half hour throughout the day. The Associated Press wrote and updated the story several times, and the news made the front page of newspapers nationwide.

While the focus was on Gleevec's effectiveness against CML, reports also touched on Gleevec's effectiveness against gastrointestinal stromal tumor, which the media persisted in calling "a rare stomach cancer."

Three days later in San Francisco, at the annual meeting of the American Society of Clinical Oncology, Dr. Charles Blanke appeared at a press conference to announce that the so-called "leukemia pill" had stunning results against gastrointestinal stromal tumor.

The next day (Monday), the Oregon Health Sciences University oncologist stood before thousands of his peers at ASCO plenary session and outlined the findings of his study on Gleevec vs. GIST.

In a phase II clinical trial involving 139 patients, the cancer had gone into remission in 59 percent of the patients, and 90 percent of patients reported major signs of clinical improvement – going off pain-relieving narcotics, returning to work, resuming activities.

So far, Blanke said, none of those who went into remission have relapsed, this over a period of 4 ½ to 10 months.

"This is exciting news, not just because these results validate the theory of targeted therapy, but because these patients have no other options," said Blanke.

As reported by CBS, the success of

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## Medicare

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afford to take this step backward. Medicare must keep pace with pharmaceutical research and development."

Pryce noted that Congress will continue to work to provide a comprehensive drug benefit to seniors, but in the meantime it is important that cancer patients do not suffer from a Medicare policy that lags behind medical technology.

"Without a change in policy, Medicare patients will be relegated to treating their disease with old therapies in doctor's offices and outpatient clinics, rather than having access to effective oral drugs that they can take in the comfort of their own homes," Pryce added.

With Pryce the battle against cancer is more than just good legislation, it's personal: her 9-year-old daughter died of neuroblastoma in September 1999.

## Meet Life Rafters Ehud and Ophir

Ehud (looking really good, too) and son-in-law Ophir. The picture was taken in the office of Dr. Allan T. van Oosterom, University of Leuven in Belgium. It was taken by Mr. Kushida, Hisayo's father. A photo of an Israeli, taken by a Japanese, in a Belgian oncologist's waiting room, and posted by an American. Shows the multi-cultural, international reach of the Life Raft Group.

## Gleevec

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Gleevec represents a sudden reversal of fortune for people diagnosed with GIST. Until now, the disease has resisted everything doctors have hit it with. Usually starting in the connective tissue of the stomach or small intestine, it strikes any of the organs in the entire length of the gastrointestinal tract. These tumors are prone to spread to other organs and are almost always unresponsive to chemotherapy or irradiation. Some tumors can be removed by surgery, but they usually return. The disease has been invariably fatal – before Gleevec.

"Late-stage GIST patients often have withstood multiple surgeries and have generally exhausted their options," Blanke told Novartis, the maker of Gleevec. "If Gleevec continues to demonstrate efficacy and safety in this setting, it may represent a major breakthrough."

It is a breakthrough that may affect more people than once thought. GIST is a type of cancer that was only recognized in the past few years; before that it was considered a gastrointestinal leiomyosarcoma. Blanke told the San Francisco Chronicle that government scientists have recently gone back over tissue samples and revised upward their estimate of the numbers of GIST cases each year, from 1,200 to between 5,000 and 10,000.

The phase II trial began in July 2000 and is being conducted at four cancer centers — OHSU, Dana-Farber Cancer Institute in Boston, Fox Chase Cancer Center in Philadelphia, and Helsinki University Central Hospital in Finland. Patients were equally randomized to either a 400 mg or 600 mg daily dose of Gleevec. At three months or less, responses were observed in 54 percent of patients.

Dr. Allan T. van Oosterom, professor of medicine at the University of Leuven in Belgium and president of the European Organization for Research and Treatment of Cancer (EORTC), told WebMD that a smaller study of 36 patients with GIST suggests that the most effective dose is actually 800 mg.

"I have two patients who didn't respond at 400 mg; we increased to 800 mg and now they are responding," van Oosterom told WebMD.

Blanke told WebMD that several other cancers have similar biological mechanisms, and OHSU is beginning a trial in small-cell lung cancer patients. Other researchers are testing the drug in hormone refractory prostate cancer and

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# ‘Off label’ use worries Gleevec researchers

Doctors conducting clinical trials of Gleevec on GIST patients say they are worried that oncologists will try the drug on the wrong patients.

Dr. Charles Blanke of Oregon Health Sciences University, and Dr. Allan T. van Oosterom, professor of medicine at the University of Leuven in Belgium and president of the European Organization for Research and Treatment of Cancer (EORTC), voiced their concerns to WebMD (www.webmd.com).

While the drug is approved for leukemia and "demonstrated efficacy in GIST," Gleevec is a targeted therapy that only works if the target is present. In solid tumors, that means that the tumor must test positive for the very specific biological mechanisms.

Patient advocates told the San Francisco Chronicle that many people with terminal disease would opt simply to pressure their doctor for a prescription.

"Once word gets out, there'll be a line out the door," the Chronicle quoted Victoria Colgan, a lung cancer survivor who was helping staff the Alliance for Lung Cancer Advocacy Support and Education booth at the American Society of Clinical Oncology conference in San Francisco.

The Chronicle also reported that the Kidney Cancer Association has been deluged with calls from patients who have heard about Gleevec's success against chronic myeloid leukemia, said Carl Dixon, president and executive director. He told the Chronicle that while Gleevec isn't designed to fight kidney cancer, this doesn't always deter people who are desperate.

"I'm sure that people are going to seek it out and that some docs will experiment with prescribing it," Dixon was quoted as saying. "If you have a patient and you have nothing else to offer, why wouldn't you?"

Now that FDA has approved Gleevec for CML, doctors are free to prescribe the drug to any cancer patient, on a so-called "off label" basis.

That worries doctors involved in the clinical trials. Van Oosterom told the Chronicle that any doctor who prescribes the drug outside of approved uses is "irresponsible."

"I don't think anyone should have this drug without proper testing," he said.

Dr. Brian Druker

Similar concerns were voiced by Dr. Brian Druker, director of the Leukemia Center at OHSU and co-developer of Gleevec. "When we developed this compound (in conjunction with Novartis), we knew it was specific enough to have limited toxicity but also might target more than one protein."

CML, GIST and the brain cancer glioblastoma are each driven by a single enzyme. Gleevec can disable these three enzymes, which are similar in structure. But most other cancers are more complicated, say the scientists, with multiple abnormalities working in concert.

"Those enzymes may be present in those cancers, but ‘present’ doesn’t necessarily mean critical to the cancers’ growth or survival," says Druker. Locking up one troublemaker in a chemically complex cancer wouldn’t create a response.

"It would be the difference between cutting off a finger," Druker says, "and putting a stake through the cancer’s heart.”

## Quote:

"For the first time, cancer researchers now have the necessary tools to probe the molecular anatomy of tumor cells in search of cancer-causing proteins. Gleevec offers proof that molecular targeting works in treating cancer, provided that the target is correctly chosen. The challenge now is to find these targets."

— Dr. Richard Klausner, director, National Cancer Institute

"I have been waiting 30 years to report results like these."

— Dr. Allan T. van Oosterom, University of Leuven, Belgium, at the American Society of Clinical Oncology annual meeting in San Francisco

"We're going from a disease that no one wanted 2 years ago, to now, when we've got patients all over the world in some peculiar way, saying: 'Gosh, if I've got to have cancer, at least I've got a GIST.'"

— Dr. George Demetri, Dana-Farber Cancer Institute in Boston

## Just call them Crazy Canucks

At least that's what they call themselves up there. These Canadian Life Rafters got together May 8 at Mt. Sinai Hospital in Toronto, Ontario, Canada. They are, from left, Linda H., Jeannette S., Keith C. and Keith's sister and caregiver, Janice C. All of them are from Ontario. You'd never know three of them have a cancer which was invariably fatal before the arrival of STI571, now Gleevec.

# Novartis ships Gleevec within 24 hours of FDA approval

EAST HANOVER, NJ. – Novartis Oncology reported that shipments of Gleevec left the company's warehouse within 24 hours of receiving approval from the U.S. Food and Drug Administration (FDA) on May 10. This is faster than any other product in the company's history.

Gleevec is an oral therapy for the treatment of patients with chronic myeloid leukemia (CML) after failure of interferon-alpha therapy.

Community pharmacies throughout the United States had Gleevec available for patients by the week of May 13-19.

This expedited shipping schedule is only the latest extraordinary investment Novartis has made in Gleevec.

Upon first hint of the dramatic potential of this new agent, Novartis rapidly invested extraordinary manpower to scale-up manufacturing and to expedite the clinical development, allowing many more patients to enter clinical studies and have access to the drug. As a result, the new drug application was filed only 32 months after the first dose in man, more than halving the

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## More Gleevec

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glioblastoma brain tumors.

Novartis has set up a toll-free information line about Gleevec, 1-877-GLEEVEC (1-877-453-3832), for medical professionals and consumers. It also offers help qualifying for patient assistance.

*Editor's note: Some figures cited by Dr. Blanke at his May 14 presentation before ASCO do not agree with abstracts on the ASCO Web site, which were submitted months ago and are*

## Who's new in the Life Raft Group

Welcome to all new members:

Janice C., whose brother is on the trial in Toronto.

John M. also on the trial in Toronto.

Jerry S., on the trial in Texas.

Sid L., on the trial in New York.

Rita G., whose father is also on the trial in Texas.

Gail W., whose mother is on the trial in Washington, D.C.

Marcel S. who is on the trial in Washington state.

Carl and Kay B.; Carl is on the trial in California.

Ron and Jo Ann M.; Ron is on the trial in Texas.

Ben V., who is on the trial in Pennsylvania.

Rita R., who is on the trial at Columbia-Pres.

Marvin F. who is on the trial in Washington, D.C.

Laurie P., for dad James on the trial in New York

Gayne E., our latest member.

# Journal reports on clinical trial patient No. 1

Someone had to be first. In the case of gastrointestinal stromal tumor treated with STI571, (now Gleevec) the first patient was a woman in Finland. She began taking the drug in March 2000, four months before the clinical trial of STI571 for GIST would begin at three cancer centers in the United States.

The following are excerpts from the case report published in the April 5 New England Journal of Medicine, used here with permission.

In October 1996, a 50-year-old, previously healthy woman presented with mild abdominal discomfort and a large mass in the upper abdomen. Surgeons subsequently removed two tumors, 6.5 and 10 centimeters in diameter, from the stomach. Also, the greater omentum and mesocolic peritoneum were removed because of the presence of multiple metastatic nodules 1 to 2 millimeters in diameter. Tests revealed the masses as GIST.

In February 1998, the woman again underwent surgery. This time recurrent tumors in the left upper abdomen, two liver metastases, and multiple small intra-abdominal metastases were removed. In September that same year, six more liver metastases and an ovarian metastasis were removed.

From November 1998 to March 1999, the woman was given seven cycles of chemotherapy for additional liver metastases. Doctors used mesna, doxorubicin, ifosfamide and dacarbazine. There was no clinical response.

In March 1999, the cancer had progressed. A metastasis that was obstructing the large bowel and 45 smaller metastases were surgically removed. Again, the patient was treated with chemotherapy. Between April 1999 and February 2000, she was given thalidomide and interferon alfa. The therapy was unsuccessful; by February 2000 the liver metastases were progressing in size and number, and several new intra-abdominal and mesenteric metastases were found by magnetic resonance imaging (MRI).

That was when the doctors at Helsinki University Central Hospital turned to a new compound – STI571.

Treatment was started in March 2000, with four 100 mg capsules of STI571 given once daily. This dose was based on evaluations of the safety and tolerability of STI571 in patients with chronic myeloid leukemia.

Toxicity was assessed at follow-up visits every two to four weeks, and blood-cell counts and blood chemical values were analyzed every one to two weeks.

The response was measured with dynamic MRI, positron-emission tomography (PET), and serial needle biopsies of a liver metastasis.

The day before the start of treatment, doctors measured eight large liver metastases and came up with a combined size of 112.5 square centimeters. On subsequent MRI scans, the size was as follows: 67 square centimeters after two weeks of treatment, 54 square centimeters at one month, 42 square centimeters at two months, 36 square centimeters at four months, 33 square centimeters at 5½ months, and 28 square centimeters at eight months. No new lesions appeared, and six of the 28 liver metastases disappeared.

As of February 2001, all tumors continued to respond to treatment, and the patient remained clinically well.

STI571 was well tolerated. No drug-related adverse effects on the liver, kidneys, or heart were observed. All of the main subjective adverse effects were mild and consisted of an increased frequency of bowel movements, occasional muscle cramps in the legs, and slight ankle edema.

*Editor's note: The Life Raft Group Newsletter thanks the New England Journal of Medicine for permission to reprint the case study, and the authors of the study: Drs. Heikki Joensuu, Peter J. Roberts, Maarit Sarlomo-Rikala, Leif C. Andersson, Pekka Tervahartiala, David Tuveson, Sandra L. Silberman, Renaud Capdeville, Sasa Dimitrijevic, Brian Druker and George D. Demetri.*

## Fast track

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typical drug development time frame of approximately six years.

The highly positive clinical results prompted FDA to grant a priority review. This resulted in an approval after a 10 week review period, making this the fastest time to market of any cancer treatment.

Patients' access to Gleevec has been a key concern of Novartis and ultimately more than 7,500 patients are currently under treatment. Of these patients, approximately 5,000 are part of an expanded access program, which was established solely to provide access to patients who were in medical need. The data from these 5,000 patients were not needed to seek marketing authorization for the drug.

Novartis has put in place a comprehensive patient assistance program for uninsured, indigent patients. In the United States, the program will be administered by Documedics. A patient assistance hotline has been established; it's 1-877-GLEEVEC (1- 877-453-3832).

Outside the U.S., patients should contact the Medical Department of the local Novartis Pharma Company.

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**Who are we and what do we do?** We are a group of GIST patients and caregivers (spouses and others) in the STI571 (Glivec) clinical trials who have come together to share our experiences and support each other. Persons not in the trial are encouraged to seek support from the broader leiomyosarcoma (LMS) community. We focus on side effects, symptoms and other drug-related issues. Members correspond privately to each other and to the wider group as appropriate .

**Privacy:** Privacy is of paramount concern, and we try to err on the side of privacy. We do not send information that might be considered private to anyone outside the group. To assist in that goal, the secure e-mail listserve does not include professional members of the various study sites. However, this newsletter does serve as an outreach and is widely distributed. Hence, all items in the newsletter are edited to maintain the anonymity of members, unless members have granted publication of more detailed information.

**Method:** Our primary means of communication is through a confidential, secure listserv operated by the Association of Cancer Online Resources, ACOR (www.acor.org).

**Disclaimer:** We are patients and caregivers, not doctors. Any information shared among the group should be used with caution, and is not a substitute for careful discussion with your doctor.

**Newsletter note:** Read at your own risk! Every effort to achieve accuracy is made, but we are human and errors occur. Please advise the newsletter editor of any errors you may find.

# Letters to the editor

Editor:

Because of the information we receive on certain lists, I have become aware of the need to support a bill introduced in congress by Rep. Deborah Pryce (Ohio, 15th District), co-chair of the House Cancer Caucus. Rep. Pryce's 9-year-old daughter died of neuroblastoma in September 1999.

The bill, HR1624, titled "Access to Cancer Therapies Act of 2001" will amend the Social Security Act to provide Medicare coverage for all oral anticancer drugs.

Without this bill, coverage of many of the new cancer treatments will be denied to Medicare recipients because of the current language of the Social Security Act.

The new bill is designed to update Medicare's anti-cancer oral drug policy to make sure seniors with cancer have access to all anti-cancer oral drugs. New oral drug therapies are being developed to treat cancer in less invasive, more effective ways. This good news about cancer therapies could mean bad news for seniors if the Medicare program is not updated.

Currently, Medicare covers anticancer oral drugs, but only if the drug is equivalent to drug therapies provided under physician services, that is administered intravenously in a doctor's office or in an outpatient department. Today, this policy covers 90 to 95 percent of cancer drug therapy.

Unfortunately, there are many new oral cancer drugs in the pipeline that will not fall under Medicare's strict definitions for coverage. Oral drugs make up only 5 percent of the oncology market today, but that will increase to 25 percent or more in the next decade.

Without a change in policy, Medicare patients will be relegated to treating their disease with old therapies in doctor's offices and outpatient clinics, rather than having access to effective oral drugs that they can take in the comfort of their own homes.

As an example, a new treatment such as Gleevec, approved by the FDA after a very short review due to its remarkable effects, is not covered by Medicare and as of today people with GIST or CML will have to pay more than $2,000 monthly to get the only drug shown to be effective against their disease.

The Senate is currently working on a similar bill, to be introduced by Senator Snowe of Maine.

I believe it is in the clear interest of the vast majority of ACOR subscribers to see this bill passed in Congress and in the Senate. We represent a large number of patients and caregivers for whom this information may be very important. It would be a shame to see patients denied access to fundamental advances in science simply due to inadequate language.

**Gilles Frydman**
ACOR.org